Optimising the management of patients with atrial fibrillation

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B.Biomed.Sci(Hons)

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Department of Epidemiology and Preventative Medicine

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“There is no ailment in which such success can be achieved, no other cardiac disorder which may be so speedily benefitted, as the well-managed case of auricular fibrillation”.

Sir Thomas Lewis (1881 – 1945)
Clinical Disorders of the Heartbeat 1912
General Declaration

Declaration for thesis based or partially based on conjointly published or unpublished work. In accordance with Monash University Doctorate Regulation 17 Doctor of Philosophy and Research Master’s regulations the following declarations are made:

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes 4 original papers and 2 Letters-to-the-Editor published in peer reviewed journals and 1 unpublished (submitted) publication. The core theme of the thesis is optimising the management of patients with atrial fibrillation using enhanced risk delineation. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the candidate, working within Preventative Health, Baker IDI Heart and Diabetes Institute under the supervision of Professor Simon Stewart and Dr Melinda Carrington.

In the case of Chapters 3 to 7 my contribution to the work involved the following:

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<tr>
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<td>3</td>
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I have not renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Signed:  

Date: 29th November, 2013

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Acknowledgements

Well here it is – the result of years on a journey of knowledge acquisition and education. And what a journey it has been. I never thought that I could do it. But I have and I can hardly believe it. There are so many people that have provided support throughout this process and, although they may not all be named here, I wish to thank them all.

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Finally, I would like to thank David and Chantal who have put their conviction in me and have opened an even bigger door for me to step through. I look forward to working with you to achieve even greater things.

I have learnt so much on this journey, not only about chronic disease management and atrial fibrillation, but about life in the world of research. I have certainly matured over the last few years and believe that I am ready for the next steps on this journey. I am truly excited about what the future holds.

I dedicate this thesis to Warwick Ball. Dad – this is for you.

Jocasta Clare Ball
29th November, 2013
Publications produced during candidature relevant to this thesis


Sliwa K, Carrington M, Klug E, Opie L, Ball J, Stewart S. Predisposing factors and incidence of newly diagnosed atrial fibrillation in an urban African community: Insights from the Heart of Soweto Study. *Heart* 2010; 96(23): 1878-82. [IF: 5.014]
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**American Heart Association Scientific Sessions 2011, Orlando - November 2011**

Awards presented during candidature

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<td>2012</td>
<td>Awarded Cardiac Society of Australia and New Zealand (CSANZ) Travelling Fellowship to the European Society of Cardiology Congress 2012.</td>
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<tr>
<td>2012</td>
<td>Awarded Baker IDI Heart &amp; Diabetes Institute Bright Sparks Program Travel Award to attend the Cardiac Society of Australia and New Zealand (CSANZ) 60th Annual Scientific Meeting.</td>
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Abstract

Background
Atrial fibrillation (AF) is the most common form of cardiac arrhythmia found in clinical practice and indeed the adult population. Although AF can present in an acute and non-sustained (paroxysmal AF) form, it typically progresses into a chronic and often silent disorder. Over a prolonged period, chronic AF is associated with detrimental mechanical changes that result in progressive cardiac dysfunction. An enhanced thrombo-embolic state coupled with blood stasis in the atria leads to increased thrombus formation. Consequently, AF is closely linked to thrombo-embolic stroke and chronic heart failure; two of the most deadly and disabling forms of cardiovascular disease. Chronic AF is, therefore, commonly associated with recurrent hospitalisations and poor patient outcomes overall; including a poor prognosis. Overall, despite the known risks, health outcomes associated with AF continue to be sub-optimal within the context of predominantly older patients who require a careful assessment of risk and individualised management to ensure the benefit-to-risk ratio of often complex therapeutic regimes are optimised.

Aims
In addition to understanding the true extent of the global burden of AF, the primary aim of this research was to establish enhanced and potentially effective methods for the assessment of risk in order to direct more individualised AF patient management in an attempt to improve outcomes. More specifically, the influence of gender, mild cognitive impairment and effective rate/rhythm control on patients with AF and as methods for risk delineation was assessed.

Methods
The framework for this research was the Standard versus Atrial Fibrillation speEific managementT studY (SAFETY), a multi-centre randomised controlled trial of a nurse-led AF-specific intervention involving home-based assessment, extensive risk profiling (over and above conventional profiling) and individualised management compared to usual post-discharge care. Participants included were those ≥ 45 years of age with
documented chronic AF for which this has been the cause of hospitalisation. For this research program, quantitative analysis to assess risk delineation strategies was undertaken using data collected at the baseline time point.

**Results**

In a comprehensive review and meta-analyses of the literature, the prevalence of AF was found to be greater than commonly reported. Here, the population prevalence was found to be between 2.5% and 3.5%, substantially higher than the reported 1.0% to 2.0%. Furthermore, the economic consequences were found to be equally as large, with up to 2.5% of health care costs in Europe, North America and Australia spent on AF alone.

When a detailed evaluation of gender differences was undertaken, key differences in the clinical presentation, thrombo-embolic risk and therapeutic management of women compared to men were detected. Most importantly, women were, on average, older than their male counterparts and were also more likely to report depressive symptoms and have poorer quality of life. There were also potentially important social, clinical and treatment differences that might adversely influence health outcomes in women.

The prevalence of cognitive impairment within this cohort was found to be substantially higher than expected, with 65% of the SAFETY cohort demonstrating mild cognitive impairment (MCI) on initial assessment. Those with MCI were less educated but at a higher thrombo-embolic risk with multiple cognitive domains being affected.

When cardiac rate and rhythm were assessed on Holter monitoring in intervention patients post-discharge, a substantial divergence between intended and detected control was found. Of those intended for rhythm control, 43% had reverted back to AF and an uncontrolled heart rate was identified in 26% of all patients. A novel method for classifying heart rate control was determined with three phenotypes being described. Patients who were more clinically complex with diagnosed coronary artery disease (CAD) and/or renal disease/dysfunction were less likely to display heart rate stability.
Conclusions

In addition to providing a more contemporary and accurate description of an evolving global epidemic of AF, this research has the potential to enhance and extend current risk delineation strategies to optimise clinical management and outcomes in high risk individuals. Specifically, by focussing on gender differences, the common presence of MCI and a frequent disconnect between intended versus achieved rate/rhythm control target this research identified a number of practical ways to enhance risk delineation in AF. Ongoing research will evaluate the cost-effectiveness of enhanced risk delineation in AF via more proactive management.
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List of Abbreviations

ACS – Acute coronary syndrome
ACT – Atrial arrhythmic Conversion Trial
ACTIVE – Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events
ADONIS – American-Australian-African trial with Dronedarone in patients with atrial fibrillation or atrial flutter for the maintenance of sinus rhythm
AF – Atrial fibrillation
AFASAK – Atrial Fibrillation, ASpirin anticoagulant therapy study
AFFIRM – Atrial Fibrillation Follow-up Investigation of Rhythm Management
ANTIPAF – Trial to investigate the efficacy of olmesartan in Paroxysmal Atrial Fibrillation
AO – Aorta
ARISTOTLE – Apixaban for the prevention of Stroke in subjects with atrial fibrillation
ATHENA – A Trial with dronedarone to prevent Hospitalization or death in patients with Atrial fibrillation
ATSI – Aboriginal and Torres Strait Islander
AV node – Atrioventricular node
AVERROES – A phase III study of apixaban in patients with atrial fibrillation
AVRO – A phase III superiority study of Vernakalant versus amiodarone in subjects with Recent Onset atrial fibrillation
BAATAF – Boston Area Anticoagulation Trial for Atrial Fibrillation
BAFTA – Birmingham Atrial Fibrillation Treatment of the Aged study
CAFA – Canadian Atrial Fibrillation Anticoagulation study
CES-D – Centre for Epidemiological Studies depression scale
CHA2DS2-VASc score – Chronic heart failure, Hypertension, Age ≥75 years (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65-74 years, Sex category (female)
CHF – Chronic heart failure
CI – Confidence interval
CRAFT – Cardiac Resynchronization in Atrial Fibrillation Trial
CVD – Cardiovascular disease
DCR – Direct current reversion
DIONYSOS – Efficacy and safety of Dronedarone versus amiodarone for the maintenance of Sinus rhythm in patients with atrial fibrillation
DMP – Disease management program
EAFT – European Atrial Fibrillation Trial
ECG – Electrocardiogram
ENGAGE AF TIMI-48 – Effective anticoagulation with factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48
EQ-5D – EuroQol 5-dimension scale
EURIDIS – EURopean trial in atrial fibrillation or flutter patients receiving Dronedarone for the maintenance of Sinus rhythm
EXPLORE-Xa – Phase 2 study of the safety, tolerability and Pilot efficacy of Oral factor Xa inhibitor betrixaban compared to warfarin
HAS-BLED score – Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65 years), concomitant Drugs/alcohol
HOT-CAFE – HOw to Treat Chronic Atrial Fibrillation
HR-QoL – Health-related quality of life
IF – Impact factor
INR – International normalised ratio
LA – Left atrium
LAA – Left atrial appendage
LV – Left ventricle
LVEF – Left ventricular ejection fraction
MCI – Mild cognitive impairment
MI – Myocardial infarction
MoCA – Montreal Cognitive Assessment
MV – Mitral valve
MWNAF – Minidose Warfarin in Nonrheumatic Atrial Fibrillation
NYHA – New York Heart Association
OPAL-2 – A study evaluating safety and tolerability of YM150 compared to warfarin in subjects with Atrial fibrillation
OR – Odds ratio
PA – Pulmonary artery
PAD – Peripheral artery disease
PALLAS – Permanent Atrial fibrillation outcome study using dronedarone on top of Standard therapy
PATAF – Primary prevention of Arterial Thromboembolism in nonrheumatic Atrial Fibrillation
PIAF – Pharmacological Intervention in Atrial Fibrillation
PV – Pulmonary vein
QoL – Quality of life
RA – Right atrium
RACE – RAte Control versus Electrical cardioversion
RCT – Randomised controlled trial
RE-LY – Randomized Evaluation of Long term anticoagulant therapy with dabigatran etexilate
ROCKET-AF – An efficacy and safety study of Rivaroxaban with warfarin for the prevention of stroke and nervous system systemic Embolism in patients with non-valvular Atrial Fibrillation
RV – Right ventricle
SA node – Sinoatrial node
SAFE-T – Sotalol Amiodarone atrial Fibrillation Efficacy Trial
SAFETY – Standard versus Atrial Fibrillation specific management Study
SF-12 – Short form 12
SI – SAFETY Intervention
SIFA – Studio Italiano Fibrillazione Atriale (Italian Study on Atrial Fibrillation)
SPAF – Stroke Prevention in Atrial Fibrillation
SPINAF – Stroke Prevention in Nonrheumatic Atrial Fibrillation
SPORTIF – Stroke Prevention using an ORal direct Thrombin Inhibitor in atrial Fibrillation
STAF – Strategies of Treatment of Atrial Fibrillation
TIA – Transient ischaemic attack
TOE – Trans-oesophageal echocardiogram
**TTE** – Trans-thoracic echocardiogram

**TV** – Tricuspid valve
Chapter 1

General Introduction
Chapter 1 describes the increasing prevalence of cardiovascular-related morbidity and mortality with a focus on one chronic cardiac condition - Atrial Fibrillation (AF). Cardiac anatomy and physiology are described in relation to the aetiology and pathophysiology of AF. Treatment options for AF are outlined including current therapeutic targets and pharmacological therapies. Finally, the role of chronic disease management programs for the optimisation of AF patient management is discussed within the context of an increasing number of cases of AF and complex therapeutic options.
Chapter 1: General Introduction

1.1 The global burden of cardiovascular disease (CVD)

Cardiovascular disease (CVD – disease of the heart and blood vessels) overwhelmingly continues to be a major cause of morbidity and premature mortality in Australia and worldwide [AIHW, 2012a]. In Australia, approximately 1.6 million males and 1.8 million females were estimated to have CVD in 2007-08 [AIHW 2011]. CVD occurred more commonly among the elderly, with 62% of those aged 75 and older having a cardiovascular condition compared with 5% of those aged less than 45 years [AIHW, 2011]. In 2009-10, CVD accounted for 11% of primary care consultations [Britt et al., 2010] and comprised 6% of all hospitalisations with a principal diagnosis of CVD (276,400 for males and 205,800 for females) [Britt et al., 2010]. An additional 640,000 hospitalisations in 2009-10 involved CVD as a secondary diagnosis. In 2008, CVD was responsible for more deaths than any other disease group (34% of the total), despite the overall mortality rate attributed to CVD continuing to fall since the 1960s [AIHW, 2011]. More specifically, coronary heart disease was the number one cause of death in Australia for males and females and accounted for 17% of all deaths and 49% of cardiovascular deaths in 2007 [AIHW, 2011]. In the same year, cerebrovascular disease (most notably stroke) was the cause of the second highest number of deaths in females and the third highest in males [AIHW, 2011]. CVD is associated with direct health care expenditure that exceeds any other disease group in Australia, costing approximately $5.9 billion in 2004-05, with just over half spent on hospital admissions [AIHW, 2011].

In Australia, individuals most affected by CVD include lower socioeconomic groups, Aboriginal and Torres Strait Islander (ATSI) people and those living in remote areas of Australia who have the highest rates of hospitalisation and death resulting from CVD [AIHW, 2011; AIHW, 2012a]. Mirroring its natural history, the greatest impact of CVD is on the elderly where hospitalisation and death rates are usually much higher than for others (aside from infants suffering from congenital heart disease) [AIHW, 2011; AIHW, 2012a]. For most cardiovascular conditions, mortality rates are higher in males than in females [AIHW, 2012a]. However, CVD is the cause of more female deaths than male deaths because of the longer life-expectancy of females [AIHW, 2012a]. Australia’s ageing population has a major influence on the measurable rise in CVD prevalence. Despite this, CVD is largely preventable and risk factor modification can
reduce clinical events and premature death in people who are at high cardiovascular risk (primary prevention) as well as in those with established CVD (secondary prevention) [AIHW, 2012b].

1.1.1 Risk factors for chronic CVD

The collective influence of social, economic, biomedical and environmental factors has driven a significant increase in the number of CVD cases in Australia and in the developed world [AIHW, 2012b]. Key modifiable health risk factors that increase the likelihood of developing CVD are those over which individuals have some influence. These can be classified as behavioural or biomedical and may influence disease onset or affect the severity, course and progression of a disease once it has developed [Begg et al., 2007; AIHW, 2011; AIHW, 2012b]. Furthermore, these factors are important targets for preventative health interventions. Table 1 outlines key modifiable behavioural and biomedical risk factors specifically related to CVD and identified within the Australian context [Begg et al., 2007; AIHW, 2011].
Table 1: Key modifiable behavioural and biomedical risk factors for CVD [Begg et al., 2007; AIHW, 2011; AIHW, 2012b].

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<th><strong>Biomedical factors</strong></th>
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<td>▪ Tobacco smoking (responsible for 10.0% of the total burden of disease and injury in Australia in 2003 for males and 6.0% for females; 8.0% overall)</td>
<td>▪ High blood pressure (7.6% of the burden of disease and injury in Australia in 2003)</td>
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<tr>
<td>▪ Insufficient physical activity (contributed 7.0% of the overall burden of disease and injury in Australia in 2003)</td>
<td>▪ High blood cholesterol (6.2% of the burden of disease and injury in Australia in 2003)</td>
</tr>
<tr>
<td>▪ Poor dietary behaviour (inadequate fruit and vegetable consumption accounted for 2.0% of the disease and injury burden among females and 3.0% among males)</td>
<td>▪ Overweight and obesity (8.0% of the burden of disease and injury in Australia in 2003)</td>
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<tr>
<td>▪ Excessive alcohol consumption (responsible for 4.0% of the total burden of disease and injury for males and 1.0% for females)</td>
<td>▪ Impaired glucose regulation</td>
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<td>▪ Depression</td>
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Some health risk factors cannot be altered (known as non-modifiable risk factors) and these include age, gender and genetic predisposition. Furthermore, being of a lower sociodemographic/socioeconomic status often cannot be easily addressed. Individuals of lower socio-economic status regularly experience inequality and disadvantage (e.g. ATSI populations or those of lower financial status) and are at increased levels of CVD risk than the general population [AIHW, 2012b].
1.2 Cardiac anatomy and physiology

1.2.1 Anatomy of the healthy human heart

The heart is composed of four “chambers” – two atria situated at the top of the heart and two ventricles below. De-oxygenated (venous) blood enters the heart via the right atrium and moves to the right ventricle where it is propelled (via myocardial [muscular] contraction through the pulmonary artery) to the lungs. It is here that oxygen is replaced within the blood cells. Following re-oxygenation within the lungs, the blood returns to the left atrium via the pulmonary veins, moves into the left ventricle and is expelled (again via myocardial contraction) to supply the remainder of the body (as arterial blood). The action of the heart is that of a pump and this is mediated by the thick muscular wall (myocardium). The main objective of the heart is to deliver blood in optimal supply and nutrient composition to visceral and peripheral organs via the circulatory system (i.e. arteries, arterioles, capillaries, venules and veins). To achieve this objective, the heart must operate with synchronicity and at optimum capacity. Figure 1 diagrammatically represents the human heart and demonstrates the pathway of normal blood flow.
Chapter 1: General Introduction

Figure 1: Anatomy of and blood flow within the healthy human heart (adjusted from Baker IDI Heart & Diabetes Institute stock diagram).

The synchronous pumping actions of the heart’s two atrioventricular pumps (right and left sides) constitute the cardiac cycle. The cycle begins with a period of ventricular relaxation (diastole) and ends with a period of ventricular contraction (systole). Cardiac muscle fibres, which allow contraction to occur and the cardiac cycle to exist, are chains of cardiac muscle cells (cardiomyocytes) joined end to end by cell junctions [Cormack, 1993; Ross, Romrell & Kaye, 1994; Gartner & Hiatt, 1997; Pinnell, Turner & Howell, 2007]. Cardiac muscular contraction is somewhat similar to skeletal muscular contraction, although some distinct differences exist. As with skeletal muscle, cardiac muscle has the properties of conductivity, contractility and excitability [Bers, 2002]. However, unlike skeletal muscle, cardiac muscle has the unique property of
automaticity, that is, automatic contraction and relaxation without external electrical stimulation from the nervous system [Mangoni & Nargeot, 2008].

1.2.2 Electrophysiology of the healthy human heart

Cardiac Conduction Pathway

Intrinsic electrical stimulation is received at the sinoatrial (SA) node (located at the top of the right atria) from the autonomic nervous system. The SA node is known as the heart’s “pacemaker”, as it initiates and regulates impulses for contraction (at approximately 60-100 times per minute). The activity of the SA node sets both the rhythm and rate of cardiac chamber contraction. From receipt at the SA node, electrical impulses are conducted through both atria, causing their contraction (Figure 2). As the signal moves through the right atria by myogenic (muscular) conduction and following a short delay (allowing for atrial contraction to take place and maximal ventricular filling), it is transmitted to the atrioventricular (AV) node which is located in the interatrial septum. From here, the impulses propagate via the Bundle of His (embedded in the interventricular septum) to the right and left bundle branches and Purkinje fibres, causing ventricular contraction. Sympathetic nervous stimulation speeds up electrical conduction and parasympathetic stimulation slows it down. Coordination of the cardiac cycle is driven by intrinsic electrical impulses and signalling mechanisms, notably those of the atrial, ventricular and nodal cardiomyocytes [Pinnell, Turner & Howell, 2007; Mangoni & Nargeot, 2008].
Chapter 1: General Introduction

**Figure 2:** Electrical signalling pathway within the healthy human heart (Mangoni & Nargeot, 2008; RA = right atrium; PV = pulmonary veins; LA = left atrium; TV = tricuspid valve; MV = mitral valve; RV = right ventricle; LV = left ventricle).

**Electrocardiography, waveforms and intervals**

The pathway of electrical events of the cardiac cycle (comprising four stages of electrical signalling) can be amplified, visualised and recorded graphically as an electrocardiogram (ECG – **Figure 3**).

**Figure 3:** Normal sinus rhythm demonstrated on ECG (from Baker IDI Heart & Diabetes patient ECG).

Each event in cardiac electrical signalling has a distinct waveform and study of an ECG can give insight into a patient’s cardiac physiology or pathophysiology [Pinnell, Turner
& Howell, 2007]. If the heart beats normally and regularly, it is in sinus rhythm. **Figure 4** represents one sinus rhythm cardiac cycle seen on ECG and displays the nomenclature of each individual waveform, interval and complex.

**Figure 4:** Normal sinus rhythm as seen on ECG.

**Table 2** explains which cardiac electrical events correspond to each wave/interval that comprises a normal sinus heart beat.
Table 2: Cardiac electrical events as displayed on ECG.

<table>
<thead>
<tr>
<th>Wave/Interval</th>
<th>Corresponding Cardiac Electrical Event</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P wave</strong></td>
<td>Electrical conduction and subsequent contraction of the right and left atria (atrial depolarisation).</td>
</tr>
<tr>
<td><strong>PR interval</strong></td>
<td>Time in which impulse travels from the SA node to the atria and downward to the ventricles.</td>
</tr>
<tr>
<td><strong>QRS complex</strong></td>
<td>Spread of electrical impulses (depolarisation) via the Bundle of His through the ventricular myocardium and subsequent ventricular contraction.</td>
</tr>
<tr>
<td><strong>T wave</strong></td>
<td>Ventricular repolarisation (no associated activity of the ventricles – a resting phase).</td>
</tr>
</tbody>
</table>

The usual fluid and tightly coordinated conduction of the heart ensures rhythmic control and optimal delivery of oxygenated blood to the tissues and organs to fulfil the metabolic requirements of the body.

1.3 The emerging epidemic of atrial fibrillation (AF)

One of the most common cardiovascular disorders is cardiac arrhythmia (rhythm irregularity) and the most common form of sustained cardiac arrhythmia observed in medical practice is atrial fibrillation (AF), a supraventricular (atrial) tachyarrhythmia [Go et al., 2001; Stewart et al., 2001]. This pattern is mirrored in all developed nations and is alarmingly gaining impetus within developing countries due to epidemiological transition and a likely overall rise in non-communicable forms of heart disease [Sliwa et al., 2010]. AF is irregular and uncoordinated activation of the atria. When AF occurs over a long period of time, detrimental mechanical changes in the atria occur and heart and vascular function are adversely affected [Shinbane et al., 1997; Stewart et al., 2002; Burstein & Nattel, 2008]. In contrast to life-threatening arrhythmias, AF may appear benign but may reveal its detrimental effects only after many years.
Among cardiovascular conditions, awareness and knowledge of AF, its pathophysiology, pharmacotherapeutic targets and management is improving. This is most likely the result of an exponential increase in the prevalence and incidence of AF cases over the last few decades and the need to address this mounting clinical (and economic) problem [Krahn et al., 1995; Wolf et al., 1996; Psaty et al., 1997; Kannel et al., 1998; Go et al., 2001; Stewart et al., 2001; Tsang et al., 2003; Stewart, 2004; Heeringa et al., 2006; Miyasaka et al., 2006; Alonso et al., 2009; Bonhorst et al., 2010; Smith et al., 2010; Chien et al., 2010; Stefansdottir et al., 2011; Piccini et al., 2012]. Compared to other cardiovascular diseases, however, few studies have provided a rich source of data about AF in Australia. Much of the data that AF prevalence and incidence statistics are derived from originate from studies conducted in Europe, the United States of America and Asia [Krahn et al., 1995; Wolf et al., 1996; Psaty et al., 1997; Kannel et al., 1998; Go et al., 2001; Stewart et al., 2001; Tsang et al., 2003; Heeringa et al., 2006; Miyasaka et al., 2006; Alonso et al., 2009; Bonhorst et al., 2010; Smith et al., 2010; Chien et al., 2010; Stefansdottir et al., 2011; Piccini et al., 2012]. Furthermore, research reports on the epidemiology and burden of AF in the developed world are heterogeneous and expansive, making a complete and accurate interpretation of the impact of AF challenging.

1.3.1 Symptomatology of AF

Those suffering from AF are often asymptomatic or symptoms are subtle and AF is only detectable on electrocardiogram (ECG) or by manual detection of an irregular pulse [Furberg et al., 1994; Page et al., 1994; Frishman et al., 1996; Kerr et al., 1996]. Therefore, AF is often diagnosed secondarily as a co-morbidity rather than being a primary reason for specialist consultation. It has been previously reported that asymptomatic events in AF patients are 12-fold more common than symptomatic events [Page et al., 1994]. Interrogation of implantable devices such as permanent pacemakers and implantable defibrillators have demonstrated that up to 50-60% of patients may have unsuspected episodes of AF that are often sustained [Garrigue et al., 1996; Defaye, Dournaux & Mouton, 1998; Levy et al., 1998].
When AF symptoms are recognised and described, they are often similar between individuals [Savelieva & Camm, 2000]. However, the symptomatology of AF is non-specific and similar to symptoms of many other cardiac and non-cardiac conditions. This is perhaps the reason why AF is not often found as a primary diagnosis. Presenting symptoms can include one, some or all of the following:

- Dyspnoea (breathlessness)
- Syncope or dizziness
- Diaphoresis (sweating)
- Fatigue or lethargy
- Feelings of anxiety
- Palpitations or “fluttering”
- Chest pain or discomfort
- Weakness

1.3.2 Aetiology of AF

AF occurs as a result of disruption to the electrical conduction system of the heart described above. The underlying cause of AF is abnormal impulse formation or impulse propagation resulting from defective (overactive or underactive) function of cardiac ion channels [Nattel & Carlsson, 2006]. Normal conduction of electrical impulses that allow the coordinated contraction of ventricles following that of the atria becomes chaotic and disordered. The result is that the atria quiver rather than contract, preventing normal blood flow within the heart. Multiple ectopic (abnormal) electrical foci develop in the right atrium surrounding the SA node [Markides & Schilling, 2003; Nattel & Carlsson, 2006; Mathew, Patel & Joseph, 2009]. These disordered signals are conducted to the left atrium and subsequently to the ventricles via the AV node. The ventricles are no longer under the direct control of the SA node and, therefore, contraction is directed by the disordered signals from the SA node and the filtration of these by the AV node.
AF is illustrated on ECG as the absence of P waves and the observation of rapid oscillations (fibrillation waves - Figure 5). In addition, the R to R intervals are irregular. The development and perpetuation of AF causes the heart to work at sub-optimal capacity.

![ECG Image]

**Figure 5:** AF demonstrated on ECG (P wave is not identifiable, oscillation waves are present and R-R intervals are irregular indicated by arrows differing in length) (from Baker IDI Heart and Diabetes patient ECG).

The initial stimulus and perpetuation of AF requires both a trigger for its onset and a substrate for its maintenance [Markides & Schilling, 2003; Mathew, Patel & Joseph, 2009]. These mechanisms are not mutually exclusive and are likely to co-exist at various times [Markides & Schilling, 2003; Mathew, Patel & Joseph, 2009].

### 1.3.3 Pathophysiology of AF

**Electrophysiological and structural cardiac remodelling**

With repeated episodes of AF, electrophysiological as well as structural remodelling occurs in the atria, which further perpetuates AF [Wijffels et al., 1995; Rostock et al., 2008]. The concept that “AF begets AF” results from the initiation of new arrhythmogenic foci outside the pulmonary veins (PVs) [Wijffels et al., 1995; Haissaguerre et al., 1998; Rostock et al., 2008]. This partly explains the modest success rate of catheter-based AF ablation in patients with permanent AF and remodelled atria. Electrophysiological remodelling includes progressive shortening of the effective refractory and action potential periods facilitating after depolarisation [Jais et al., 2002]. Structural remodelling may occur due to AF itself or as a consequence of hypertension.
or heart failure [Allessie, Ausma & Schotten, 2002]. This leads to atrial cardiomyocyte death, increased interstitial fibrosis, loss of gap junctions and impairment of cellular coupling [Polyakova et al., 2008]. This structural remodelling may also facilitate re-entry, which further perpetuates AF [Polyakova et al., 2008].

**Thrombopathogenesis**

Clinical bleeding and thrombosis results from a disturbance in the balance between a complex network of procoagulant and anticoagulant factors. Effective homeostasis is dependent on an optimal balance of these factors. AF promotes a prothrombotic (clotting) state within the body partially due to the lack of optimal cardiac pumping and stasis of blood that occurs particularly in the left atrium [Blackshear & Odell, 1996; Watson, Shantsila & Lip, 2009]. In addition, various abnormal changes related to AF and its comorbidities impart a synergistic effect in maintaining a hypercoagulable state [Lip, 1995; Watson, Shantsila & Lip, 2009].

The pathogenesis of thrombus formation and the significant risk of stroke and thromboembolism that results from AF can be explained with reference to Virchow’s triad, a description of three primary interactions that occur in the complex procoagulant/anticoagulant factor network [Watson, Shantsila & Lip, 2009]. The triad states that interactions occur between the blood vessel (including fixed and dynamic responses), blood flow and blood constituents (soluble and cellular) [Kroll et al., 1996] and abnormalities in one or all of these results in thrombogenesis (Figure 6). Virchow’s triad can be recognised as 1) endothelial or endocardial damage or dysfunction (and related structural abnormal changes), 2) abnormal blood stasis and 3) abnormal haemostasis, platelets and fibrinolysis [Sanfilippo et al., 1990; Freedman & Loscalzo, 1997; Heppell et al., 1997; Roldan et al., 1998; Goldsmith et al., 2000; Cai et al., 2002; Mahe et al., 2002; Boos, Anderson & Lip, 2006; Choudhury et al., 2007; Watson, Shantsila & Lip, 2009]. Abnormal changes in all these variables are evident in AF, leading to a hypercoagulable state within patients, although the details of such changes remain to be fully elucidated. Inflammation and oxidative stress (e.g. decreased nitric oxide bioavailability) have been implicated in the initiation and perpetuation of AF,
however, evidence suggests that these mechanisms also stimulate and promote the prothrombotic state [Cai et al., 2002; Boos, Anderson & Lip, 2006; Watson, Shantsila & Lip, 2009].

**Figure 6:** Virchow’s triad in the context of AF.

### 1.3.4 AF forms and sub-types

**Acute or transient AF**

The simplest form of AF is a singular or incidental *de novo* episode that is self-terminating and never returns [Camm et al., 2010]. An episode of acute or transient AF can be the result of ischaemia, cardiac surgery/procedure or overindulgence in drugs or alcohol (i.e. the “Holiday Heart” syndrome) [Balbao, de Paola & Fenelon, 2009].

**Chronic AF**

The other major form of AF is chronic in nature and four sub-types of this form are defined [Camm et al., 2010]. Each is not static or isolated and often one leads to the
next temporally longest (Figure 7). Episodes of recurrent “paroxysmal” AF are self-limiting and self-terminating and persist for less than 7 days (and usually only last 24 hours to a few days) [Camm et al., 2010]. Episodes of “persistent” AF last longer than 7 days and may require termination (i.e. restoration of sinus rhythm) by pharmacological or electrical cardioversion but can often be recurrent, reverting back into fibrillation [Camm et al., 2010]. “Long-standing persistent” AF lasts greater than or equal to 1 year at which point a successful rhythm control strategy is undertaken [Camm et al., 2010]. “Permanent” AF does not respond to cardioversion and, therefore, is continuous in nature and significantly detrimental to the cardiovascular system if left untreated for long periods [Camm et al., 2010]. By far the most prevalent form of AF is paroxysmal AF, accounting for 35-66% of all diagnosed cases of AF [Davidson et al., 1989].

**Figure 7:** Subtypes of AF and temporal progression.
Lone AF

When AF occurs in the absence of underlying clinical or echocardiographic injury and in the absence of known risk factors, it is known as lone AF [Gersh & Solomon, 1999]. Lone AF that occurs in families is known as familial (genetic or heritable) AF. This additional manifestation of AF is believed to be due to certain chromosomal abnormalities, although these have not been clearly distinguished or defined to date [Brugada et al., 1997; Chen et al., 2003; Darbar et al., 2003; Ellinor et al., 2003; Fox et al., 2004; Yang et al., 2004; Ellinor et al., 2005; Hong et al., 2005; Xia et al., 2005; Gollob et al., 2006; Olson et al., 2006; Otway et al., 2007; Chen et al., 2007; Hodgson-Zingman et al., 2008].

Risk factors and causes of AF

There are multiple risk factors and causes of AF including metabolic, toxic, endocrine, structural and underlying genetic factors that have a strong influence on its development (Table 3) [Camm et al., 2010]. Some risk factors are modifiable and, therefore, the risk of AF decreases as the risk factor is controlled. However, some risk factors for AF are inherent and non-modifiable (e.g. gender or ethnicity).
**Table 3:** Risk factors that potentially predispose to AF [Camm et al., 2010].

<table>
<thead>
<tr>
<th>Reversible causes of AF</th>
<th>AF with associated heart disease</th>
<th>AF associated with medical conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drugs</strong></td>
<td>Atrial pressure elevation</td>
<td>Atrial dilation</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Hypertension</td>
<td>Obesity</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Valvular heart disease</td>
<td>Sleep apnoea</td>
</tr>
<tr>
<td>Cigarettes</td>
<td>Myocardial disease leading to</td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>systolic or diastolic dysfunction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intra-cardiac tumours or thrombi</td>
<td></td>
</tr>
<tr>
<td><strong>Surgery</strong></td>
<td>Atrial ischaemia (ischaemic heart disease)</td>
<td>Subarachnoid haemorrhage</td>
</tr>
<tr>
<td>Cardiac, pulmonary,</td>
<td>Coronary artery disease</td>
<td>Major ischaemic stroke</td>
</tr>
<tr>
<td>oesophageal, or general surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Endocrine disorders</strong></td>
<td>Congenital heart disease</td>
<td></td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Atrial septal defect</td>
<td></td>
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<tr>
<td>Phaeochromocytoma</td>
<td></td>
<td></td>
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<tr>
<td>Diabetes</td>
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<td></td>
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<tr>
<td><strong>Inflammatory atrial disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pericarditis</td>
<td>Amyloidosis</td>
<td></td>
</tr>
<tr>
<td>Myocarditis</td>
<td>Age-induced atrial fibrotic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>changes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Haemochromatosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Endomyocardial fibrosis</td>
<td></td>
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<tr>
<td></td>
<td>Primary or metastatic disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>in or adjacent to the atrial wall</td>
<td></td>
</tr>
<tr>
<td><strong>Infiltrative atrial disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial pressure elevation</td>
<td>Enhanced automaticity</td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>(focal AF)</td>
<td></td>
</tr>
<tr>
<td>Electrophysiological abnormalities</td>
<td>Conduction abnormality</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(re-entry)</td>
<td></td>
</tr>
</tbody>
</table>

**Triggers**

There are many triggers (different to risk factors or initiators) for the onset of AF [Katan & Schouten, 2005; Conen et al., 2008; Heeringa et al., 2008; Schoonderwoerd et al., 2008]. Of course, persistence of these triggers leads to extension of the episode of AF that was triggered. **Figure 8** outlines some triggers that have already been
identified, although research is currently being conducted to elucidate these further [Katan & Schouten, 2005; Conen et al., 2008; Heeringa et al., 2008; Schoonderwoerd et al., 2008; Camm et al., 2010]. Eventually, AF persists in lieu of triggers [Camm et al., 2010].

**Figure 8:** Some factors that act as triggers for AF (Blue = physiological trigger; pink = drug-induced trigger; orange = clinical trigger).

### 1.4 Current health care of patients with AF

There are many treatment modalities for AF which vary in complexity. Currently, no truly safe therapies exist. Those that do exist carry side effects and incur multiple interactions. Treatment goals for AF are to relieve symptoms foremost, reduce severe complications (stroke, systemic embolism, heart failure and mortality) and improve quality of life (QoL) [Camm et al., 2010; Thrall et al., 2006]. Management is individually tailored to achieve these goals in parallel wherever possible. Prevention of severe complications relies on the use of anti-thrombotic therapy, control of the ventricular rate and adequate control of concomitant cardiac conditions [Camm et al., 2010]. Symptom relief may also require reversion of the heart to normal sinus rhythm via the use of cardioversion techniques, antiarrhythmic drugs or ablation [Camm et al., 2010].
1.4.1 Aims of AF management

AF is a complex, diverse and multi-faceted condition made even more complicated by the fact that patients are more likely to be elderly and frail with multiple co-morbidities and potentially poor treatment adherence. The appropriate approach to the management of AF is dependent on the clinical context in which it is found. Assessment of the optimal method of management for an AF patient involves a number of key principles and AF-specific management should always have these three major aims [Camm et al., 2010]:

1. To balance the risk of thrombo-embolism (clotting) and haemorrhage (bleeding) by the correct and monitored usage of anti-platelet and/or anti-coagulant therapy;

2. To control the heart rate or rhythm, which is dependent on the sub-type of AF;

3. To minimise the adverse consequences of AF on cardiac structure and function.

Each of these aims intends to reduce symptoms (if present and feasible), maximise QoL and minimise the ultimately negative consequences of AF in afflicted individuals.

1.4.2 Current treatment options for patients with AF

Treatment of AF is based on the diagnosed subtype of AF that a patient is afflicted with (i.e. paroxysmal, persistent or permanent). Treatment involves medication and/or electrical therapy due to the electrical nature of the disorder. The major aim of treatment for AF is to revert the heart back and maintain sinus rhythm and/or control the rate of ventricular contraction [Camm et al., 2010]. If these strategies are not possible, the aim of management is to prevent potentially severe complications including systemic thrombo-embolism, stroke or death. Symptom relief is also a major aim of treatment including relief of palpitations, shortness of breath, chest pain, lightheadedness, exercise intolerance and fatigue. It is also important to improve patient QoL [Thrall et al., 2006].
The choice of treatment or management strategy must be adjusted to incorporate individual circumstances such as co-morbidities, age and symptom severity. It is important to note that the management strategies employed in the treatment of AF are not mutually exclusive. The management strategies utilised include anticoagulation, rate- or rhythm-control (Figure 9).

**Figure 9:** Therapeutic strategies utilised in the management of AF.

There is a fine balance required in attempting to achieve the correct method of management and multiple factors need to be considered. Evidence-based best practice research has informed guidelines worldwide outlining many aspects of the management of patients with AF [Lip, Rudolf & Kakar, 2007; Cairns et al., 2011; Camm...
et al., 2010; Gillis & Skanes, 2011; Gillis et al., 2011; Healey et al., 2011; Stiell & Macle, 2011]. Guidelines of the collaboration of the European Society of Cardiology and European Heart Rhythm Association (ESC/EHRA) are most influential due to their comprehensibility. These guidelines do not indicate achievement of sinus rhythm “at all costs” in all patients, nor do they suggest that rate control is uniformly an appropriate first-line alternative for all, or even most, patients [Reiffel, 2008]. Reiffel (2008) stated that selectivity and goal reality are the keys to the proper therapeutic and management choices in AF patients.

**Surgical/invasive interventions**

A number of alternative non-pharmacological therapies have been developed over recent years for prevention and control of AF [Camm et al., 2010]. Surgical ablation uses a technique called the “Maze” procedure which involves creating incisions at critical locations within the atria (often the AV node) that create barriers (lesions) to the erratic electrical conduction [Cox et al., 1995]. By cutting and stitching, scars are formed which do not conduct electrical signals causing disruption to the pattern of fibrillation waves. This approach to treatment of AF is seen as a secondary option, as it involves open heart surgery and cardiopulmonary bypass [Camm et al., 2010]. Catheter radiofrequency ablation is often employed to replicate results of the Maze procedure (i.e. to create linear scars in the atrial endocardium) or to create circumferential electrical isolation of the entire pulmonary vein musculature which is often implicated in AF, without the need for open heart surgery [Packer, Asirvatham & Munger, 2003]. Catheter ablation has been shown to improve symptoms, left ventricular function, exercise capacity and QoL [Hsu et al., 2004]. AF can also be suppressed via atrial pacing, either in the right atrium alone or in multiple atrial locations [Andersen et al., 1997]. Pacing mechanisms include preventing bradycardia-induced dispersion of repolarisation, suppression of atrial premature beats and maintenance of AV synchrony [Knight et al., 2005].
Rate control versus rhythm control

Rate control

Rate control attempts to control the subsequent erratic ventricular contraction that occurs as a result of AF. It is a proven treatment for most patients with persistent AF [Sopher & Camm, 1996; Hohnloser & Li, 1997; Riley & Pritchett, 1997; Kowey et al., 1998; Pratt, 1998; Wakatare & Camm, 1998; Segal et al., 2000] and is absolutely required is cases of permanent AF, when reversion to sinus rhythm is not achievable. Rate control is achieved with medication used as monotherapy or in combination therapy. Digoxin is often used for monotherapy, although there is a potential for toxicity and a need for intense blood monitoring to ensure the patient is within the therapeutic range [Camm et al., 2010]. Furthermore, limitations exist because sympathetic nervous system drive can overcome the vagomimetic properties of this medication, as in situations of exertion (e.g. during exercise) [Segal et al., 2000]. Therefore, digoxin by itself is often useful only in elderly patients or those who have a sedentary lifestyle [Segal et al., 2000]. The use of β-blockers in heart rate control has been shown to be more effective during exercise but the combination therapy of digoxin and β-blockers has shown consistent rate control when at rest and during times of exertion which, of course, is the ideal situation for patients being rate control managed for AF [Segal et al., 2000].

Non-dihydropyridine calcium channel antagonists are also used in rate control and, when used in combination with digoxin, provide good control of mean heart rate at rest, during exercise and over a 24 hour period [Segal et al., 2000]. Class IC and class III anti-arrhythmics which block sodium channels and prolong the refractory period, respectively, are also used for rate control management in AF [Segal et al., 2000]. Results of a number of AF randomised controlled trials (RCTs) including AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management), RACE (Rate Control versus Electrical Cardioversion), PIAF (Pharmacological Intervention in Atrial Fibrillation), STAF (Strategies of Treatment of Atrial Fibrillation) and HOT-CAFÉ (How to Treat Chronic Atrial Fibrillation) have illustrated that successful rate control can be achieved [Sopher & Camm, 1996; Hohnloser & Li, 1997; Riley & Pritchett, 1997; Kowey et al., 1998; Pratt, 1998; Wakatare & Camm, 1998; Segal et al., 2000].
Rhythm control

The aim of rhythm control is to restore sinus rhythm, essentially converting the heart back to normal rhythm through cardioversion. Both paroxysmal and persistent AF can be managed with rhythm control, although, often persistent AF becomes resistant to rhythm control and rate control is implemented [Camm et al., 2010]. Cardioversion can be either pharmacological (oral or intravenous) or electrical, but both therapeutic modes are designed to revert the heart back into sinus rhythm.

Pharmacological cardioversion is performed by the administration of anti-arrhythmic medications, the most common of which is amiodarone. This type of cardioversion may take minutes to several days to occur. Many of the pharmacological agents used to achieve cardioversion have negative inotropic properties that reduce the force of the myocardial contractions with adverse consequences [Zimetbaum, 2007]. Other common adverse effects of anti-arrhythmic therapy include pulmonary, hepatic, thyroid, ophthalmologic and dermatologic effects [Zimetbaum, 2007].

Alternatively, electrocardioversion involves cardiac defibrillation to “shock” the heart back into sinus rhythm. Prior to this procedure being performed, a patient must have been successfully anti-coagulated with warfarin for a number of weeks (usually 4 weeks), as electrocardioversion can dislodge a pre-existing thromboembolus in the atria which has formed as a result of AF, causing blockage, stroke or even death [Camm et al., 2010]. Becoming increasingly common in clinical practice is the use of transoesophageal echocardiography (TOE or TEE) prior to electrocardioversion when an episode of AF has extended more than 48 hours [Camm et al., 2010]. This imaging technique is used to stratify stroke risk in AF patients and to guide cardioversion [Camm et al., 2010]. It is implemented in the weeks following appropriate anticoagulation to assess the presence or absence of a thromboembolus. If a thromboembolus is detected, additional anticoagulation will be administered prior to electrocardioversion. When electrocardioversion is performed, anticoagulation is continued afterwards [Camm et al., 2010].
Control for optimal patient outcomes

Given the benefits and risks of all therapeutic options, many different factors must be taken into consideration when deciding on the method of treatment for a patient, whether rate or rhythm control (Table 4).

Table 4: Indications for rate or rhythm control in persistent AF*.

<table>
<thead>
<tr>
<th>Rate-control strategy</th>
<th>Preferred initial option for:</th>
<th>Rhythm-control strategy</th>
<th>Preferred initial option for:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Older people (&gt;65 years)</td>
<td>• Younger people (&lt;65 years)</td>
<td>• People with unacceptable arrhythmia-related symptoms</td>
<td></td>
</tr>
<tr>
<td>• People with coronary artery disease</td>
<td>• People presenting for the first time with lone AF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• People with contraindications to anti-arrhythmic drugs</td>
<td>• AF secondary to a treated/corrected precipitant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Those unsuitable for cardioversion</td>
<td>• People with congestive heart failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• People without congestive heart failure</td>
<td></td>
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</table>

*Adapted from the National Collaborating Centre for Chronic Conditions – Atrial Fibrillation: National clinical guideline for management in primary and secondary care [NCC-CC, 2006].

Worldwide, there have been a number of RCTs specifically investigating the efficacy of rate versus rhythm control for AF. In five of the most well-known RCTs and counter-intuitive to expected clinical benefits, all demonstrated that a rhythm control strategy for management of AF conferred no survival advantage over a rate control strategy [Reiffel, 2008]. Both the AFFIRM and RACE trials demonstrated a trend towards an increased risk of mortality with a rhythm control strategy compared to a rate control strategy [Wyse et al., 2002; Van Gelder et al., 2002]. Additionally, a trend was identified suggesting that the death rate at 5 years was higher amongst those in the AFFIRM rhythm control cohort (p=0.08) [Wyse et al., 2002]. However, no significant difference between the two groups was found when the composite end-points (death, disabling stroke, disabling anoxic encephalopathy, major bleeding or cardiac arrest) were
analysed and compared [Wyse et al., 2002]. Results from the RACE study suggested that rate control satisfied the standard for non-inferiority (equality) and approached that of superiority compared to a rhythm control strategy [Van Gelder et al., 2002]. At all points of follow-up in the PIAF study, symptomatic improvement was comparable between the two treatment arms, although there was a significant difference in the number of hospital re-admissions between the groups (24% in the rate control group and 69% in the rhythm control group; p=0.001) [Hohnloser, Kuck & Lilienthal, 2000]. Additionally, no differences were described in the occurrence of the primary composite end-point within results of the STAF study (death, stroke or transient ischaemic attack, systemic embolism or cardiopulmonary resuscitation) or the HOT-CAFÉ study (all-cause mortality, number of thrombo-embolic events, or intracranial or other major haemorrhage) [Carlsson et al., 2003; Opolski et al., 2004].

**Anti-thrombotic pharmacotherapies**

Anti-thrombotic therapy is required in all cases of AF because stasis of blood occurs in the atria (particularly in the left atrial appendage [LAA]) due to the lack of atrial contraction and, therefore, ejection of blood during fibrillation. Oral antithrombotic therapy substantially minimises the risk of a thrombo-embolic event. Warfarin (an anticoagulant) and aspirin (an antiplatelet agent) are the most common oral antithrombotics used in AF management. It has been shown that warfarin can decrease the risk of undergoing a thrombo-embolic event by 67% compared to aspirin which can decrease the risk by 22% [Lip & Lim, 2007; Lip et al., 2010]. Along with being the most effective treatment for prevention of thrombo-embolic events, however, oral anticoagulants come with an increased risk of major haemorrhage [Connolly et al., 2008; Camm et al., 2010; Lip et al., 2010]. There is an extremely small therapeutic window and a tight balance between too much and too little is required to prevent significant morbidity due to adverse effects of the medication [Connolly et al., 2008; Lip et al., 2010]. Intensive monitoring is required via the international normalised ratio (INR) pathology test to determine the biological effect of the anticoagulant as well as time in therapeutic range and, subsequently the dosage required to maximise this and prevent an elevated INR (bleeding risk) or sub-therapeutic INR (clotting risk). An INR
between 2.0 and 3.0 is the target, as an INR of >3.0 is associated with an increased risk of bleeding events (odds ratio = 3.2) and an INR <2.0 is associated with an increased risk for ischaemic events (odds ratio = 5.07) [Reynolds et al., 2004; Connolly et al., 2008].

**Newly emerging therapies for the management of AF**

Currently, there is competition within the pharmaceutical industry in the development of new therapeutic agents to replace warfarin and aspirin for the gold-standard management of AF. A newly emerging area of AF therapy development appears promising but also carries a warning surrounding the introduction of new therapies into “real-world” AF patient cohorts outside of clinical trial conditions. Investigators worldwide are developing and testing new antithrombotic and antiarrhythmic agents.

**Clinical trials of new pharmacotherapies**

The development of ximelagatran, a direct thrombin inhibitor, showed early promise but soon became damaged by the unacceptable levels of hepatotoxicity inflicted on treatment participants [Jacobs & Stessman, 2011]. The three largest contemporary clinical trials of new agents involved the antithrombotic therapies dabigatran (RE-LY), rivaroxaban (ROCKET-AF) and apixaban (ARISTOTLE) [Connolly et al., 2009; Patel et al., 2011; Granger et al., 2011]. All three of these have proven at least non-inferior, if not superior, to warfarin for thromboprophylaxis in AF [Connolly et al., 2009; Patel et al., 2011; Granger et al., 2011]. The introduction and worldwide approval of dabigatran in mid-2011 has been overshadowed by the issue of severe safety advisories of the bleeding risks associated with its use in elderly patients and patients with renal dysfunction that became evident in the latter part of the year including a warning of potential fatality [Food and Drug Administration (FDA) <http://www.fda.gov/Drugs/DrugSafety/ucm282724.htm>, 2011; Therapeutic Goods Administration (TGA) <http://www.tga.gov.au/safety/alerts-medicine-dabigatran-111005.htm>, 2011; Safe and Quality Use of Medicines Group, New Zealand Ministry of Health, <www.safeuseofmedicines.co.nz>, 2011; European Medicines Agency Press Office,
In addition, whilst on trial, 21% of participants in both dabigatran treatment arms were discontinued from therapy at two years [Connolly et al., 2009]. Apixaban showed superiority in comparison to warfarin in AF patients, however, once again, high discontinuation rates of patients whilst on trial were demonstrated [Granger et al., 2011].

A similar balance between benefit and risk has been demonstrated in the development of new antiarrhythmic therapies for AF. Most notably, dronedarone was initially shown to be a safe and effective multi-channel blocker [Singh et al., 2007]. Results from ATHENA showed that a 24% reduction in cardiovascular hospitalisation or death in patients with paroxysmal or persistent AF is achievable when 400mg of dronedarone is added to standard rate control therapies and anticoagulation [Hohnloser et al., 2009]. Furthermore, reductions in death from any cause (16% trend), cardiovascular death (30%) and arrhythmic death (45%) were illustrated [Hohnloser et al., 2009]. Dronedarone reduced the mean ventricular rate over 24 hours during AF as well as during exercise without affecting exercise capacity [Hohnloser et al., 2009]. However, the PALLAS study (a follow-up trial of dronedarone in patients with permanent AF) was suspended due to a significant increase in cardiovascular events observed in the treatment arm [Connolly et al., 2011]. Table 5 summarises the historical progress and key clinical research that has been undertaken in the development of fundamental pharmaceuticals for the treatment of AF up until the present day, including those that are used in current clinical practice and those which have failed introduction into the “real world”.

The issues surrounding the development of new AF therapies reflect the inherent risks with administration of drugs in patients who are often elderly with multiple co-morbidities. The results of seminal trials demonstrate some notable hindrances and mandate a renewed focus on the non-pharmacological management strategies for AF.
Table 5: Summary of clinical research undertaken in the development of therapies for the treatment of AF (see “List of Abbreviations” for study names).

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year published</th>
<th>Study drug/intervention</th>
<th>Dosing</th>
<th>No. of participants</th>
<th>Study design</th>
<th>Study endpoints</th>
<th>Key research findings</th>
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<tbody>
<tr>
<td><strong>Rate/rhythm control therapies</strong></td>
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<tr>
<td>PIAF</td>
<td>2000</td>
<td>Beta-blocker, calcium-channel blocker or digoxin vs. many antiarrhythmics and/or electrical cardioversion</td>
<td>Chosen by treating physician</td>
<td>252</td>
<td>Randomised controlled trial; Phase III</td>
<td>Symptomatic improvement</td>
<td>Achieved in 60.8% of rate control and 55.1% of rhythm control but not significant</td>
</tr>
<tr>
<td>AFFIRM</td>
<td>2002</td>
<td>Beta-blocker, calcium-channel blocker or digoxin vs. many antiarrhythmics and/or electrical cardioversion</td>
<td>Chosen by treating physician</td>
<td>4,060</td>
<td>Randomised controlled trial; Phase III</td>
<td>All-cause mortality</td>
<td>Noninferiority of rate control over rhythm control; mortality similar in both groups; no difference in thrombo-embolic events; hospitalisation and adverse events more frequent in rhythm control; no survival advantage for either rate or rhythm control</td>
</tr>
<tr>
<td>RACE</td>
<td>2002</td>
<td>Digoxin, calcium-channel blocker or beta-blocker vs. electrical cardioversion and sotalol, flecaïnide, propafenone or amiodarone</td>
<td>Chosen by treating physician</td>
<td>522</td>
<td>Randomised controlled trial; Phase III</td>
<td>Composite of cardiovascular mortality, heart failure, embolism, bleeding, pacemaker insertion, severe adverse events</td>
<td>Noninferiority of rate control over rhythm control; mortality similar in both groups; no difference in thrombo-embolic events; adverse events more frequent in rhythm control</td>
</tr>
<tr>
<td>STAF</td>
<td>2003</td>
<td>Beta-blocker, calcium-channel blocker or digoxin vs. many antiarrhythmics and/or electrical cardioversion</td>
<td>Chosen by treating physician</td>
<td>200</td>
<td>Randomised controlled trial; Phase III</td>
<td>Composite of overall mortality, cerebrovascular complications, CPR; embolic events</td>
<td>No difference between rate and rhythm control for number of patients reaching endpoint</td>
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<tr>
<td>Trial</td>
<td>Year published</td>
<td>Study drug/intervention</td>
<td>Dosing</td>
<td>No. of participants</td>
<td>Study design</td>
<td>Study endpoints</td>
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<tr>
<td>HOT-CAFÉ</td>
<td>2004</td>
<td>Beta-blocker, calcium-</td>
<td>Chosen by treating physician</td>
<td>205</td>
<td>Randomised controlled trial;</td>
<td>Composite of mortality, thrombo-embolic complications, intracranial or other</td>
<td>No difference between rate and rhythm control for number of patients reaching endpoint</td>
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<tr>
<td></td>
<td></td>
<td>channel blocker or digoxin vs. many antiarrhythmics and/or electrical cardioversion</td>
<td></td>
<td></td>
<td>Phase III</td>
<td>major haemorrhage</td>
<td></td>
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<tr>
<td>CRAFT</td>
<td>2004</td>
<td>Vernakalant vs. placebo</td>
<td>0.5mg/kg then 1mg/kg if required; 2mg/kg IV bolus then 3mg/kg if required</td>
<td>56</td>
<td>Randomised, double-blind;</td>
<td>Conversion to sinus rhythm (SR)</td>
<td>Significant conversion to SR within 60 minutes; no difference in adverse event rate</td>
</tr>
<tr>
<td>SAFE-T</td>
<td>2005</td>
<td>Amiodarone vs. placebo; sotalol vs. placebo</td>
<td>Amiodarone 800mg daily (2 weeks), 600mg daily (2 weeks), 300mg daily (first year), 200mg daily thereafter; sotalol 80mg twice daily (first week) then 160mg twice daily thereafter</td>
<td>665</td>
<td>Randomised, double-blind;</td>
<td>Pharmacological cardioversion to SR</td>
<td>Cardioversion occurred after 28 days in 27% of amiodarone treated, 24% of sotalol treated and 0.8% of placebo treated patients; amiodarone and sotalol equally effective in converting to SR; amiodarone superior for maintaining SR</td>
</tr>
<tr>
<td>EURIDIS</td>
<td>2007</td>
<td>Dronedarone vs. placebo</td>
<td>400mg twice daily</td>
<td>618</td>
<td>Randomised controlled trial;</td>
<td>AF recurrence; thrombo-embolic events</td>
<td>Dronedarone superior than placebo for maintaining SR; rate of recurrent AF 67% with dronedarone, 77.5% with placebo; treatment successfully delayed time to first recurrence</td>
</tr>
<tr>
<td>ADONIS</td>
<td>2007</td>
<td>Dronedarone vs. placebo</td>
<td>400mg twice daily</td>
<td>619</td>
<td>Randomised controlled trial;</td>
<td>AF recurrence; thrombo-embolic events</td>
<td>Dronedarone superior than placebo for maintaining SR; rate of recurrent AF 61% with dronedarone, 75% with placebo; treatment successfully delayed time to first recurrence</td>
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<td>Trial</td>
<td>Year published</td>
<td>Study drug/intervention</td>
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<td>No. of participants</td>
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<tr>
<td>ACT I</td>
<td>2008</td>
<td>Vernakalant vs. placebo</td>
<td>3mg/kg IV bolus followed by 2mg/kg if required</td>
<td>356</td>
<td>Randomised, double-blind; Phase III</td>
<td>Conversion to SR</td>
<td>Significant conversion to SR within 90 minutes; no difference in adverse event rate</td>
</tr>
<tr>
<td>ACT II</td>
<td>2009</td>
<td>Vernakalant vs. placebo</td>
<td>3mg/kg IV bolus followed by 2mg/kg if required</td>
<td>190</td>
<td>Randomised, double-blind; Phase III</td>
<td>Conversion to SR</td>
<td>Significant conversion to SR within 90 minutes; no difference in adverse event rate</td>
</tr>
<tr>
<td>ATHENA</td>
<td>2009</td>
<td>Dronedarone vs. placebo</td>
<td>400mg twice daily</td>
<td>4,628</td>
<td>Randomised controlled, double-blind, parallel arm; Phase III</td>
<td>Composite endpoint of cardiovascular mortality and cardiovascular hospitalisation</td>
<td>Significant reduction in rate of composite endpoint; increased incidence of gastrointestinal intolerance</td>
</tr>
<tr>
<td>ACT III</td>
<td>2010</td>
<td>Vernakalant vs. placebo</td>
<td>3mg/kg IV bolus followed by 2mg/kg if required</td>
<td>265</td>
<td>Randomised, double-blind; Phase III</td>
<td>Conversion to SR</td>
<td>Significant conversion to SR within 90 minutes; no difference in adverse event rate</td>
</tr>
<tr>
<td>ACT IV</td>
<td>2010</td>
<td>Vernakalant vs. placebo</td>
<td>3mg/kg IV bolus then 2mg/kg if required</td>
<td>234</td>
<td>Multicentre, open-label; Phase III</td>
<td>Conversion to SR</td>
<td>Significant conversion to SR within 90 minutes; no difference in adverse event rate</td>
</tr>
<tr>
<td>RACE II</td>
<td>2010</td>
<td>Lenient vs. strict rate control</td>
<td>Lenient – target resting heart rate below 110bpm Strict – target heart rate below 80bpm at rest and below 110bpm during moderate exercise</td>
<td>614</td>
<td>Randomised, open-label, noninferiority; Phase III</td>
<td>Composite of cardiovascular mortality, hospitalisation for heart failure, embolic events, bleeding events, life-threatening arrhythmic events</td>
<td>Noninferiority of lenient vs strict control; frequencies of the primary outcome similar; frequencies of symptoms and events similar; more patients reached heart-rate target in the lenient-control group</td>
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<td>Trial</td>
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<td>Study drug/intervention</td>
<td>Dosing</td>
<td>No. of participants</td>
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<tr>
<td>DIONYSOS</td>
<td>2010</td>
<td>Dronedarone vs. amiodarone</td>
<td>Dronedarone 400mg twice daily; amiodarone 400mg twice daily</td>
<td>504</td>
<td>Randomised, double-blind, parallel arm; Phase III</td>
<td>Recurrence of AF; premature discontinuation</td>
<td>Dronedarone less efficient at maintaining SR than amiodarone; rate of recurrent AF 63% with dronedarone, 42% with amiodarone; significantly fewer adverse events with dronedarone</td>
</tr>
<tr>
<td>PALLAS</td>
<td>2011</td>
<td>Dronedarone vs. placebo</td>
<td>400mg twice daily</td>
<td>3,236</td>
<td>Randomised controlled trial; Phase III</td>
<td>Composite endpoint of cardiovascular mortality, thromboembolic events and heart failure hospitalisation</td>
<td>Stopped prematurely due to increased event rates in treatment group; mortality, rates of stroke and heart failure hospitalisation twofold in treatment group compared to placebo</td>
</tr>
<tr>
<td>AVRO</td>
<td>2011</td>
<td>Vernakalant vs. Amiodarone</td>
<td>3mg/kg IV bolus then 2mg/kg if required</td>
<td>232</td>
<td>Randomised, double-blind; Phase III</td>
<td>Conversion to SR</td>
<td>Significant conversion to SR within 90 minutes; no difference in adverse event rate</td>
</tr>
<tr>
<td>ACTIVE I</td>
<td>2011</td>
<td>Irbesartan vs. placebo</td>
<td>150mg daily for 2 weeks then 300mg daily</td>
<td>9,000</td>
<td>Randomised, double-blind; Phase III</td>
<td>Major cardiovascular events</td>
<td>No reduction in events in treatment group; heart failure hospitalisations significantly lower in treatment group</td>
</tr>
<tr>
<td>ANTIPAF</td>
<td>2011</td>
<td>Olmesartan vs. placebo</td>
<td>Olmesartan 40mg daily</td>
<td>422</td>
<td>Randomised, double-blind, parallel arm; Phase III</td>
<td>Percentage of days with documented episodes of paroxysmal AF (AF burden)</td>
<td>AF burden not significantly different between groups; time to first recurrence, time to persistent AF and number of hospitalisations not different; time to prescription of recovery medication (amiodarone) earlier in placebo group</td>
</tr>
<tr>
<td>Trial</td>
<td>Year published</td>
<td>Study drug/intervention</td>
<td>Dosing</td>
<td>No. of participants</td>
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<tr>
<td><strong>Anti-thrombotic therapies</strong></td>
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<tr>
<td>AFASAK I</td>
<td>1989</td>
<td>Warfarin vs. placebo; Aspirin vs. placebo;</td>
<td>Aspirin 75mg daily</td>
<td>1,007</td>
<td>Randomised controlled trial (aspirin and placebo arms double-blind); Phase III</td>
<td>Thrombo-embolic complications</td>
<td>No significant difference between aspirin and placebo groups; significant difference in events between three groups; occurrence of thromboembolism increased with duration of AF; 67% reduction in risk of non-fatal stroke with warfarin; overall results in favour of warfarin; no difference in vascular and all-cause mortality</td>
</tr>
<tr>
<td>BAATAF</td>
<td>1990</td>
<td>Warfarin vs. placebo</td>
<td>Low-dose warfarin</td>
<td>420</td>
<td>Randomised, open-label; Phase III</td>
<td>Ischaemic stroke; systemic embolism</td>
<td>Stopped prematurely due to favourable treatment efficacy; 86% reduction in risk of stroke with warfarin; no difference in risk of stroke for AF sub-types</td>
</tr>
<tr>
<td>SPAF I</td>
<td>1991</td>
<td>Warfarin vs. placebo; Aspirin vs. placebo</td>
<td>Aspirin 325mg daily</td>
<td>1,330</td>
<td>Randomised, open-label, blinded event adjudication; Phase III</td>
<td>Stroke and systemic embolism events</td>
<td>Stopped at interim analysis due to treatment efficacy; ischaemic stroke rate significant in placebo group; warfarin significantly reduced stroke; aspirin reduced stroke</td>
</tr>
<tr>
<td>CAFA</td>
<td>1991</td>
<td>Warfarin vs. placebo</td>
<td>Adjusted-dose warfarin</td>
<td>378</td>
<td>Randomised, double-blind; Phase III</td>
<td>Composite of nonlacunar stroke, cerebral haemorrhage, systemic embolism and fatal haemorrhage</td>
<td>Stopped prematurely due to results of AFASAK and SPAF I becoming public; a 37% risk reduction for ischaemic stroke was seen with warfarin; no statistical difference in bleeding events</td>
</tr>
<tr>
<td>SPINAF</td>
<td>1992</td>
<td>Warfarin vs. placebo</td>
<td>Adjusted-dose warfarin</td>
<td>571</td>
<td>Randomised, double-blind; Phase III</td>
<td>Cerebral infarction; cerebral haemorrhage; mortality</td>
<td>Stopped at interim analysis due to marked decrease in cerebral infarction in warfarin group</td>
</tr>
<tr>
<td>Trial</td>
<td>Year published</td>
<td>Study drug/intervention</td>
<td>Dosing</td>
<td>No. of participants</td>
<td>Study design</td>
<td>Study endpoints</td>
<td>Key research findings</td>
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<tr>
<td>EAFT</td>
<td>1993</td>
<td>Warfarin vs. placebo; Aspirin vs. placebo; Warfarin vs. aspirin</td>
<td>Aspirin 300mg daily</td>
<td>1,007</td>
<td>Randomised, double-blind (aspirin and placebo only); Phase III</td>
<td>Composite endpoint of mortality from vascular disease, stroke, myocardial infarction or systemic embolism</td>
<td>Significant reduction in endpoint events with warfarin; incidence of bleeding low in both warfarin and aspirin groups; no intracranial bleeding in warfarin group</td>
</tr>
<tr>
<td>SPAF II</td>
<td>1994</td>
<td>Warfarin vs. aspirin</td>
<td>Aspirin 325mg daily</td>
<td>1,100</td>
<td>Randomised, open-label, blinded event adjudication; Phase III</td>
<td>Stroke and systemic embolism events</td>
<td>Small absolute reduction in stroke by warfarin over aspirin; high rate of intracranial bleeding with warfarin in older patients</td>
</tr>
<tr>
<td>SPAF III</td>
<td>1996</td>
<td>Adjusted dose warfarin vs. aspirin plus fixed low-dose warfarin; aspirin-treated low-risk cohort</td>
<td>Aspirin 325mg daily; fixed low-dose warfarin 1 to 3mg daily</td>
<td>1,044</td>
<td>Randomised controlled trial; Phase III</td>
<td>Stroke risk stratification efficacy; efficacy and safety of adjusted-dose warfarin with aspirin plus fixed low-dose warfarin</td>
<td>Stopped at interim analysis due to treatment efficacy; combination of low-dose warfarin plus aspirin insufficient for stoke prevention; warfarin to an INR of 2-3 offers large benefits over aspirin plus fixed low-dose warfarin for high-risk patients; patients whose stroke risk is low when given aspirin can be identified (SPAF risk stratification scheme)</td>
</tr>
<tr>
<td>SIFA</td>
<td>1997</td>
<td>Warfarin vs. indobufen</td>
<td>Indobufen 100mg to 200mg twice daily</td>
<td>916</td>
<td>Randomised controlled trial; Phase III</td>
<td>Composite endpoint of nonfatal stroke, intracerebral bleeding, pulmonary or systemic embolism, myocardial infarction, cardiovascular mortality</td>
<td>Incidence of combined endpoint not significantly different between groups; increased incidence of ischaemic stroke in indobufen group</td>
</tr>
<tr>
<td>AFASAK II</td>
<td>1998</td>
<td>Fixed low-dose warfarin vs. aspirin; adjusted warfarin vs. aspirin; fixed low-dose warfarin plus aspirin</td>
<td>Aspirin 300mg daily</td>
<td>677</td>
<td>Randomised controlled trial; Phase III</td>
<td>Bleeding events associated with incidence of thromboembolic events</td>
<td>Stopped at interim analysis due to evidence of inefficiency of low-intensity therapy plus aspirin; fixed low-dose warfarin and aspirin alone or in combination associated with minor and major bleeding</td>
</tr>
<tr>
<td>Trial</td>
<td>Year published</td>
<td>Study drug/intervention</td>
<td>Dosing</td>
<td>No. of participants</td>
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<tr>
<td>MWNAF</td>
<td>1998</td>
<td>Fixed low-dose warfarin vs. aspirin; adjusted warfarin vs. aspirin</td>
<td>Fixed low-dose warfarin 1.25mg daily</td>
<td>303</td>
<td>Randomised, open-label; Phase III</td>
<td>Ischaemic stroke, peripheral or visceral embolism, cerebral or fatal bleeding, vascular death</td>
<td>Discontinued prematurely due to results of SPAF III; rate of primary events not significantly different; rate of ischaemic stroke significantly higher in fixed low-dose warfarin group; major bleeding more frequent in standard treatment group</td>
</tr>
<tr>
<td>PATAF</td>
<td>1999</td>
<td>Fixed low-dose warfarin vs. aspirin; adjusted warfarin vs. aspirin</td>
<td>Aspirin 150mg daily</td>
<td>729</td>
<td>Randomised, open label; Phase III</td>
<td>Vascular death, stroke, systemic embolism or major haemorrhage</td>
<td>No significant differences between treatment groups; higher rate of major bleeding in antiplatelet group</td>
</tr>
<tr>
<td>SPORTIF II</td>
<td>2003</td>
<td>Ximelagatran vs. warfarin</td>
<td>Ximelagatran 20mg twice daily, 40mg twice daily, 60mg twice daily</td>
<td>254</td>
<td>Randomised, double-blind; Phase III</td>
<td>Noninferiority; reduction in embolic events; evaluation of bleeding complications</td>
<td>Less embolic events and no major bleeds with ximelagatran; number of minor and multiple bleeds low but slight increase with increased dose; hepatic toxicity in treatment cohort</td>
</tr>
<tr>
<td>SPORTIF III</td>
<td>2003</td>
<td>Ximelagatran vs. warfarin</td>
<td>Ximelagatran 36mg twice daily</td>
<td>3,407</td>
<td>Randomised controlled trial, open-label; Phase III</td>
<td>Noninferiority; reduction in embolic events; evaluation of bleeding complications</td>
<td>Noninferior to warfarin; no difference in composite endpoint rates; total bleeding rates (major plus minor) lower with ximelagatran; hepatic toxicity in treatment cohort</td>
</tr>
<tr>
<td>SPORTIF V</td>
<td>2005</td>
<td>Ximelagatran vs. warfarin</td>
<td>Ximelagatran 36mg twice daily</td>
<td>3,922</td>
<td>Randomised controlled trial, double-blind; Phase III</td>
<td>Noninferiority; composite endpoint of stroke and systemic embolism</td>
<td>Noninferior to warfarin; no difference in composite endpoint rates; total bleeding rates lower with ximelagatran; hepatic toxicity in treatment cohort</td>
</tr>
<tr>
<td>Trial</td>
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<td>Study drug/intervention</td>
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<tr>
<td>ACTIVE W</td>
<td>2006</td>
<td>Clopidogrel + aspirin vs. warfarin;</td>
<td>Clopidogrel 75mg daily; aspirin 75-100mg daily</td>
<td>6,706</td>
<td>Randomised, open-label, parallel arm; Phase III</td>
<td>Composite endpoint of embolic event, myocardial infarction or cardiovascular mortality</td>
<td>Discontinued prematurely due to clopidogrel + aspirin being clearly inferior to warfarin; significantly more primary events in clopidogrel + aspirin group; greater reduction in vascular events and lower risk of major bleeding in patients on warfarin at study entry</td>
</tr>
<tr>
<td>BAFTA</td>
<td>2007</td>
<td>Warfarin vs. aspirin</td>
<td>Aspirin 75mg daily</td>
<td>973</td>
<td>Randomised controlled trial; Phase III</td>
<td>Fatal or disabling stroke, intracranial haemorrhage or clinically significant embolic event</td>
<td>Primary event rate in warfarin group half that of the aspirin group; yearly risk of extracranial haemorrhage was not significantly different</td>
</tr>
<tr>
<td>ACTIVE A</td>
<td>2009</td>
<td>Clopidogrel + aspirin vs. placebo + aspirin</td>
<td>Clopidogrel 75mg daily; aspirin 75-100mg daily</td>
<td>7,554</td>
<td>Randomised, double-blind; Phase III</td>
<td>Composite endpoint of embolic event, myocardial infarction or cardiovascular mortality</td>
<td>Significant reduction in risk of major vascular events but increased risk of major bleeding events in clopidogrel + aspirin</td>
</tr>
<tr>
<td>Tecarfarin</td>
<td>2009</td>
<td>Tecarfarin vs. warfarin</td>
<td>10 to 40mg daily</td>
<td>66</td>
<td>Open-label; Phase IIA</td>
<td>Safety; tolerability; TTR</td>
<td>TTR of 71.4% after 3 weeks; only 10% of patients had a TTR &lt;45%</td>
</tr>
<tr>
<td>AZD0837</td>
<td>2009</td>
<td>AZD0837 vs. warfarin</td>
<td>150mg twice daily, 350mg twice daily</td>
<td>523</td>
<td>Non-randomised, open-label; Phase II</td>
<td>Noninferiority; embolic events; bleeding complications</td>
<td>Lower dose similar safety profile to warfarin and more tolerable; fewer bleeding events (not significant); higher rate of minimal bleeding events with higher dose; increase in serum creatinine noted at both doses</td>
</tr>
<tr>
<td>AZD0837</td>
<td>2010</td>
<td>AZD0837 vs. warfarin</td>
<td>150mg twice daily, 300mg twice daily, 450mg daily, 200mg twice daily</td>
<td>1,084</td>
<td>Randomised, double-blind; Phase II</td>
<td>Noninferiority; bleeding complications; creatinine; alanine aminotransferase; bilirubin</td>
<td>Bleeding events less common in 150, 300 and 200mg groups, similar to warfarin in 450mg group; higher discontinuation rates in treatment group; increase in serum creatinine</td>
</tr>
<tr>
<td>Trial</td>
<td>Year published</td>
<td>Study drug/intervention</td>
<td>Dosing</td>
<td>No. of participants</td>
<td>Study design</td>
<td>Study endpoints</td>
<td>Key research findings</td>
</tr>
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<td>---------------------------------------------</td>
<td>--------------------</td>
<td>----------------------------------------</td>
<td>------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>RE-LY</td>
<td>2011</td>
<td>Dabigatran vs. warfarin</td>
<td>110mg twice daily, 150mg twice daily</td>
<td>18,113</td>
<td>Randomised, open-label, noninferiority; Phase III</td>
<td>Noninferiority; reduction in embolic events; evaluation of bleeding complications</td>
<td>Noninferior to warfarin; higher dose significantly more effective than warfarin with similar frequency of haemorrhagic stroke; lower dose similar to warfarin with significantly lower haemorrhagic events</td>
</tr>
<tr>
<td>ROCKET-AF</td>
<td>2011</td>
<td>Rivaroxaban vs. warfarin</td>
<td>15mg daily, 20mg daily</td>
<td>14,000</td>
<td>Randomised, double-blind, noninferiority; Phase III</td>
<td>Noninferiority; reduction in embolic events; evaluation of bleeding complications</td>
<td>Noninferior to warfarin; did not achieve superiority in intention-to-treat; significantly reduced intracranial bleeding; overall major bleeding events similar</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>2011</td>
<td>Apixaban vs. warfarin</td>
<td>5mg twice daily</td>
<td>18,000</td>
<td>Randomised, double-blind, noninferiority; Phase III</td>
<td>Noninferiority; stroke or systemic embolism; major bleeding events; all-cause mortality</td>
<td>Superiority of apixaban over warfarin; rates of major bleeding events, haemorrhagic stroke and all-cause mortality significantly lower in treatment group</td>
</tr>
<tr>
<td>AVERROES</td>
<td>2011</td>
<td>Apixaban vs. aspirin</td>
<td>5mg twice daily</td>
<td>5,600</td>
<td>Randomised, double-blind, noninferiority; Phase III</td>
<td>Noninferiority; Vascular events; major bleeding</td>
<td>Stopped at interim analysis due to treatment efficacy; reduction of ischaemic stroke statistically significant without increasing major bleeding</td>
</tr>
<tr>
<td>ENGAGE AF TIMI-48</td>
<td>Not yet published</td>
<td>Edoxaban vs. warfarin</td>
<td>30mg daily, 60mg daily</td>
<td>20,500</td>
<td>Randomised, double-blind, noninferiority; Phase III</td>
<td>Noninferiority; embolic events; evaluation of bleeding complications; all-cause mortality</td>
<td>Underway</td>
</tr>
<tr>
<td>EXPLORE-Xa</td>
<td>Not yet published</td>
<td>Betrixaban vs. warfarin</td>
<td>40mg daily, 60mg daily, 80mg daily</td>
<td>508</td>
<td>Randomised, double-blind; Phase II</td>
<td>Noninferiority; occurrence of major or clinically relevant non-major bleeding events</td>
<td>Fewer major and clinically relevant non-major bleeding with 40mg dose; 60mg and 80mg doses had similar bleeding rates to warfarin</td>
</tr>
<tr>
<td>Trial</td>
<td>Year published</td>
<td>Study drug/intervention</td>
<td>Dosing</td>
<td>No. of participants</td>
<td>Study design</td>
<td>Study endpoints</td>
<td>Key research findings</td>
</tr>
<tr>
<td>-------</td>
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<td>-----------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>OPAL-2</td>
<td>Not yet published</td>
<td>Darexaban (YM-150) vs. warfarin</td>
<td>6 doses</td>
<td>1,280</td>
<td>Randomised, double-blind; Phase II</td>
<td>Noninferiority; major or clinically relevant non-major bleeding events</td>
<td>Not detailed</td>
</tr>
</tbody>
</table>
1.5 Standard risk delineation strategies for AF management

1.5.1 Thrombo-embolic risk

All individuals with AF should be prescribed anti-thrombotic therapy. Most require anticoagulants such as warfarin or the newly marketed dabigatran, rivaroxaban or apixaban, but many are prescribed aspirin alone or in combination with additional antiplatelet agents such as clopidogrel. To determine the extent of anti-thrombotic therapy required, all AF patients should be assessed using the stroke risk stratification tools that exist. Currently, the most comprehensive of these tools is the CHA2DS2-VASc [chronic heart failure (CHF), hypertension, age ≥75 years (doubled), diabetes, stroke (doubled), vascular disease, age 65-74, and sex category (female)] score, which takes a risk-factor approach, recommending the use of antithrombotic therapy on the basis of the presence or absence of stroke risk factors [Lip & Halperin, 2010]. Calculation of the CHA2DS2-VASc score takes into consideration “major” risk factors in addition to “clinically relevant non-major” risk factors. Table 6 outlines these factors that influence thrombo-embolic risk [Lip & Halperin, 2010].

Table 6: “Major” and “clinically relevant non-major” risk factors taken into account in the calculation of the more comprehensive risk assessment – the CHA2DS2-VASc score [Lip & Halperin, 2010].

<table>
<thead>
<tr>
<th>“Major” risk factors</th>
<th>“Clinically relevant non-major” risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Previous stroke, transient ischaemic attack (TIA) or</td>
<td>- Heart failure or moderate to severe LV systolic dysfunction (e.g. left ventricular ejection fraction [LVEF] ≤ 40%)</td>
</tr>
<tr>
<td>systemic embolism</td>
<td></td>
</tr>
<tr>
<td>- Age ≥ 75 years</td>
<td>- Hypertension</td>
</tr>
<tr>
<td></td>
<td>- Diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>- Female sex</td>
</tr>
<tr>
<td></td>
<td>- Age 65-74 years</td>
</tr>
<tr>
<td></td>
<td>- Vascular disease*</td>
</tr>
</tbody>
</table>

* Prior myocardial infarction (MI), peripheral artery disease (PAD), aortic plaque.
Support for this approach has come from various published analyses [Stroke in AF Working Group, 2007; Hughes & Lip, 2008]. This risk stratification scheme is a point-based scoring system which gives one point for each risk factor except age ≥ 75 years and stroke/TIA/thromboembolism which attracts two points each. When scored, patients are classified as either being at low (with a score = 0), intermediate (score = 1) or high (score ≥2) risk. It is appropriate that those at lower stroke risk be prescribed aspirin or aspirin plus clopidogrel, but those at higher stroke risk should be prescribed warfarin (or another newer anticoagulant). The components of this risk score are detailed in Table 7 [Lip & Halperin, 2010].

When anticoagulant therapy is being considered, an extensive evaluation of the pros and cons of such therapy should be conducted in consultation with the patient and incorporate an evaluation of the risk of bleeding complications, the ability to safely sustain adjusted chronic anticoagulation and patient preferences [Camm et al., 2010].

**Table 7**: Risk factor-based approach to assess thrombo-embolic therapy requirements expressed as a point-based scoring system – the CHA₂DS₂-VASc score [Lip & Halperin, 2010].

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Letter in acronym</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure/LV dysfunction</td>
<td>C</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension (even if being treated)</td>
<td>H</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td>A, A</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>D</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA/thromboembolism</td>
<td>S, S</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease (prior MI, PAD, aortic plaque)</td>
<td>V</td>
<td>1</td>
</tr>
<tr>
<td>Age 65-74 years</td>
<td>A</td>
<td>1</td>
</tr>
<tr>
<td>Sex category (i.e. female sex)</td>
<td>Sc</td>
<td>1</td>
</tr>
<tr>
<td><strong>Maximum score</strong></td>
<td></td>
<td>9*</td>
</tr>
</tbody>
</table>

*Note: Maximum score is 9 as age may contribute 0, 1 or 2 points.*
The annual adjusted stroke rate according to each possible total CHA2DS2-VASc score was also determined through empirical epidemiological research (Table 8) [Lip et al., 2010].

Table 8: Adjusted stroke rate according to CHA2DS2-VASc score [Lip et al., 2010].

<table>
<thead>
<tr>
<th>CHA2DS2-VASc score</th>
<th>Adjusted stroke rate (%/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>1</td>
<td>1.3%</td>
</tr>
<tr>
<td>2</td>
<td>2.2%</td>
</tr>
<tr>
<td>3</td>
<td>3.2%</td>
</tr>
<tr>
<td>4</td>
<td>4.0%</td>
</tr>
<tr>
<td>5</td>
<td>6.7%</td>
</tr>
<tr>
<td>6</td>
<td>9.8%</td>
</tr>
<tr>
<td>7</td>
<td>9.6%</td>
</tr>
<tr>
<td>8</td>
<td>6.7%</td>
</tr>
<tr>
<td>9</td>
<td>15.2%</td>
</tr>
</tbody>
</table>

According to the adjusted stroke rates for each possible total CHA2DS2–VASc score, the recommendations for provision of AF thromboprophylaxis are as follows [Lip & Halperin, 2010]:

- **CHA2DS2–VASc score ≥ 2**: Oral anticoagulation.
- **CHA2DS2–VASc score = 1**: Either oral anticoagulation or aspirin 75-325 mg daily (oral anticoagulation is preferred at this score).
- **CHA2DS2–VASc score = 0**: Either aspirin 75-325 mg daily or no antithrombotic therapy (no antithrombotic therapy is preferred at this score).

### 1.5.2 Haemorrhagic risk

A practical risk score to estimate the 1-year risk of major bleeding (intracranial, hospitalisation, haemoglobin decrease >2g/L, and/or transfusion) in AF was established by Pisters et al. in 2010 (although this is not used in the clinical setting as readily as the
CHA₂DS₂-VASc score) [Pisters et al., 2010]. Calculation of the HAS-BLED score can be undertaken for all patients currently prescribed anti-thrombotic medication or being considered for this type of therapy and indicates a patient’s suitability [Pisters et al., 2010]. HAS-BLED takes into consideration 7 clinical characteristics (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly [>65 years], concomitant drugs/alcohol) and awards points in a similar manner to the CHA₂DS₂-VASc score (Table 9) [Pisters et al., 2010].

**Table 9:** Risk factor-based approach to assess major bleeding risk (associated with anti-thrombotic therapy use) expressed as a point-based scoring system – the HAS-BLED score [Pisters et al., 2010].

<table>
<thead>
<tr>
<th><strong>Clinical characteristic</strong></th>
<th><strong>Letter in acronym</strong></th>
<th><strong>Points</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>H</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal renal and liver function (1 point each)</td>
<td>A</td>
<td>1 or 2</td>
</tr>
<tr>
<td>Stroke (history of)</td>
<td>S</td>
<td>1</td>
</tr>
<tr>
<td>Bleeding (history of or predisposition to)</td>
<td>B</td>
<td>1</td>
</tr>
<tr>
<td>Labile INRs</td>
<td>L</td>
<td>1</td>
</tr>
<tr>
<td>Elderly (e.g. age &gt;65 years)</td>
<td>E</td>
<td>1</td>
</tr>
<tr>
<td>Drugs or alcohol (concomitant use of drugs such as anti-platelet agents, non-steroidal anti-inflammatory drugs, or alcohol abuse etc – 1 point each)</td>
<td>D</td>
<td>1 or 2</td>
</tr>
<tr>
<td><strong>Maximum score</strong></td>
<td></td>
<td>9</td>
</tr>
</tbody>
</table>

A score of ≥ 3 indicates that a patient is at “high risk” of a haemorrhagic event and that some caution and regular review of the patient is needed following the initiation/continuation of anti-thrombotic therapy, whether this is warfarin, aspirin alone, aspirin with clopidogrel or the newer anti-thrombotic agents [Pisters et al., 2010].
1.5.3 Use of echocardiography

Echocardiography is useful as a diagnostic tool for determining the potential origin of AF (e.g. valvular dysfunction, rheumatic heart disease or hypertrophic cardiomyopathy). It may also be used to stratify thrombo-embolic risk. Impaired left ventricular systolic function on trans-thoracic echocardiography (TTE), thrombus identification, dense spontaneous echo contrast or reduced velocity of blood flow in the LAA, and complex atherosclerotic plaque in the thoracic aorta on trans-oesophageal echocardiography (TOE) are all indicative of the presence of a thromboembolism or a high risk of developing a thrombus, providing evidence for the use of oral anticoagulation to reduce the risk of stroke [Camm et al., 2010]. TOE is also used to guide electro-cardioversion by assessing the presence or absence of a thrombus in the left atrium or LAA, which contraindicates this method of AF treatment. However, the absence of a detectable thrombus does not prevent stroke occurrence following cardioversion in the absence of anticoagulation therapy [Black et al., 1994; Camm et al., 2010].

1.6 Disease management in AF

1.6.1 Disease management programs (DMPs)

As the name suggests, disease management programs (DMPs) aim to streamline the management of a chronic disease, improve the quality of care, improve patient outcomes (including prolonging survival and improving QoL), promote patient self-care and reduce associated healthcare costs [Krumholz et al., 2006]. Today, physicians and specialists are excessively time-poor to systematically improve the quality of care of patients [Casalino 2005]. The emergence of multidisciplinary DMPs attempts to address the “quality chasm” in outpatient care [Casalino, 2005]. Furthermore, specialist nurse-led interventions could partially address the shortage of specialist physicians, especially as the population ages [Phillips et al., 2005]. Nurses possess skills in discharge planning and post-discharge care of patients that specialist physicians often do not have. Previous clinical research studies into the efficacy of DMPs have reported significant and consistent reductions in hospital utilisation, particularly in readmission rates [Philbin, 1999; McAlister et al., 2001; Gonseth et al., 2004; McAlister et al., 2004;
Furthermore, improvements in QoL, prolonged survival rates and reduced costs due to chronic diseases have also been demonstrated [Stewart, Pearson & Horowitz, 1998; Stewart et al., 1998; Stewart, Marley & Horowitz, 1999; Stewart et al., 1999; Stewart & Horowitz, 2002a; Stewart & Horowitz, 2002b; Thompson, Roebuck & Stewart, 2005; Inglis et al., 2006; Pearson et al., 2006; Stewart et al., 2012]. These improvements have been shown to be enhanced with increasing complexity of DMP protocols. For example, heart failure DMPs containing an additional component for hospital discharge planning, immediate post-discharge follow-up and no delay in continuity of the intervention after hospital discharge (i.e. complex programs) have been shown to be the most successful [Stewart, Pearson & Horowitz, 1998; Stewart et al., 1998; Stewart, Marley & Horowitz, 1999; Stewart et al., 1999; Stewart & Horowitz, 2002a; Stewart & Horowitz, 2002b; Phillips et al., 2005; Thompson, Roebuck & Stewart, 2005; Inglis et al., 2006; Pearson et al., 2006; Stewart et al., 2012]. Results have shown a trend towards a 70% relative reduction in risk for first readmission, two fewer hospital days utilised per patient per readmission (p= 0.02) and a 70% reduction in risk of heart failure readmission relative to usual care (p= 0.01) [Phillips et al., 2005]. A meta-analysis demonstrated that the most successful specialist nurse-led DMPs have the following components in common [Phillips et al., 2005]:

- Discharge planning
- Pre-discharge disease-specific education (for patients, families and/or caregivers including utilising multimedia, group sessions and printed material)
- Post-discharge disease-specific education (for patients, families and/or caregivers including utilising multimedia, group sessions and printed material)
- Medication counselling, review and optimisation
- Self-care behaviour (including dietary restrictions and self-monitoring of symptoms)
- Increased communication between providers
- Home visit (within 2 weeks of discharge to reinforce disease-specific education)
• Telephone follow-up (scheduled nurse-directed as well as patient initiated)
• Specialist nurse
• Nurse-led disease-specific clinics (nurse has ready/easy contact with supervising specialist physician)

1.6.2 AF-specific disease management

Current treatment of AF is not simply the administration and action of pharmaceuticals; it is a fine balance between management of multiple factors that add multi-factorial difficulty to treatment plans. Subsequently, individuals with AF may fail to gain the maximum benefit from current generic treatment plans. With the significant rise in the number of cases of AF seen globally and the estimated 5.6 million patients who will be affected by AF in the US by the year 2050 [Go et al., 2001], interventional and individualised treatment plans must be developed, attempted and implemented.

It has been previously demonstrated that an individualised yet generic DMP, including a component of post-discharge home visits, improved health outcomes compared to that of usual care in hospitalised patients with chronic forms of AF [Inglis et al., 2004]. During a median 5-year follow-up, this program was associated with a 27% and 20% reduction in unplanned hospital re-admissions and related bed days, respectively (p<0.05 for both). More recently, the results of an AF-specific disease management program of software-determined, guideline-based care delivered in a nurse-driven clinic setting (AF-Clinic) were published [Hendriks et al., 2012]. Following a mean of 22-months follow-up, 14% of intervention patients compared with 21% of usual care patients reached the composite end-point of heart failure, thrombo-embolic events, bleeding events, treatment-induced adverse events and cardiovascular death. Death and hospitalisations were significantly lower among patients treated in the AF Clinic suggesting that this form of AF-specific intervention improves patient outcomes compared to usual care [Hendriks et al., 2012].
There is a paucity of data describing the effects of a DMP designed specifically to optimise treatment and subsequent outcomes in AF. However, this is a presently relevant area of preventative health efforts with the potential for small changes to result in larger gains.

### 1.6.3 The need for extended risk delineation to optimise AF-specific disease management

Stratification of risk and, therefore, stratified care allows a potentially more personalised treatment plan. The impact of AF on patients can differ substantially based on the context in which it is found (e.g. associated risk factors and co-morbid conditions). Standard risk delineation methods described above may not go far enough to establish the most effective methods of management for complex, high-risk AF patients. More extensive and innovative risk delineation can direct management that is more specific for the patient involved and therefore potentially more successful for patient outcomes. The challenge remains to identify novel risk factors via a systematic approach in order to properly and effectively delineate differences and direct individualised management.

### 1.7 Summary and gaps to be addressed

AF is an emerging epidemic that shows no signs of abating. The overall picture of the epidemiological burden and impact of AF in the developed world is difficult to interpret given the expanding volume of relevant reports. There is a need for systematic review and comprehensive synthesis of these reports to comprehend the true extent of the influence of this complex condition. Therefore, the clinical picture of AF can be more completely understood, allowing more directed management programs to be developed with the potential for implementation. The focus should be on more comprehensively risk profiling AF patients to prevent generalised management that is currently utilised and is not optimal for all. Standard risk delineation tools only provide limited profiling. Therefore, novel methods of risk delineation in AF patients should be determined that have the potential for improving management and future outcomes.
Chapter 2

Research Aims and Hypotheses
Chapter 2 articulates the key aims, hypotheses and research streams for this thesis. The rationale and thesis structure are summarised and the research publications resulting from this research program are outlined.
As described in Chapter 1, AF poses an increasing and challenging burden to our ageing populations from an individual to societal perspective [Go et al., 2001]. In order to best respond to these challenges, it is imperative that the evolving burden of AF is closely monitored and characterised. This will ensure that appropriate health resources are directed towards AF – particularly if, as suspected, it has already become a major contributor to CVD-related morbidity and mortality in Australia and beyond. To date, there have been few attempts to systematically review the natural history and burden of AF and this gap in the literature will be addressed in part in this thesis.

At the individual patient level, there is clear scope to apply the kind of strategies used to improve health outcomes in CHF in the setting of AF. As outlined in Chapter 1, this is particularly true for those unfortunate enough to be hospitalised with a chronic form of AF. As with the successful development of dedicated CHF management programs to cost-effectively reduce highly preventable (and costly) hospital admissions and prolong survival, there is scope to develop better risk delineation strategies and dedicated management programs focussing on the optimal management of AF. Again, there is a paucity of research focussing on AF management programs and this thesis describes a program of research exploring key aspects around individualised AF management.

The primary aim of the series of studies described in this thesis was to contribute new knowledge on enhanced and effective methods for the assessment of risk in order to direct more individualised AF-specific patient management. It was hypothesised that refined methods of enhanced risk delineation would be identified. Individualised management strategies may have the potential for improving patient outcomes, although the definitive assessment of this (i.e. their cost-effectiveness) is beyond the scope of this research program.

This research program, beginning in Chapter 3, entails an analysis and review of the broad range of research literature in order to clearly define and clarify the extent of the global burden of AF and to summarise the clinical need for more effective risk-
Chapter 2: Research Aims and Hypotheses

delineation and management strategies. **Chapter 3**, therefore, presents collated and synthesised data from the largest and most robust scientific reports on AF via a systematic review and meta-analysis of contemporary literature. Specifically, the following areas were investigated and are described:

- Antecedents (modifiable and non-modifiable risk factors) of AF
- Incidence and prevalence of AF
- Life-time risk of AF
- Primary/community care consultations related to AF
- AF-related hospitalisation
- Health outcomes (prognosis; AF and other CVD; stroke and AF; CHF and AF; acute coronary syndrome [ACS] and AF; AF and other co-morbidities)
- Economic burden of AF
- Future burden of AF

It was hypothesised that a more accurate, valid and comprehensive description of the evolving burden of AF would be established and would confirm a profound clinical, individual, social and economic dilemma. Furthermore, an improved understanding of the key epidemiological drivers and natural history of AF would be established. These data have been published as the following peer-reviewed manuscript:


As an important framework for this research, **Chapter 4** describes the clinical conundrums surrounding the optimal management of chronic forms of AF via the purpose, study rationale, overall hypothesis and design of the Standard versus Atrial Fibrillation spEcific managemenT studY (SAFETY). SAFETY is a prospective, multi-centre, randomised controlled trial of an AF-specific, nurse-led disease management intervention compared to usual post-hospital discharge health care. The primary
chapter 2: research aims and hypotheses

endpoint of SAFETY is event-free survival from all-cause mortality or unplanned hospital readmission during 18-36 months follow-up. This methodology paper has been published as the following peer-reviewed manuscript:


Furthermore, the importance of AF-specific disease management and the value of the SAFETY trial were re-iterated in the following Letter-to-the-Editor:


Following on from the findings of the systematic review described in Chapter 3, three broad categories of patient-specific factors were assessed for suitability for enhanced risk delineation – inherent to the individual (Chapter 5), acquired risk (Chapter 6) and critical management issues incorporating benefit-to-risk of pharmacological treatments and follow-up strategies (Chapter 7).

The results of detailed clinical phenotyping on the representative cohort of hospitalised patients with chronic forms of AF recruited and randomised into the SAFETY trial are reported in Chapter 5. Consistent with the study hypothesis, these data are presented on a gender-specific basis with exploration of potentially important clinical differences; particularly in respect to thrombo-embolic risk and therapeutic management of these patients. Furthermore, comparisons of the age and gender profile of the SAFETY trial cohort relative to large and influential clinical trials of new pharmacological agents are also described. It was hypothesised that gender-based differences would exist in the clinical presentation, thrombo-embolic risk and therapeutic management within a cohort of high risk patients hospitalised with a diagnosis of chronic AF that comprise
the SAFETY trial cohort. It was further hypothesised that, subject to detailed clinical phenotyping, these differences would have important clinical implications in respect to disease management requirements. These data have been published as the following peer-reviewed manuscript:


**Chapter 6** describes the extent of mild cognitive impairment (MCI) in this cohort of typically older and non-demented patients. This involved analysis of basic clinical and demographic data in addition to the results of the Montreal Cognitive Assessment (MoCA) – a MCI screening tool administered to all suitable patients during index hospitalisation and at the point of recruitment into the SAFETY trial. It was hypothesised that MCI would be a common co-morbidity in the SAFETY trial cohort. It was further hypothesised that certain patient-specific characteristics would be determined that define patients with AF who are more likely to display concurrent MCI. Again, it was hypothesised that this would have important clinical implications, particularly with respect to self-management and overall disease management requirements. These data have been published as the following peer-reviewed manuscript and Letter-to-the-Editor:


Chapter 2: Research Aims and Hypotheses

Chapter 7 describes detailed 24 hour, 3-channel ECG Holter monitoring data collected at 7 – 14 days post-index hospital discharge among individuals randomised to the study intervention arm of the SAFETY trial (n = 133). It also describes the development and results of a novel method used to phenotype heart rate and rhythm in this cohort. Finally, it explores the potential for this classification system to better predict and detect future clinical stability and key clinical outcomes (including thrombo-embolism and cardiac dysfunction) during longer-term follow-up. It was hypothesised that previously undetected clinical instability (as determined on analysis of 3-channel ECG Holter monitoring of SAFETY trial participant’s heart rate and rhythm 7 – 14 days post-hospital discharge) would be highly prevalent in this cohort; with serious implications for clinical management target and goal-setting. It was further hypothesised that these data would provide the platform for a novel classification system to inform stratification of patients into different risk groups for whom varying strengths of intervention may be required to achieve or re-establish clinical stability. These data have been submitted for publication in a peer-review journal as the following manuscript:

**Ball J, Carrington MJ, Thompson DR, Horowitz JD, Stewart S.** ECG Holter monitoring for enhancing risk delineation: rate and rhythm control phenotypes in recently hospitalised individuals with chronic atrial fibrillation. Submitted 14th November, 2013 to *Europace* (IF: 2.765).

Chapter 8 summarises the overall findings of this body of research and discusses the implications of this work. The limitations of this research are discussed and general conclusions are presented. Future directions of this research are also suggested.

Figure 10 summarises the structure of this thesis and the resulting publications. It can be seen that there will be a total of seven publications comprising five chapters (Chapters 3 – 7) of this thesis.
Figure 10: Thesis outline.
Chapter 3

Global Burden of AF
Chapter 3 summarises the results of a systematic analysis and synthesis of the vast body of literature describing key aspects of the epidemiology and global burden of AF. The burden of AF is described from an individual to whole society perspective. Specifically, existing data were pooled and formal meta-analyses conducted to investigate a number of parameters; including a pooled estimate of the current population prevalence of AF and the risk of developing AF in the presence of common antecedents. Data are also presented for men and women separately. Finally, the relationship between AF and other common co-morbidities is also presented.

This chapter includes the following peer-reviewed and published report:

Declaration for Thesis Chapter 3

Declaration by candidate

In the case of Chapter 3, the nature and extent of my contribution to the work was the following:

<table>
<thead>
<tr>
<th>Nature of contribution</th>
<th>Extent of contribution (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conception and design, acquisition of data, analysis and interpretation of data; drafting of the article and revision; final approval of the version to be published.</td>
<td>65%</td>
</tr>
</tbody>
</table>

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

<table>
<thead>
<tr>
<th>Name</th>
<th>Nature of contribution</th>
<th>Extent of contribution (%) for student co-authors only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Melinda J. Carrington</td>
<td>Interpretation of data; drafting of the article and revision; final approval of the version to be published.</td>
<td>N/A</td>
</tr>
<tr>
<td>Professor John J.V. McMurray</td>
<td>Interpretation of data; drafting of the article and revision; final approval of the version to be published.</td>
<td>N/A</td>
</tr>
<tr>
<td>Professor Simon Stewart</td>
<td>Conception and design, interpretation of data; drafting the article and revision; final approval of the version to be published.</td>
<td>N/A</td>
</tr>
</tbody>
</table>
The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate’s and co-authors’ contributions to this work.*

<table>
<thead>
<tr>
<th>Candidate’s Signature</th>
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<td>29th November, 2013</td>
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<th>Main Supervisor’s Signature</th>
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Preface

As described in Chapter 1, AF is a common cardiac arrhythmia that is predicted to become the next global cardiac epidemic observed in clinical practice. Exactly how large the epidemic is and how broadly it extends is difficult to discern, given the enormous but heterogeneous number of existing research reports describing the epidemiology of AF from different perspectives. Therefore, to obtain an accurate picture of the scale of the individual, clinical and economic problem of AF, a comprehensive synthesis and review of the largest and most robust research reports was undertaken. The review and subsequent meta-analyses conducted frame the need for the current research program of assessing enhanced risk delineation strategies as a means to optimise the management of patients with AF. Data on the following themes were included in the published research report:

- Antecedents (modifiable and non-modifiable risk factors) of AF
- Incidence and prevalence of AF
- Life-time risk of AF
- Primary/community care consultations related to AF
- AF-related hospitalisation
- Health outcomes (prognosis; AF and other CVD; stroke and AF; CHF and AF; ACS and AF; AF and other co-morbidities)
- Economic burden of AF
- Future burden of AF
Atrial fibrillation: Profile and burden of an evolving epidemic in the 21st century

Jocasta Ball a, b, Melinda J. Carrington a, b, John J.V. McMurray c, Simon Stewart a, b, *

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b Department of Epidemiology and Preventative Medicine, Monash University, Melbourne, Australia
c Institute of Cardiovascular and Medical Sciences, University of Glasgow, Scotland, UK

1. Introduction

Atrial fibrillation (AF), the most common sustained cardiac arrhythmia and one of the most common cardiovascular conditions overall, is a “spectrum disorder” that spans isolated and benign episodes of electrical disturbance to a chronic condition that results in cardiac remodelling and functional impairment. AF is undoubtedly a progressive disorder with paroxysmal episodes becoming more frequent and persistent and persistent episodes often becoming permanent. Classification of AF sub-types reflects this natural history comprising “first diagnosed” AF, self-terminating paroxysmal episodes (transient to persistent) and the long-standing and permanent form of AF that defies attempts to achieve sinus rhythm [1]. However, much of the literature describing its epidemiology does not differentiate between paroxysmal versus persistent forms of AF: the minimum common standard for its detection being an episode of AF captured on ECG.

Advances have been made over recent decades to – a) improve our understanding of the evolving burden of AF, b) increase surveillance for its presence, c) accurately diagnose and characterise the sub-type of AF presentation (i.e., “first diagnosed”, paroxysmal, persistent or permanent) and d) improve its therapeutic management through the combination of pharmacological [2,3], interventional [4,5] and surgical [6] strategies. However, AF continues to have a significant impact on quality of life [7], morbidity and mortality [8]. In high income countries, the number of affected individuals is projected to increase exponentially over the next four decades [9]. Parallel increases in low-to-middle income countries due to epidemiological transition and an overall rise in non-communicable forms of heart disease are also likely [10]. Overall, therefore, AF exerts a major but evolving public health, social and economic burden worldwide. Notwithstanding the caveats and limitations to providing a succinct review of a large and heterogeneous literature base, the overall aim of this report is to provide an accurate, valid and comprehensive description of the evolving burden of AF by collating and synthesising data from the largest and most robust scientific reports.

2. Methods

2.1. Search strategy

Initially, all relevant publications and research reports on the epidemiology and global burden of AF were identified using specific search terms (refer to Appendix 1) via PubMed (incorporating literature that would be identified from many other bibliographic databases such as MEDLINE [11]). Searches were limited to English-language material published up to
May, 2012. No restriction on earliest publication date was imposed. Therefore, manuscripts from as early as 1985 were included.

2.1.1. Inclusion/exclusion criteria
Following an independent review, a consensus approach was applied (by JB and SS) to categorise all publications for the purpose of inclusion, classification and described outcomes. The titles and abstracts of potentially relevant publications were scrutinised for eligibility and were included if they focussed on the epidemiology and global burden of chronic AF, methods of AF management (other than surgical methods) in humans, and were available in English-language. Studies were not considered for review if full-text manuscripts were not available, if the focus was on transient forms of AF, or if they related to certain procedures or co-morbid conditions. Reviews of the literature, animal or in vitro studies, single participant case studies, opinions, studies published in non-standard non-peer reviewed publications such as letters, opinions, or editorials were also excluded. A minimum sample size of 750 individuals per clinical study was enforced. The reference lists of included papers were further examined for relevant studies.

A total of 3114 relevant citations of different publication types were identified (see Fig. 1). Initial review of their titles and abstracts revealed that 653 (21.0%) were either partial or incomplete records, duplicates, or not specific to the population or outcomes relevant to this review. The remaining 2461 studies revealed that 2279 (92.6%) were ineligible for full-text appraisal because the study design, target population or outcome was not relevant to the topic, Narrative reviews, personal experiences, or other forms of research that would not enable data abstraction, appraisal and assessment were also excluded. Ultimately, 182 eligible and unique studies were used to generate this report.

2.1.2. Data extraction and analysis
For each article included in the final appraisal and summary process, the key findings were summarized. Where possible and when comparable data was available, meta-analyses (see below) were conducted to generate pooled estimates from the selected studies in a non-systematic fashion. A formal meta-analysis was not undertaken for some areas where only limited data were available (including lesser researched antecedents and AF incidence).

Pooled risk estimates and 95% confidence intervals (CIs) were calculated for age- and sex-adjusted odds ratios (ORs) or hazard ratios (HRs) via direct comparison meta-analyses. The log of the ratio and its standard error was calculated and these data were entered into Review Manager (RevMan) 5.1.7 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012). Risks were pooled using the generic inverse variance method and a random effects model was used as a conservative approach due to expected heterogeneity across studies. The I² statistic was used to estimate the proportion of variance in the pooled estimate due to heterogeneity. Pooled prevalence estimates and 95% CIs (overall and stratified by gender) were determined by random effects meta-analysis using the inverse variance method in StatsDirect 2.7.9 (StatsDirect Ltd., Altrincham, UK, 2012) with between study heterogeneity assessed and quantified using the I² statistic. Only adjusted prevalence estimates (e.g. age) were used in these meta-analyses.

2.1.3. AF definition and diagnosis
A diagnosis of AF in all studies was defined as at least one documented episode, a documented history (including in-patient AF ICD-9/10 code as the principal or co-morbid discharge diagnosis) or discovery on admission/clinic ECG. ECG data were verified by one or more cardiologists.

3. Results
3.1. Epidemiology of atrial fibrillation
3.1.1. Antecedents
There are numerous reports of modifiable and non-modifiable risk factors that contribute to the development of AF. Table 1 provides a summary of the most commonly reported contributors to AF. These include socio-demographic factors, adverse lifestyle choices, cardiovascular conditions and other co-morbid conditions [12–33]. The population prevalence of each of the common antecedents for AF is increasing as advances in medical therapies and technologies that are extending life-expectancy in high income countries. Fig. 2A to G shows pooled risk estimates for the following antecedents of AF — male gender, hypertension, acute coronary syndrome (ACS), diabetes, hyperthyroidism, obesity and smoking. Due to heterogeneity, pooled analyses for chronic heart failure [CHF], cerebrovascular disease and valvular disease are not presented. Overall, being male increased the risk of AF by 64% (OR 1.64, 95% CI 1.45 to 1.86). A diagnosis of hypertension, ACS, diabetes or hyperthyroidism increased the likelihood of AF by 73% (OR 1.73, 95% CI 1.31 to 2.28), 77% (HR 1.77, 95% CI 1.44 to 2.19), 44% (OR 1.44, 95% CI 1.07 to 1.94) and 68% (HR 1.68, 95% CI 1.29 to 2.18), respectively. Furthermore, being obese (BMI ≥ 30 kg/m²) increased the
### Table 1
Commonly reported antecedents leading to increased risk of developing AF

<table>
<thead>
<tr>
<th>Antecedent</th>
<th>Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic profile</strong></td>
<td></td>
</tr>
<tr>
<td>Advancing age: likelihood of AF increases with advancing age</td>
<td>Benjamin et al. (1994), Stewart et al. (2001), Tsang et al. (2003), Tsang et al. (2005) and Schnabel et al. (2009)</td>
</tr>
<tr>
<td>- Independent predictor of incident AF (OR 1.3, 95% CI 1.2 to 1.4/decade; Stewart et al., 2001)</td>
<td>Benjamin et al. (1994), Feinberg et al. (1995) and Stewart et al. (2001)</td>
</tr>
<tr>
<td>- With each advancing decade of age, likelihood of developing AF increases by 2.1-fold (95% CI 1.8 to 2.5) in men and 2.2-fold (95% CI 1.9 to 2.6) in women (Benjamin et al., 1994)</td>
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<tr>
<td>Male gender: likelihood of AF increases if male</td>
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<tr>
<td>- Men at 1.5 times greater risk (95% CI 1.3 to 1.8) of AF (although absolute number of women exceeds men due to greater longevity; Benjamin et al., 1994)</td>
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</tr>
<tr>
<td>- Independent predictor of incident AF (OR 3.4, 95% CI 1.1 to 10.2; Stewart et al., 2001)</td>
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<tr>
<td>- Gender has been shown to influence the presence or absence of certain risk factors for AF</td>
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<tr>
<td><strong>Caucasian: likelihood of AF increases if Caucasian</strong></td>
<td>Pasy et al. (1997), Alonso et al. (2009), Benjamin et al. (2009) and Marcus et al. (2010)</td>
</tr>
<tr>
<td>- In Western nations, race has an influence on the risk of developing AF</td>
<td></td>
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<tr>
<td>- In the Atherosclerosis Risk in Communities (ABC) Study, the risk of AF was shown to be higher in Caucasians than in individuals of African descent, despite risk factors for AF being more prevalent in the latter group (Alonso et al., 2009)</td>
<td></td>
</tr>
<tr>
<td><strong>Lower socio-economic background: likelihood of AF increases if of lower socio-economic status</strong></td>
<td>Stewart et al. (2001) and Mattioli et al. (2005)</td>
</tr>
<tr>
<td>- Men with AF more likely to be from lower socio-economic background</td>
<td></td>
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<tr>
<td><strong>Adverse lifestyle factors</strong></td>
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<tr>
<td>Smoking: likelihood of AF increases if a current or former smoker</td>
<td>Kannel et al. (1998), Heeringa et al. (2008) and Chamberlain et al. (2011)</td>
</tr>
<tr>
<td>- Responsible for a 40% increased risk in women (95% CI not reported; Kannel et al., 1998)</td>
<td>Djuousse et al. (2004), Frost and Vestergaard (2004), Mukamal et al. (2005), Mukamal et al. (2007) and Conen et al. (2008)</td>
</tr>
<tr>
<td>- Hazard ratios [HRs] for AF were 1.12 (95% CI 1.0 to 1.57) in former smokers, 2.05 (95% CI 1.71 to 2.47) in current smokers and 1.58 (95% CI 1.35 to 1.85) in ever smokers (Chamberlain et al., 2011)</td>
<td>Wang et al. (2004), Frost, Hune and Vestergaard (2005), Miyasaka et al. (2006), Dublin et al. (2006), Tsang et al. (2008), Rosengren et al. (2009), Tedsø et al. (2010) and Long et al. (2011)</td>
</tr>
<tr>
<td>Alcohol: likelihood of AF increases with increasing alcohol intake</td>
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<tr>
<td>- Greater than 3 alcoholic drinks per day for men and women significantly influences development of AF (34%, 95% CI 1% to 78%; Djuousse et al., 2004)</td>
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<tr>
<td>- Adjusted HRs for AF associated with obesity (BMI≥30 kg/m²) were 1.52 (95% CI 1.09 to 2.13) and 1.46 (95% CI 1.03 to 2.07) for men and women, respectively (Wang et al., 2004)</td>
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<tr>
<td>- Could account for approximately 60% (95% CI 32% to 100%) of estimated increase in age- and sex-adjusted AF incidence (Miyasaka et al., 2006)</td>
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<tr>
<td><strong>Cardiovascular conditions</strong></td>
<td></td>
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<tr>
<td>Hypertension: likelihood of AF increases if co-morbidly hypertensive (even if treated)</td>
<td>Kannel et al. (1982), Benjamin et al. (1994), Wolf et al. (1996), Kannel et al. (1998), Van Gelder et al. (2006) and Schnabel et al. (2009)</td>
</tr>
<tr>
<td>- Imposes a 70% (OR 1.7, 95% CI 1.3 to 2.2) greater risk of AF in women and 80% (OR 1.8, 95% CI 1.4 to 2.3) greater risk in men (Benjamin et al., 1994)</td>
<td>Furberg et al. (1994), Pasy et al. (1997) and Tsang et al. (2001)</td>
</tr>
<tr>
<td>Left atrial enlargement: likelihood of AF increases if left atrium enlarged</td>
<td>Benjamin et al. (1994) and Kannel et al. (1998)</td>
</tr>
<tr>
<td>- Associated with an increase in the risk of AF</td>
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<tr>
<td>- Associated with a 4-fold increased risk (OR 3.8, 95% CI 2.6 to 5.6) in women and 3-fold increased risk (OR 3.0, 95% CI 1.9 to 4.8) in men (Benjamin et al., 1994)</td>
<td>Wolf et al. (1996), Kannel et al. (1998), Schnabel et al. (2009) and Nichols, Reinier and Chugh, (2009)</td>
</tr>
<tr>
<td>- Men with AF more likely to have LHV detected on ECG</td>
<td>Krah et al. (1995), Wolf et al. (1996), Kannel et al. (1998), Stewart et al. (2001) and Poc et al. (2012)</td>
</tr>
<tr>
<td>- Women with AF have more severe stroke than those without (Kimura, Minematsu &amp; Yamaguchi, 2005)</td>
<td>Hurwitz et al. (1990) and Muller et al. (1993)</td>
</tr>
<tr>
<td>Type 2 diabetes: likelihood of AF increases with co-morbid type 2 diabetes</td>
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<tr>
<td>- Diabetic women have 2-fold greater chance (OR 2.1, 95% CI 1.5 to 2.8) of developing AF; men have a 70% increased risk (OR 1.7, 95% CI 1.2 to 2.3; Kannel et al., 1998)</td>
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<tr>
<td>- Risk of AF increased with acute myocardial infarction (AMI), Relative Risk [RR] = 1.62, 95% CI 2.59 to 5.07, angina (RR = 2.84, 95% CI 1.91 to 4.21) and ST-T wave abnormalities on ECG (RR = 2.21, 95% CI 1.62 to 3.00; Krah et al., 1995)</td>
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<tr>
<td>- Men with AF more likely to show ECG evidence of past AMI</td>
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<tr>
<td>- AF occurrence associated with CAD significantly increases long-term mortality risk (HR 3.77, 95% CI 3.37 to 4.21; Jabe et al., 2011)</td>
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<tr>
<td><strong>Other cardiac diseases (including pericardial diseases; congenital diseases; cor pulmonale; conduction disorders): likelihood of AF increases if diagnosed with other cardiac disease</strong></td>
<td></td>
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<tr>
<td>- Anatomic substrate for AF after operation for congenital heart disease thought to result from intracavitary surgery, cardiopulmonary bypass, myocardial scarring, and different zones of myocardial discontinuity unrelated to &quot;normal&quot; anatomic obstacles</td>
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<tr>
<td>- AF occurs more frequently in patients with atrioventricular re-entrant tachycardia (AVRT) than the general population</td>
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<tr>
<td>- AF more frequent in patients with both paroxysmal supraventricular tachycardia (PSVT) due to AVRT and in PSVT due to atrioventricular nodal re-entrant tachycardia (AVNRT)</td>
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</table>
All studies clearly demonstrate that incident AF increases with advancing age, remaining scarce until around the seventh decade where it exponentially increases in successive decades [34]. Data from a number of studies are indicative of the increase in the incidence of AF with age and the association with male gender [35–37,39–44]. Incidence rates per 1000 person-years were similar in the Manitoba and Rotterdam Study cohorts (2.3 and 3.3 in those aged 60 and 64–66 years, respectively; and 16.9 and 18.2 in those aged 85 years and older, respectively) [35,39]. Reported incidence ranged from 0 per 1000 person-years in females aged 45–49 years in the Renfrew–Paisley cohort to 40 per 1000 person-years in males aged 85 years or more in Olmstead County [36,37]. Overall, incidence was higher in men than women across all studies in all age strata. Reports analysing the association between race and incidence of AF consistently show that in Caucasians, gender differences are slightly more pronounced [9,45–49].

### 3.1.3. Prevalence

Overall, there is evidence of increasing prevalence over time of AF both on an age-adjusted and absolute basis. The prevalence of AF is very low before the age of 40 years and increases exponentially beyond the age of 65 years [50]. Moreover, the Framingham Study investigators provided evidence for a steady increase in the point prevalence of AF between the 1960s and 1980s [34]. The point prevalence of AF in the general population at the end of the 20th century was reported to be around 1–2% [9]; ranging from 0.1% of adults aged 55 years or less, increasing to 10% or more in those aged 80 years or more [9,50]. Prevalence of AF is consistently higher in men than women across the majority of the study cohorts in most age strata. Within the different study cohorts, point prevalence ranged from 0.1% at the lowest in females aged younger than 55 years [9,44] to 27.8% in males aged 85 years or more (between 2006 and 2008) within the Reykjavik Study cohort [44]. The pooled prevalence estimate of AF in adults (Fig. 3A to C) was 2.8% (95% CI 2.3% to 3.4%) overall (on an age- and sex-adjusted basis), 3.3% (95% CI 2.7% to 4.0%) in males (age-adjusted).
and 2.4% (95% CI 1.9% to 2.9%) in females (age-adjusted). Due to the hidden burden of asymptomatic and transient sub-types of the arrhythmia (i.e. paroxysmal AF), the annual prevalence of AF is likely to be under-estimated [15,51,52].

3.1.4. Life-time risk

The Framingham Heart Study, after a 38-year follow-up, demonstrated that life-time risk of developing AF was about one in four in North American men and women aged 40 years or more [53]. Even in the absence of CHF or acute myocardial infarction (AMI), the life-time risk for developing AF was shown to be one in six (16%) [53]. Congruent with these findings, the Rotterdam Study (mean 7-year follow-up) found a similar life-time risk for developing AF of 23.8% for men and 22.2% for women from the age of 55 years onwards [39].

3.1.5. Primary/community care consultations

Large-scale studies (predominantly UK-based) have examined the contribution of AF to community/primary consultations within well-defined population areas. Fig. 4 shows age-specific case presentations where AF was listed as a diagnosis derived from a range of UK studies [54–57] during the period 1987 to 2001. It shows a consistent age-related gradient in AF case presentations from less than 0.5% of cases in those aged approximately 40 years (less than 0.1% cases in younger age groups) to 6–12% of cases in those aged 85 years or more. Data from the Netherlands showed similar trends [58]. Overall, the burden of AF in primary care rises from approximately 0.1% of case presentations in those aged less than 40 years up to approximately 9–10% in those aged 85 years or more, reflecting reported whole population prevalence estimates. Overall, the proportion of primary care cases attributable to AF appears to be increasing. Consistent with population prevalence data, this increase is predominantly attributable to affected individuals aged 65 years or more.

3.1.6. AF-related hospitalisation

Fig. 5 summarises temporal trends in the population rate of AF-related hospitalisations as the primary diagnosis in a range of countries. In all countries there was evidence of an increasing rate of hospitalisation over time (with the most striking increases in those aged 65 years
or more) [34] for hospitalisations where AF was listed as the primary or secondary (data not shown) diagnosis. Overall, the ratio of hospitalisations where AF was recorded as a primary versus secondary cause was approximately 1 to 2 [59]. As such, Fig. 5 also shows the rate of all AF-related hospitalisations in two European countries, the USA and Canada, showing a broadly consistent range of hospitalisation rates between 35 and 110 admissions/10,000 population during the period 1996–2006. Overall, women were hospitalised more often than men on an annual basis but age-standardised rates were greater in men than women [59,60]. Furthermore, women hospitalised with AF were generally older than men; the most common concurrent diagnoses being CHF, stroke and coronary artery disease (CAD) [59,60].

3.2. Health outcomes

3.2.1. Prognosis

Large population studies identify AF as an independent predictor of both cardiovascular and all-cause mortality [16,59–62]. Age-standardised death rates related to AF were reported to have increased from 27.6% in 1980 to 69.8% in 1998 [60]. On an adjusted basis, AF was associated with a 1.5-fold (95% CI 1.2 to 1.8) and 1.9-fold (95% CI 1.5 to 2.2) increased risk of death in men and women, respectively, during the 38-year follow-up in the Framingham cohort [61]. Additionally, the risk of mortality conferred by AF did not significantly vary by age [61]. In both younger and older age groups, the mortality of men and women with AF was substantially greater than for non-AF subjects (p < 0.0001) [61]. In those aged 55–74 years at the 10 year follow-up time point, 61.5% of men and 57.6% of women with AF had died versus 30.0% and 20.9% of men and women, respectively, who did not have AF [61]. In the Renfrew/Paisley population cohort (aged 45–64 years) in Scotland, AF was an independent predictor of all-cause mortality in women (RR = 2.2; 95% CI 1.5 to 3.2) and men (RR = 1.5; 95% CI 1.2 to 2.2) over a 20-year follow-up [16]. Additionally, AF was associated with cardiovascular mortality in women (RR = 2.8; 95% CI 1.9 to 4.2) and men (RR = 1.8; 95% CI 1.3 to 2.8) [16]. Overall, women with AF had an approximately 5-fold increase in the risk of a cardiovascular event (hospitalisation or death) compared with an approximately 2-fold increased risk in men [16]. Of women and men with AF at baseline, 89% versus 66% had a cardiovascular event, and 86% versus 72%, respectively, died during the 20-year follow-up (both p < 0.001) [16].

Stewart and colleagues (2002) examined trends in case-fatality rates in patients admitted for the first time with AF in Scotland between 1986 and 1995. Over the 10-year follow-up period, 30-day case-fatality declined from 4.0 to 3.1% in men (p < 0.001) and 4.1 to 3.8% (p < 0.01) in women [8]. Case fatality between 31 days and 2 years also fell from 24 to 22% in men and 27 to 25% (both p < 0.001) in women [8]. After adjustment, the risk of case-fatality at 30 days in 1995 significantly declined by 21% (p < 0.05) and 24% (p < 0.05) in men and women, respectively, in comparison to the 1986 cohort. Case fatality between 31 days and 2 years also declined significantly in men (30%, p < 0.05) and women (20%, p < 0.05) relative to 1986 [8].

3.3. AF and other cardiovascular disease

Chronic AF is associated with age-related conditions and the clinical sequelae of AF are multiple. In older individuals, lone AF is uncommon.
<table>
<thead>
<tr>
<th>Study (Author year)</th>
<th>Country/ study design</th>
<th>Study size (n)</th>
<th>Age group (years)</th>
<th>Incidence/1000 person-years</th>
<th>Point prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATRIA Study — 1996 to 1997 (Go et al., 2001) [9]</td>
<td>USA/ cross-sectional</td>
<td>17,974</td>
<td>&lt;55</td>
<td>–</td>
<td>0.1 (f); 0.2 (m)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>55–99</td>
<td>–</td>
<td>0.4 (f); 0.9 (m)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>60–64</td>
<td>–</td>
<td>1.0 (f); 1.7 (m)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>65–69</td>
<td>–</td>
<td>1.7 (f); 3.0 (m)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>70–74</td>
<td>–</td>
<td>3.4 (f); 5.0 (m)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>75–79</td>
<td>–</td>
<td>5.0 (f); 7.3 (m)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>80–84</td>
<td>–</td>
<td>7.2 (f); 10.3 (m)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥85</td>
<td>–</td>
<td>9.1 (f); 11.1 (m)</td>
</tr>
<tr>
<td>Cardiovascular Health Study (CHS) — 1989 to 1993 (Furberg et al., 1994) [127]</td>
<td>USA/ observational</td>
<td>5201</td>
<td>65–69</td>
<td>–</td>
<td>2.8 (f); 5.9 (m)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>70–79</td>
<td>–</td>
<td>5.9 (f); 5.8 (m)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥80</td>
<td>–</td>
<td>6.7 (f); 8.0 (m)</td>
</tr>
<tr>
<td>Framingham Study — 1968 to 1989 (Wolf et al., 1996) [34]</td>
<td>USA/ prospective observational</td>
<td>5070</td>
<td>65–74</td>
<td>–</td>
<td>3.5 (f); 3.9 (m)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>75–84</td>
<td>–</td>
<td>5.4 (f); 6.1 (m)</td>
</tr>
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<td></td>
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<td>85–89</td>
<td>–</td>
<td>7.4 (f); 7.5 (m)</td>
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<td></td>
<td>90–94</td>
<td>–</td>
<td>7.7 (f); 8.4 (m)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>95+</td>
<td>–</td>
<td>8.5 (f); 10.3 (m)</td>
</tr>
<tr>
<td>Manitoba Study — 1948 to 1992 (Krahn et al., 1995) [35]</td>
<td>Canada/ prospective observational</td>
<td>3983</td>
<td>50–59</td>
<td>–</td>
<td>1.2 (f); 1.7 (m)</td>
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<td>60–69</td>
<td>–</td>
<td>1.6 (f); 1.6 (m)</td>
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<td>70–79</td>
<td>–</td>
<td>5.5 (f); 8.2 (m)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>≥80</td>
<td>–</td>
<td>11.9 (f); 7.4 (m)</td>
</tr>
<tr>
<td>Medicare Beneficiary Study — 1993 to 2007 (Piccini et al., 2012) [42]</td>
<td>USA/ retrospective observational</td>
<td>433,123</td>
<td>65–69</td>
<td>–</td>
<td>1.94 (f); 1.93 (m)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(66–69 for prevalence data)</td>
<td>–</td>
<td>3.04 (f); 3.03 (m)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>70–74</td>
<td>–</td>
<td>3.61 (f); 2007</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>75–79</td>
<td>–</td>
<td>5.01 (f); 5.00 (m)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥85</td>
<td>–</td>
<td>5.81 (f); 2007</td>
</tr>
</tbody>
</table>

(continued on next page)
Even in its simplest form, AF can result in decreased exercise tolerance and, given increased risk of thrombo-embolic events, may adversely affect cognitive function [63]. Ott and colleagues (1997) found that dementia and sub-types of Alzheimer’s disease and vascular dementia may be related to AF even in the absence of clinical stroke [63]. The three conditions that most frequently co-exist with AF are stroke, CHF and ACS. The complexity of AF is demonstrated when considering the causal pathways between AF and these conditions as it is often indistinguishable which comes first; in particular AF can be both the cause and consequence of CHF and stroke.

3.3.1. Stroke and AF

Many population-based epidemiological and clinical studies demonstrate that AF is a major independent risk factor for stroke, imparting a 3- to 5-fold increased risk at all ages [64]. Within the Manitoba Follow-Up Study, AF independently increased the risk of stroke (RR = 2.07) [35]. Between 15% and 30% of all acute stroke patients are reportedly found to be in AF at the time of clinical presentation [65–67]. Furthermore, one in every five strokes occurs in a person with AF [1] and strokes associated with AF are typically more severe [68], resulting in greater disability, longer in-patient stay and a lower rate of discharge to home [62]. In the Copenhagen Stroke Study, AF was found to be associated with a 70% increase in mortality, a 40% decrease in the relative chance of discharge to a patient’s own home, a 20% increase in the length of hospital stay and a marked increase in impairment and disability in survivors [65]. In the Framingham cohort, ischaemic stroke associated with AF was nearly twice as likely to be fatal compared to non-AF related stroke [69]. Post-stroke mortality was also significantly increased in AF-related stroke patients and 30-day mortality was greater in AF strokes than in non-AF strokes (25% versus 14%; OR 1.84 95% CI 1.04 to 3.27) [69]. With increasing age, the effects of hypertension, CAD and CHF on stroke incidence decreased. Importantly, this same pattern of diminishing influence with advancing age was not observed with AF and, in fact, the percentage of strokes attributable to AF increased with age (Table 3; [12,64]). Within the Framingham cohort, 23.5% of strokes occurred as a direct result of AF in 80–89 year olds [64]. In the same age group, 31% of all strokes were associated with AF [64]. In a study of incident stroke following first hospitalisation for AF in Sweden between 1987 and 2006, a considerable decrease in the risk of ischaemic stroke in these cases over time was observed [70]. Alternatively, there was
an apparent trade-off towards more haemorrhagic stroke (still a small proportion of all strokes). Overall, this study observed a decline in the incidence of stroke in hospitalised AF patients by 32% over 20 years of follow-up (HR 0.68; 0.66–0.71; p < 0.0001) [70].

### 3.3.2 Chronic heart failure and AF
AF has been shown to independently contribute to the development of CHF over the longer-term (so-called tachycardia-induced cardiomyopathy [16,71,72]) and impair haemodynamic function acutely due to the rapid heart rate and increased myocardial oxygen demand. Yet CHF can also lead to AF due to progressive cardiac dysfunction and associated pathological changes (including myocardial fibrosis [73,74]). Atrial fibrosis (a form of structural remodelling) has been shown to be a common occurrence in AF and likely contributes to slow and/or heterogeneous electrical conduction evident in AF. Fibrosis alters atrial function and interacts with other pathophysiological components to promote AF occurrence and maintenance (“AF begets AF”) [74]. AF reportedly increases the risk of CHF by approximately 3-fold [16,35] and 42% of AF patients have CHF at some point during their lifetime [75]. Among 931 Framingham Study participants diagnosed with CHF, 24% had prior or concurrent AF; a further 17% were subsequently diagnosed with AF. Overall, the total proportion of CHF patients with AF at any

---

**A: Pooled AF prevalence overall**

<table>
<thead>
<tr>
<th>Study</th>
<th>Proportion (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furberg et al., 1994 (&gt;=65 years)</td>
<td>0.054 (0.048, 0.060)</td>
</tr>
<tr>
<td>Wolf et al., 1996 (1968-1970; 65-84 years)</td>
<td>0.029 (0.021, 0.039)</td>
</tr>
<tr>
<td>Wolf et al., 1996 (1971-1973; 65-84 years)</td>
<td>0.040 (0.032, 0.050)</td>
</tr>
<tr>
<td>Wolf et al., 1996 (1975-1977; 65-84 years)</td>
<td>0.052 (0.043, 0.062)</td>
</tr>
<tr>
<td>Wolf et al., 1996 (1979-1981; 65-84 years)</td>
<td>0.056 (0.047, 0.066)</td>
</tr>
<tr>
<td>Wolf et al., 1996 (1983-1985; 65-84 years)</td>
<td>0.053 (0.044, 0.063)</td>
</tr>
<tr>
<td>Wolf et al., 1996 (1987-1989; 65-84 years)</td>
<td>0.066 (0.056, 0.078)</td>
</tr>
<tr>
<td>Go et al., 2001 (all ages)</td>
<td>0.010 (0.009, 0.010)</td>
</tr>
<tr>
<td>Stewart et al., 2001 (45-64 years)</td>
<td>0.006 (0.005, 0.008)</td>
</tr>
<tr>
<td>Tsang et al., 2003 (1960-1969; all ages)</td>
<td>0.012 (0.008, 0.018)</td>
</tr>
<tr>
<td>Tsang et al., 2003 (1970-1979; all ages)</td>
<td>0.024 (0.018, 0.032)</td>
</tr>
<tr>
<td>Tsang et al., 2003 (1980-1989; all ages)</td>
<td>0.058 (0.048, 0.069)</td>
</tr>
<tr>
<td>Heeringa et al., 2006 (&gt;=55 years)</td>
<td>0.054 (0.049, 0.060)</td>
</tr>
<tr>
<td>Bonhorst et al., 2010 (&gt;=40 years)</td>
<td>0.025 (0.022, 0.028)</td>
</tr>
<tr>
<td>Chen et al., 2010 (&gt;=35 years)</td>
<td>0.010 (0.007, 0.014)</td>
</tr>
<tr>
<td>Smith et al., 2010 (45-74 years)</td>
<td>0.010 (0.009, 0.011)</td>
</tr>
<tr>
<td>Stefansdottir et al., 2011 (1998-1999; &gt;=20 years)</td>
<td>0.016 (0.015, 0.017)</td>
</tr>
<tr>
<td>Stefansdottir et al., 2011 (2000-2002; &gt;=20 years)</td>
<td>0.017 (0.016, 0.018)</td>
</tr>
<tr>
<td>Stefansdottir et al., 2011 (2003-2005; &gt;=20 years)</td>
<td>0.018 (0.017, 0.019)</td>
</tr>
<tr>
<td>Stefansdottir et al., 2011 (2006-2008; &gt;=20 years)</td>
<td>0.019 (0.018, 0.020)</td>
</tr>
</tbody>
</table>

**Combining Proportion (95% confidence interval) 0.028 (0.023, 0.034)**

**Heterogeneity:** Tau² = 0.01; Cochran Q = 2873.86, df = 19 (P < 0.0001); I² = 99%

---

**Legend:**
- Prospective observational study
- Retrospective observational study
- Case-control study
- Cross-sectional study

**Fig. 3.** Pooled AF prevalence estimates overall (A) and for men (B) and women (C) separately (represented as black diamonds) from population studies. Forest plots showing age-adjusted (and sex-adjusted for overall data only) prevalence proportions (red boxes) with 95% confidence limits (black bars).
point in time was 41% in this cohort [75]. In the Manitoba Follow-Up Study, it was shown that AF independently increased the risk of CHF (RR = 2.98) [35]. Stewart and colleagues (2002) showed that AF was an independent risk factor for CHF, particularly in women, in the Renfrew/Paisley cohort [16]. In the Framingham cohort, it was found that CHF imposes a 4.5-fold increased risk in men and a 5.9-fold increased risk in women [12]. The population-attributable risk of CHF in contributing to incident cases of AF was found to be 10% in men and 12% in women [12].

### 3.3.3. Acute coronary syndrome and AF

ACS is closely associated with the development of AF. Our pooled analyses show that a diagnosis of ACS increased the likelihood of AF by 77% (HR 1.77, 95% CI 1.44 to 2.19; Fig. 2C). Acute AF occurs in

#### B: Pooled AF prevalence in men only

<table>
<thead>
<tr>
<th>Study</th>
<th>Proportion (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furberg et al., 1994 (&gt; = 65 years)</td>
<td>0.062 (0.052, 0.072)</td>
</tr>
<tr>
<td>Wolf et al., 1996 (1968-1970; 65-84 years)</td>
<td>0.031 (0.019, 0.048)</td>
</tr>
<tr>
<td>Wolf et al., 1996 (1971-1973; 65-84 years)</td>
<td>0.052 (0.037, 0.070)</td>
</tr>
<tr>
<td>Wolf et al., 1996 (1975-1977; 65-84 years)</td>
<td>0.066 (0.050, 0.086)</td>
</tr>
<tr>
<td>Wolf et al., 1996 (1979-1981; 65-84 years)</td>
<td>0.078 (0.061, 0.098)</td>
</tr>
<tr>
<td>Wolf et al., 1996 (1983-1985; 65-84 years)</td>
<td>0.075 (0.059, 0.094)</td>
</tr>
<tr>
<td>Wolf et al., (1987-1989; 65-84 years)</td>
<td>0.096 (0.076, 0.120)</td>
</tr>
<tr>
<td>Go et al., 2001 (all ages)</td>
<td>0.011 (0.011, 0.011)</td>
</tr>
<tr>
<td>Stewart et al., 2001 (45-64 years)</td>
<td>0.008 (0.006, 0.010)</td>
</tr>
<tr>
<td>Tsang et al., 2003 (1969-1969; all ages)</td>
<td>0.013 (0.007, 0.023)</td>
</tr>
<tr>
<td>Tsang et al., 2003 (1970-1979; all ages)</td>
<td>0.021 (0.013, 0.034)</td>
</tr>
<tr>
<td>Tsang et al., 2003 (1980-1989; all ages)</td>
<td>0.051 (0.037, 0.068)</td>
</tr>
<tr>
<td>Heeringa et al., 2006 (&gt; = 55 years)</td>
<td>0.060 (0.051, 0.069)</td>
</tr>
<tr>
<td>Bonhorst et al., 2010 (&gt; = 40 years)</td>
<td>0.025 (0.021, 0.030)</td>
</tr>
<tr>
<td>Chien et al., 2010 (&gt; = 35 years)</td>
<td>0.014 (0.009, 0.021)</td>
</tr>
<tr>
<td>Smith et al., 2010 (45-74 years)</td>
<td>0.016 (0.014, 0.019)</td>
</tr>
<tr>
<td>Stefansdottir et al., 2011 (1998-1999; &gt; = 20 years)</td>
<td>0.019 (0.017, 0.021)</td>
</tr>
<tr>
<td>Stefansdottir et al., 2011 (2000-2002; &gt; = 20 years)</td>
<td>0.021 (0.019, 0.023)</td>
</tr>
<tr>
<td>Stefansdottir et al., 2011 (2003-2005; &gt; = 20 years)</td>
<td>0.022 (0.020, 0.024)</td>
</tr>
<tr>
<td>Stefansdottir et al., 2011 (2006-2008; &gt; = 20 years)</td>
<td>0.023 (0.021, 0.025)</td>
</tr>
</tbody>
</table>

**Fig. 3 (continued).**

Heterogeneity: Tau² = 0.01; Cochran Q = 1631.56, df = 19 (P < 0.0001); I² = 99%
approximately 5–23% of patients with an AMI [76–78] and is an independent predictor of increased in-hospital and long-term mortality [79–81]. AF-related adverse events are most probably due to impaired coronary perfusion and left ventricular function during episodes of high rapid and irregular ventricular rates in addition to neurohormonal activation [79]. A number of factors are associated with increased risk of AF in the setting of AMI. These include increased age, higher heart rates at admission and left ventricular dysfunction/CHF [78,80,82]. Advanced CHF was shown to be the most significant predictor of associated AF (OR 1.58; 95% CI 1.45 to 1.73) followed by advanced age (OR 1.17; 95% CI 1.16 to 1.18) and elevated heart rate on admission (OR 1.13; 95% CI 1.12 to 1.13) which is possibly a surrogate of left ventricular dysfunction and impaired haemodynamics [82]. No difference concerning the incidence of AF in AMI with and without ST-segment elevation has been
demonstrated [83]. The presence of AF in patients with AMI is well documented as a powerful adverse prognostic factor. This is potentially due to it being an early indicator of underlying left ventricular systolic dysfunction with elevated filling pressures and atrial volume overload unmasked at high heart rates [79]. AF during hospitalisation is associated with higher in-hospital mortality rates (OR 1.39; 95% CI 1.28 to 1.42) [82] whilst 30-day case-fatality for patients with AMI has been shown to be higher in those with AF (OR 1.3; 95% CI 1.2 to 1.4) than without, with no difference demonstrated between the sub-types of AF [84].

3.3.4. AF and other co-morbidities
Hypertension, valvular heart conditions, diabetes mellitus and chronic kidney disease (CKD) also commonly co-exist with AF [34]. Hypertension has been shown to be the most important co-morbid contributor to the burden of AF and can potentially explain more than one fifth of all AF cases [85]. Hypertension imposes a 70% greater risk of AF in women and an 80% greater risk in men [12]. In comparison to hypertension, only 3% of AF cases have been shown to be attributable to diabetes mellitus [85]. Women with diabetes have a reportedly 2-fold greater chance of AF and men a 70% increased risk [12]. Women with AF have been found to have higher diastolic blood pressure and blood glucose concentrations [37]. CKD is also a common co-morbidity found in combination with AF and, regardless of severity, is associated with an increase in the prevalence of AF [85].

3.4. Economic burden of AF
Studies from a range of high income countries have examined the overall and direct cost of AF from a health care cost perspective — see Fig. 6. Annual proportions of overall health care expenditure attributable
to AF (including direct and indirect costs) ranged from 0.8% in Poland (2006) totalling €526 million to 2.48% in Italy (2006) totalling €3286 million [86–93]. As expected, the largest proportion of direct health care costs associated with AF was hospitalisations. For example, 44% of the $US6.65 billion spent on AF in 2005 was attributable to hospital episodes where AF was the principal diagnosis (Fig. 8, Appendix 2). Increased age, being female and Caucasian has been associated with lower AF-related health care costs [88]. An emergency hospitalisation and/or concurrent CHF, stroke or pulmonary disease was associated with greater costs [87,88,94]. Apparently hidden "part" of the direct costing of AF relates to long term nursing home care of patients. Stewart and colleagues (2004) showed that, the cost of long term nursing home care post-hospital discharge for AF in 1995 was approximately €66 million (16% of total "direct" costs). With increases in the prevalence of AF and admissions into nursing homes, this cost rose to approximately €160 million (20% of total "direct" costs) in 2000 [87]. In a survey of national nursing home data from 1985 to 2004 in the USA, the prevalence of AF within nursing homes significantly increased from 2.8% in 1985 to 10.9% in 2004 [95].

### 4. Discussion

With a clear understanding of the caveats around trying to categorise and describe a nebulous body of studies and reports focussing on AF, this report provides a contemporary picture of the evolving impact of AF, predominantly from a high-income country perspective. As expected, all relevant data indicate that the current clinical and financial burden of AF is profound and shows no signs of slowing in the foreseeable future. Paraadoxically, this phenomenon largely reflects improved longevity overall and survival from previously fatal cardiac events. As such, an improved understanding of the key epidemiological drivers and natural history of AF must be utilised to focus efforts towards the development of cost-effective population prevention and clinical management strategies to limit its future individual to whole-society impact.

Both the incidence and the prevalence of AF appear to have risen in recent decades. Incidence of AF consistently increases with age and on an age-adjusted basis, more men than women are affected. The overall prevalence of AF has been previously estimated at approximately 1% [96–99]. As expected, overall prevalence of AF among men (pooled estimate 3.3% [95% CI 2.7% to 4.0%]) remains consistently higher than women (2.5% [95% CI 1.9% to 2.9%]) but the absolute reported number of women affected is often greater due to greater longevity overall. As reported by Lip and colleagues (2012) in a systematic review of 38 studies describing the burden of AF in regions outside North America and Europe, the burden of AF extends beyond high income countries; reported AF prevalence in community-based studies ranging from 0.1% to 4.0% [154]. The reported prevalence of AF in primary care surveys mirrors population prevalence estimates and highlights a high burden of AF management in the community health care setting. The historical pattern of hospital admissions with a primary diagnosis of AF demonstrates a gradual increase in Europe, the USA, Asia and Australia on an age-adjusted basis. Alternatively, rates of hospitalisation in those aged 65 years or more and/or where AF is coded as a secondary diagnosis are rapidly increasing. The historical ratio of an approximate 1:2 primary to secondary discharge diagnosis of AF by the year 2050 [96]. Overall, the prevalence of AF in the USA was predicted to be approximately 2.8 million [9], 3.5 million [96] or 6.3–7.0 million [36] by the end of 2012. Differences in methodology undoubtedly accounted for the variance in estimates but all agreed that historical highs in relation to AF are yet to be reached. Again, due to the prevalence of asymptomatic AF, projections of AF prevalence may be underestimated. Moreover, the underlying prevalence of AF will undoubtedly vary within different sub-groups of the population.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Relative risk of a stroke in persons with AF and other cardiovascular conditions according to age: the Framingham Study [12].</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Ratios</td>
<td>50–59 yrs</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>4.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3.5</td>
</tr>
<tr>
<td>CAD</td>
<td>2.9</td>
</tr>
<tr>
<td>CHF</td>
<td>3.9</td>
</tr>
</tbody>
</table>
| * | p<0.001 or 0.01, adjusted for other stroke risk factors.

Fig. 6. Estimated health care costs of AF in a range of countries as a proportion of health care spending [● = direct costs only; ■ = direct and indirect costs] [86–90,93].
AF is consistent with AF presenting (more often than not) as a complex and challenging clinical case of concurrent ACS, CHF or stroke in an older individual. Concurrently, AF is clearly associated with considerable morbidity and mortality within populations whose survival from other clinical conditions is improving. New therapeutics have and will continue to be developed to improve the pharmaceutical management of AF patients, although the introduction of such therapies has been problematic in the "real world" patient population[97–105] and acceptance and use of anti-coagulant therapy vary widely among countries[154].

Data from estimates of the direct and indirect costs of AF[86–95] and future projections of the burden of AF[9,36,96] both confirm the current, substantial burden of AF and a dramatic escalation in that burden (both from a health care and whole-societal perspective) in the coming decades. As hospitalisations are the primary cost driver in the management of AF, the economic burden of AF is almost certain to grow exponentially as health care becomes more expensive and changes to treatment practice are implemented over time. However, projections for the future burden of AF must be interpreted with some caution given that there are factors that may well negatively or positively impact on its incidence and prevalence. For example, the true prevalence of asymptomatic and paroxysmal forms of AF remains unknown and most probably under-appreciated. Alternatively, the current impact of highly prevalent antecedents/co-morbidities such as hypertension and CHF may well fall over time with improved therapies and management[155].

Some specific limitations/caveats require comment. Perhaps the most notable is the enormous quantity of data focussing on AF and its heterogeneity. A systematic approach to identifying key information was applied wherever possible, but the inadvertent exclusion of relevant and important data cannot be excluded. In addition, some included studies had less than ideal designs, which in itself introduces inherent bias. The lack of clarity surrounding AF sub-type in many studies is also worthy of comment. This may have wide-reaching implications in the application of findings to different population groups. Finally, numerous scales, instruments and methods for data extrapolation were used to measure a range of outcomes in different studies, potentially limiting the strength of evidence presented. As suggested by Lip and colleagues (2012), a more accurate understanding of the global burden of AF is premised on the availability of high-quality epidemiological studies incorporating multiple global populations[154].

This report reinforces that AF imposes a substantial public health, social and economic global burden with some striking and broadly consistent trends identified across high income countries. Furthermore, this burden is growing substantially and has already reached "epidemic" proportions. Substantial integrated efforts to address the complex causes and clinical presentation of AF are required to attenuate future AF-related morbidity, mortality and overall economic costs.

Author declaration

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

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Appendix 3. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2012.12.093.

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O'Malley MH. Genomic determinants of atrial fibrillation: SNPs are riding the wavelets. Heart Rhythm 2006;3(7):813–4.


Summary

This published manuscript confirms the enormity of the current and future burden of AF. It also describes the complexity of this condition and the strong links that exist between AF and other common cardiac antecedents and co-morbidities. In addition, the substantial impact of AF on primary, secondary and tertiary health care providers and the health care systems worldwide is also demonstrated. Health outcomes for individuals affected by AF can be particularly poor, making it a personally and economically costly condition. The economic burden of AF is consequentially large with estimated health care costs ranging from 0.81% to 2.49% of health care spending (direct plus indirect costs) in a number of countries in Europe, North America and Australia. With predicted increases in AF prevalence in high-income countries over the next three to four decades, the need for health care spending will increase in parallel.

The most notable finding of this report was that prevalence rates of AF may be higher than generally reported (originally estimated to be 1.0% to 2.0%). When all current evidence was combined, point (population) prevalence of AF was estimated to be 2.8% on an age- and sex-adjusted basis (95% confidence interval [CI] 2.3% to 3.4%), 3.3% in males (95% CI 2.7% to 4.0%) and 2.4% in females (age-adjusted; 95% CI 1.9% to 2.9%). Therefore, the impact of AF may be greater than first believed and methods to reduce its influence require immediate, focused and multi-disciplinary action.

To our knowledge, these data provide the most accurate, valid and comprehensive description of the growing burden of AF to date. They demonstrate that AF is an evolving and global epidemic with widespread effects on individuals, populations and health care systems. These effects require immediate attention and remedial action. As part of any response, attempts to optimise the management and health outcomes of those already affected by AF may go a long way to effectively reducing the overall burden of this often silent condition. The current body of research was undertaken as a consequence.
Chapter 4

Research Platform and Methods
Chapter 4 introduces the research platform on which this research program was conducted – the Standard versus Atrial Fibrillation spEcific managemenT studY (SAFETY). The rationale and design of SAFETY is presented and the specific methodology used for this research program is summarised.

This chapter includes the following peer-reviewed and published report and Letter-to-the Editor:


Declaration for Thesis Chapter 4

Declaration by candidate

In the case of Chapter 4, the nature and extent of my contribution to the work was the following:

<table>
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<td>Conception and design, analysis and interpretation of data; drafting of the article and revision; final approval of the version to be published.</td>
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<td>Extent of contribution (%)</td>
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The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

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<tr>
<th>Name</th>
<th>Nature of contribution</th>
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<tbody>
<tr>
<td>Dr Melinda J. Carrington</td>
<td>Conception and design, analysis and interpretation of data; drafting of the article and revision; final approval of the version to be published.</td>
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<td>Drafting of the article and revision; final approval of the version to be published.</td>
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<tr>
<td>Professor Simon Stewart</td>
<td>Conception and design, analysis and interpretation of data; drafting of the article and revision; final approval of the version to be published.</td>
<td>N/A</td>
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The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate’s and co-authors’ contributions to this work*. 

Candidate’s Signature

Main Supervisor’s Signature

Date 29th November, 2013
Chapter 4: Research Platform and Methods

Preface

To appropriately prevent or minimise the extent of AF-related morbidity and mortality described in Chapter 3, there is a critical need to evaluate and further develop the most appropriate and informative methods for patient assessment and applying cost-effective patient management. To achieve this, the design, analysis and implementation of high quality and potentially successful management programs is imperative. This research program of assessing enhanced methods of risk delineation goes somewhat towards beginning to develop such programs.

In order to accurately fulfil the aims of this research program, data from comprehensively profiled patients with chronic AF was used. These AF patients constitute the cohort of the Standard versus Atrial Fibrillation spEcific managemenT studY (SAFETY) – an appropriately powered, multicentre, randomised controlled trial of a nurse-led, AF-specific management intervention compared to usual post-discharge care [Carrington et al., 2013]. SAFETY is currently ongoing and is due to be completed at the end of 2013, with results available in early 2014. This novel and pragmatic trial assesses the effectiveness of an AF-specific and individualised management program for the post-discharge management of patients hospitalised with a diagnosis of chronic AF. Notwithstanding the pilot study undertaken by Inglis et al. assessing the efficacy of a non-specific nurse-led management intervention versus usual post-discharge care in patients with AF [Inglis et al., 2004] and the largest AF-specific management study to date involving nurse-led care using a guideline-based computer program in a clinic setting versus usual care [Hendriks et al., 2012], SAFETY represents one of the most comprehensive management studies of its kind.

Whilst remaining an in-patient (during their index hospitalisation), comprehensive baseline profiling was undertaken on each patient enrolled in SAFETY which involved the collection of basic socio-demographic, past medical history and current admission data (including AF-related history). In addition, face-to-face questionnaires were administered at the time of recruitment (wherever feasible) during a semi-structured interview to assess patient experiences with AF, lifestyle, HR-QoL, depression status
Table 10 summarises the questionnaires that were administered during data collection.

**Table 10: Questionnaires administered to SAFETY cohort patients and data collected**

<table>
<thead>
<tr>
<th>Administered questionnaire</th>
<th>Profiling data collected</th>
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<tr>
<td>Investigator-designed AF experiences questionnaire</td>
<td>Patient-reported symptoms of AF</td>
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<td></td>
<td>Patient-reported triggers of AF</td>
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<td></td>
<td>AF knowledge and awareness (of AF episodes, symptoms and triggers)</td>
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<tr>
<td>Investigator-designed lifestyle questionnaire</td>
<td>Cigarette and alcohol consumption</td>
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<tr>
<td></td>
<td>Exercise habits</td>
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<td></td>
<td>Sleep habits</td>
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<tr>
<td>EuroQol 5-dimension scale (EQ-5D)</td>
<td>HR-QoL</td>
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<tr>
<td>Short Form 12 (SF-12)</td>
<td>HR-QoL</td>
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<tr>
<td>ARROLL</td>
<td>Depression status</td>
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<tr>
<td>Centre for Epidemiological Studies Depression Scale (CES-D)</td>
<td>Depression status</td>
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<tr>
<td>Montreal Cognitive Assessment (MoCA)</td>
<td>Cognitive function</td>
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The following manuscript describes the SAFETY trial in detail and reinforces why the study establishes a platform for assessing enhanced methods of risk delineation for use in the chronic AF population to optimise management. It outlines the purpose and rationale behind conducting SAFETY and describes the study’s main objectives, hypothesis and endpoints. SAFETY involves a mean follow-up period of 18 – 36 months and is due to be completed in early 2014. The current research program, however, utilises data collected during in-patient stay and up to 7 – 14 days post-hospital discharge only (from intervention patients only). Results of the risk delineation strategies analysed within this body of research were used to direct and optimise the individual AF-specific management delivered to SAFETY intervention patients.
Navigating the fine line between benefit and risk in chronic atrial fibrillation: Rationale and design of the Standard versus Atrial Fibrillation spEci fic managemenT study (SAFETY)

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ABSTRACT

Background: Health outcomes associated with atrial fibrillation (AF) continue to be poor and standard management often does not provide clinical stability. The Standard versus Atrial Fibrillation spEci fic managemenT study (SAFETY) compares the efficacy of a post-discharge, nurse-led, multi-disciplinary programme to optimise AF management with usual care.

Methods: SAFETY is a prospective, multi-centre, randomised controlled trial with blinded-endpoint adjudication. A target of 320 hospitalised patients with a chronic form of AF will be randomised (stratified by “rate” versus “rhythm” control) to usual post-discharge care or the SAFETY Intervention (SI). The SI involves home-based assessment, extensive clinical profiling and the application of optimal gold-standard pharmacology which is individually tailored according to a “traffic light” framework based on clinical stability, risk profile and therapeutic management. The primary endpoint is event-free survival from all-cause death or unplanned readmission during 36 months follow-up. Secondary endpoints include rate of recurrent hospital stay, treatment success (i.e. maintenance of rhythm or rate control and/or application of anti-thrombotic therapy without a bleeding event) and cost-effectiveness.

Results: With study recruitment to be completed in early 2012, the results of this study will be available in early 2014.

Conclusions: If positive, SAFETY will represent a potentially cost-effective and readily applicable strategy to improve health outcomes in high risk individuals discharged from hospital with chronic AF.

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1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia with a lifetime risk of around one in four among North Americans and Europeans [1,2]. Described as the next cardiac “epidemic” [2], the consequences will not be benign given that chronic AF is independently associated with substantial morbidity and mortality [3,4]. Accordingly, contemporary studies suggest that both the primary care [5] and hospital burden [3,6] attributable to AF is increasing in parallel with ageing populations in whom cardiac risk factors and other forms of heart disease are highly prevalent [6]. AF has also started to appear in historically high numbers in low-to-middle income countries [7]. From a cardiovascular perspective, the nexus between AF and two common causes of death and disability, stroke and chronic heart failure (CHF), is of concern given a two-way “cause and effect” relationship—AF is associated with a 4–5 fold increase in the risk of stroke [8] and is found in up to 25% patients with an acute ischaemic stroke. Moreover, AF-related strokes are more severe and more debilitating than those associated with other aetiologies with worse short and long-term survival [9]. Similarly, individuals with AF are approximately 2.5-fold more likely to develop CHF [10]. Data from the EuroHeart Failure Survey showed that one third of patients...
hospitalised for CHF had AF prior to hospitalisation and 9% were diagnosed with new onset AF during that admission [11]. A recent meta-analysis of 16 studies reported a two-fold increase in mortality associated with AF in those with both preserved and impaired systolic function [12]. Overall therefore, AF poses a significant public health and clinical challenge that has many parallels to that of CHF. For example, the evolution of anti-thrombotic therapy was recently advanced with the results of the ARISTOTLE Study [13] demonstrating that apixaban (a direct factor Xa inhibitor) was superior to warfarin in preventing stroke or embolism whilst being associated with less bleeding and more prolonged survival. However, treatment discontinuation rates were high in both groups. Unfortunately, a conservative approach by clinicians has resulted in a substantial treatment “gap” in AF management to date [14–16]. Moreover, the number of older individuals with chronic forms of AF in whom residual issues of the real-world effectiveness and safety will need to be addressed is likely to rise [17]. In CHF, this critical issue was addressed through the development of dedicated management programmes that simultaneously reduced recurrent hospital stay and prolonged survival [18].

This paper reviews the challenges and clinical conundrums that have shaped the design of the Standard versus Atrial Fibrillation spEcific managementT studY (SAFETY), with respect to balancing the fine line between benefit and risk in applying modern therapeutics in typically elderly and fragile patients who have been hospitalised with a chronic form of AF. Preliminary studies have explored the benefits of applying AF-specific disease management via home-based management [19] and a specialist AF clinic [20]. This prospective, multicentre, randomised study will determine if a multidisciplinary, nurse-led, home-based programme of AF-specific management delivered post-acute hospitalisation will improve health outcomes relative to standard management in patients with chronic AF.

2. Study rationale

2.1. Therapeutic targets in AF

There are three key priorities underlying the management of AF (particularly chronic forms), which vary in importance according to the clinical profile of the affected individual:

1. Reduce the risk of a thrombo-embolic event: an ischaemic stroke, as the most common and deadly form of such events, is the primary target for prevention. The intensity and potency of treatment is dependent on the risk of stroke and is balanced by the counter risk of bleeding events (e.g. a fatal haemorrhagic stroke).

2. Reduce the risk of developing left ventricular dysfunction: mechanical and structural changes in the atria and ventricle are both directly and indirectly linked to the fast and chaotic nature of uncontrolled AF (particularly in its chronic forms). The application of treatments designed to either revert patients to normal sinus rhythm or a slower ventricular response rate is balanced by the counter risk of adverse events (e.g. a pharmacological toxicity-induced pro-arrhythmic effect in addition to hepato-toxicity and adverse drug-to-drug interactions [21]). Cardio-protective agents (e.g. angiotensin inhibitors) designed to preserve ventricular function have potentially deleterious effects on renal function (particularly in older individuals).

3. Improve clinical stability and symptom control: patients with a rapid ventricular response are prone to increased AF-related symptoms (e.g. dyspnoea and palpitations) and acute deterioration in ventricular function, particularly those with already compromised left ventricular function. Once again, the risk of therapies designed to control the ventricular rate that cause a degree of “harm” is high—particularly in elderly individuals where issues around treatment doses and reversal of atrial electrical remodelling remain.

The appropriate treatment designed to balance these interrelated therapeutic targets from an optimal benefit-to-risk perspective is often difficult to determine, particularly given a range of competing therapeutic options in this clinical setting.

2.2. Matching treatment with risk: Scylla and Charybdis in AF

Determining individual risk in AF, both of haemodynamic compromise and of embolic complications is critical to optimal management primarily because all treatment options carry a substantial “downside”. Specifically, all (including modern) therapeutics that are used to keep patients in sinus rhythm (whether by pharmacological intervention or by AF ablation) and/or free from an ischaemic stroke, involve a risk of potentially fatal complications [22]. All therapeutics, therefore, require a more structured approach to management to reach their full potential in a real-world setting. Beyond invasive techniques such as catheter ablation that are intrinsically limited by cost [23] and availability of specialist personnel and equipment in a minority of highly selected cases, the predominant strategy used to manage AF continues to be pharmacological therapy.

2.2.1. Anti-platelet/anti-coagulation therapy (all patients)

At minimum, patients with AF require anti-platelet therapy (e.g. aspirin and/or clopidogrel). Up until recently the administration of anti-coagulants such as the vitamin K antagonist warfarin, while considerably reducing embolic risk, also significantly increases the risk of bleeding complications in elderly, frail, individuals or in patients in whom compliance with medication is imperfect [22]. This has posed two significant clinical problems that is: a) “high risk” patients are often not appropriately identified, therefore, their clinical stability may be compromised and; b) continuous and intensive monitoring is required (via the international normalised ratio (INR)) to titrate warfarin therapy to maintain therapeutic levels of anti-coagulation without straying into levels of bleeding risk. Fortunately, thrombin inhibitors now provide a potentially cost-effective alternative to warfarin in many (but not all) patients with chronic forms of AF without the need for continuous monitoring and dose adjustment. Whilst showing early clinical promise, the application of ximelagatan was derailed by unacceptable levels of hepatotoxicity [24]. The real vanguard of such therapy, therefore, began with dabigatran etexilate (the second major drug in this class of agents) that was compared (in two doses) to open-label warfarin in the RE-LY Study in patients with AF and at risk of stroke [15]. Whilst dabigatran therapy compared favourably to warfarin (the 150 mg twice daily arm being associated with lower rates of stroke and systemic embolism with similar rates of major haemorrhage), 21% of patients in both dabigatran treatment arms were discontinued from therapy at two years. Moreover, whilst demonstrating a more predictable pharmacokinetic and better safety profile in clinical trials [14,15] than warfarin, there are residual concerns over its use in elderly patients (the vast majority of patients with chronic forms of AF); particularly in those with renal dysfunction [24,25]. The results of the ARISTOTLE Trial have further strengthened the role of thrombin inhibitors with 5 mg twice daily of apixaban proving to be superior to warfarin (blinded protocol) in preventing stroke or systemic embolism, reducing bleeding events and prolonging survival in patients with AF over median follow-up of 1.8 years. However, high rates of treatment discontinuation in this trial, when combined with residual concerns over other agents in this class, clearly indicate that warfarin therapy will still be required in this clinical setting.

Clinical heterogeneity, therefore, still predicates a careful approach to the management of AF with individualised consideration of therapeutic targets (minimisation of thrombotic events) and risk of adverse events (minimisation of bleeding events). Traditionally, the CHADS2 Score [26] (empirically derived from epidemiological observations) provides an approximate index to calculate the risk of
stroke and need for aggressive anti-thrombotic therapy. The recent application of a more comprehensive thrombo-embolic risk prediction score [22], the CHA2DS2-VASc score, has further delineated influential factors in thrombotic pathogenesis and has clarified anti-thrombotic therapy indications.

2.2. Rate or rhythm control

This remains one of the most contentious issues in AF management given that expected benefits from rhythm control (i.e. sustained reversion to sinus rhythm) has not proven to be superior to rate control [27]. Rate control is achieved with pharmacologic agents used as mono-therapy or in combination therapy [22]. It is this component of AF management that is often the most vexing for both clinicians and patients—particularly when poorly controlled patients are often unable to exercise without becoming symptomatic. Additionally, it is often rate control therapy that is most poorly managed and is an important driver of hospital re-admission for AF patients [28,29]. Similarly, both electrical and (acute and longer-term) pharmacological cardioversion of AF has proven problematic with poor rates of sustained conversion in the former [30] and cardio-toxic effects associated with the latter [28]. Many of the drugs used as a key component of “rate” or “rhythm” control pose a danger to those patients with left ventricular systolic dysfunction (LVSD) due to negative inotrope effects (e.g. calcium antagonists). The delicate balance between benefit-to-risk in controlling rate and rhythm in AF is perhaps best reflected in the current evidence surrounding dronedarone. This multi-channel blocker (with a component of calcium antagonism) was initially shown to be a safe and effective (predominantly via reduced cardiovascular hospitalisations) treatment option for patients with paroxysmal and persistent forms of AF [31]. However, the PALAS study was recently suspended due to a significant increase in cardiovascular events observed in the treatment arm [32], reflecting the inherent risks with administration of anti-arrhythmic drugs in patients who are often elderly with multiple co-morbidities. Key indicators of clinical success in the management of AF, therefore, also includes extent of rhythm and rate control, particularly in those with underlying LVSD, as a means to prevent tachycardia-induced cardiomyopathy and clinical instability.

2.3. Early evidence in favour of disease management in AF

We have previously demonstrated, for the first time, that an individualised yet generic disease management programme, including a component of post-discharge home visits improved health outcomes compared to that of usual care in hospitalised patients with chronic forms of AF [33]. During a median 5-year follow-up, this programme was associated with a 27% and 20% reduction in unplanned hospital re-admissions and related bed days, respectively (p < 0.05 for both). More recently, the results of an AF-specific disease management programme of software-determined, guideline-based care delivered in a nurse-driven clinic setting (AF-Clinic) were presented [34]. Following a mean of 22-months follow-up, 14% of intervention patients compared with 21% of usual care patients reached the composite endpoint of heart failure, thrombo-embolic events, bleeding events, treatment-induced adverse events and cardiovascular death. Deaths and hospitalisations were significantly lower among patients treated in the AF Clinic suggesting that this form of AF-specific intervention improves patient outcomes compared to usual care [20].

2.4. An AF-specific approach

These data reinforce our contention that two components of management, when combined with the proven benefits of our generic approach to chronic disease management (demonstrated in a broad group of patients with chronic disease [35,36] as well as in patients with CHF [33,36]) will provide incremental benefits to patients with AF via a disease-specific approach:

- Improved delineation (over and above that of conventional profiling) of underlying risk of thrombo-embolic events, progressive cardiac dysfunction and poorly controlled clinical status via enhanced evaluation of the following:
  - Haemodynamic risk—by analysis of left ventricular systolic and diastolic function, valvular function and N-terminal pro-Brain Natriuretic Peptide [NT-proBNP] release;
  - Embolic risk—via CHA2DS2-VASc score, and incrementally by evaluation of specific markers of atrial distension (echocardiography), endothelial dysfunction, platelet and inflammatory activation;
  - Accurate assessment of subclinical LV dysfunction—by analysis of global longitudinal strain, a more reproducible marker of systolic function than conventional parameters such as ejection fraction, that is predictive of outcome and sensitive to mild LV dysfunction [37]. As ejection fraction is used extensively in the literature, this will be measured using 3D imaging [38].
  - Optimisation of patient psychosocial adaptation to the requirements of pharmacotherapy of AF

- Based on the above, a more individualised and careful approach to managing affected patients, focussing on therapeutic strategies that best achieve the following:
  - Optimal balance between the risk of thrombo-embolic versus bleeding events;
  - Optimising underlying cardiac function and structure by rate control and cardio-protection to in those with underlying LVSD;
  - Minimal AF-related symptoms and clinical instability.

As such, these principles have been applied in designing the SAFETY Study.

3. Study design

Fig. 1 shows the design of the SAFETY study. A target of 320 eligible patients will be recruited from three tertiary referral hospitals in South Australia, Victoria and the Australian Capital Territory. Patients will be subject to stratified randomisation (according to baseline intention to apply “rate” or “rhythm” control) to either usual care (UC) or the nurse-led, home-based SAFETY intervention (SI) at a ratio of 1:1.

To our knowledge, the SAFETY study will be the first prospective, multi-centre, randomised trial of home-based disease management incorporating better risk delineation and AF-specific components of treatment designed to specifically improve health outcomes in patients with chronic, non-valvar forms of AF.

3.1. Study hypothesis

Using a multicentre, randomised clinical trial design, we will test the following null hypothesis: in hospitalised patients with chronic forms of AF; a specific programme of enhanced risk delineation combined with an AF-specific form of chronic disease management (the SAFETY Intervention [SI] comprising both pharmacological and non-pharmacological components) will show no difference in the composite endpoint of all-cause mortality and/or unplanned hospital readmission (measured as event-free survival and days out-of-hospital-alive) relative to UC during follow-up of 18–36 months.

3.2. Study endpoints

The primary endpoint of SAFETY is event-free survival from all-cause death or unplanned readmission during 18–36 months follow-up. This endpoint will be examined in respect to both the absolute number and timing of events and “days out of hospital alive”. Primary endpoints will be adjudicated (including probable causality) by
blinded Endpoint Committee. Just as the primary endpoint of the study reflects optimised prevention of haemodynamic and embolic complications of AF, the principle secondary objectives of the study are to improve risk indexation with regard to each of these categories of complications. Hence, in addition to the primary (composite) endpoints, we will prospectively examine the following according to the absolute number, timing and frequency of events (where appropriate), as detected during any documented health care contact or during structured monitoring over study follow-up:

- Cardiovascular morbidity and mortality (with a particular focus on events relating to stroke, heart failure and falls), duration and rate of hospital stay;
- All-cause hospital stay;
- Cost of health care;
- Change in health-related quality of life and function;
- Changes in left ventricular systolic and diastolic function;
- Failure to maintain treatment targets as indicated by any of the following events during study follow-up:
  - Any bleeding or thrombo-embolic events requiring hospitalisation;
  - Any AF-related hospital admission;
  - Reversion to AF from sinus rhythm when target goal is stipulated (at baseline) to be “rhythm control strategy”;
  - Documented target heart rate (rest and exercise) greater than that stipulated by the treating physician at baseline as part of a “rate” or “rhythm” control strategy;
  - For those prescribed warfarin, time in therapeutic range;
  - Changes in a number of novel markers of endothelial and platelet function [39], as well as inflammatory activation.

3.3. Participants

A systematic screening programme of in-patients at participating hospitals will be undertaken to identify eligible patients. Consistent with our previous trials examining the benefits of disease management [19,33,40], a “real life” approach to patient recruitment will be applied.

3.4. Inclusion and exclusion criteria

Patients admitted to hospital will be included if they fulfil all of the following criteria:

- Documented diagnosis of sustained forms of AF (recurrent paroxysmal, persistent or permanent AF);
- Live independently in the community or their own home post-hospitalisation;
• Live within a 40 km radius of the treating hospital;
• Are able and willing to provide written informed consent to participate in the study (this includes the ability to understand and speak English fluently and that the patient is cognitively intact).

Patients will be excluded if they fulfil any of the following criteria:

• Aged <45 years;
• Primary diagnosis of valvular heart disease;
• Scheduled catheter ablation procedure;
• Pre-existing CHF as evidenced by the combination of symptoms indicative of NYHA Classes III–IV with a documented left ventricular ejection fraction (LVEF) <45%;
• Alcohol induced AF;
• Transient forms of AF associated with AMI and/or pericarditis;
• Terminal condition/malignancy requiring palliative care.

3.5. Study data

A comprehensive range of socio-demographic and clinical profiling data will be collected at baseline, 12 months and 24 months (where available) post-discharge during study follow-up. Baseline profiling will include category of AF, treatment goals (e.g. rate versus rhythm control) in addition to the CHA₂DS₂-VASc score [22,26,41–43] and the HAS-BLED score [44]. A Charlson Index of Co-morbidity Score [45] will also be calculated. Health related quality of life will be measured using the MOS SF-12 and EQ-5D [46,47], the number of agents and doses per day and introduce tools such as the CES-D Scale [50] if positive. Additionally, information on lifestyle patterns and influences, health knowledge, self-care abilities and treatment adherence will also be sought. Holter 24 h ECG monitoring will also be undertaken and analysed on a blinded basis on all surviving patients at baseline (intervention patients only) and 12 months post-index discharge [51]. Two prospectively planned sub-studies of platelet function and the utility of advanced imaging to enhance risk delineation will also be undertaken.

3.6. SAFETY intervention (SI)

Table 1 and Fig. 2 show the traffic light system our group has developed with respect to patient management within a disease management setting and how it will be applied as part of the AF-specific SI. Every SI patient is subject to a comprehensive home visit in the 7–14 days post-hospitalisation by a specialist cardiac nurse. Additional home visits can be arranged as required. The main objectives of the AF-specific SI are to:

• Apply enhanced risk delineation to adjust the level of surveillance and support received;
• Establish a clear treatment plan using expert guidelines, both standard and enhanced risk delineation to provide maximal protection against embolic events, bleeding and cardiac dysfunction and to optimise clinical stability and symptom control;
• Coordinate and enhance the above treatment plan with individualised support for the patient and/or carers;
• Provide the SI according to the clinician nominated treatment strategy (i.e. rate versus rhythm control).

As indicated, a care plan for each patient will be established at baseline (or within 7 days if not practical) according to conventional clinical profiling. The patient’s management plan will be further refined based on the results of more advanced profiling, with consideration of the inclusion of cardio-protective therapy (if not already prescribed) in the form of an Angiotensin-Converting Enzyme (ACE) inhibitor or Angiotensin-II Receptor Blocker (ARB) +/- more intensive rate or rhythm control and anti-thrombotic therapy. Sub-optimal self-care behaviours, including treatment non-adherence, will prompt simplification of pharmacological therapy to minimise the number of agents and doses per day and introduce tools such as a medication planner to improve compliance. The application of AF-specific pharmacological therapy will be carefully monitored as part of patient management. A purposefully designed educational manual (Living with Atrial Fibrillation) will be provided to patients and their families that explains AF, symptoms and treatments.

In collaboration with the patient, their family/carers and health care team (including community pharmacists), the main objective is to apply gold-standard guidelines for the best-practice treatment of AF and the management of associated diseases including hypertension, hypercholesterolemia, diastolic dysfunction and ischaemic heart disease in order to reduce the probability of further morbidity and premature death. We anticipate that there will be prolonged benefits derived from positive changes in individual patients (e.g. better self-care/increased vigilance) and their health care team (e.g. increased pharmacist supervision).

3.7. Anti-coagulation/anti-platelet therapy

Appropriate therapy for optimal prevention of thrombo-embolic events is applied on a pro-active basis (this includes incorporating new anti-thrombotic therapy as they become available). Those prescribed warfarin therapy are assessed for potential self-monitoring and titration of therapy using a point-of-care INR monitor with

Table 1

Overall risk assessment and management strategy in SAFETY.

<table>
<thead>
<tr>
<th>Priority</th>
<th>Clinical status</th>
<th>Management</th>
<th>Risk profile</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>High/intense</td>
<td>Clinically unstable</td>
<td>Key deficits</td>
<td>Multiple risk factors</td>
<td>Urgent intervention to promote clinical stability; ongoing surveillance to optimise management and minimise risk factors</td>
</tr>
<tr>
<td>Medium</td>
<td>Stable</td>
<td>Areas of deficit</td>
<td>1 or more risk factors</td>
<td>Sustained follow-up to optimise management and address identified factor(s) contributing to increased risk</td>
</tr>
<tr>
<td>Low</td>
<td>Stable</td>
<td>Gold-standard</td>
<td>No risk factors</td>
<td>No further intervention other than routine contact and surveillance</td>
</tr>
</tbody>
</table>
close support from the cardiac nurse. As indicated, a key therapeutic goal is maximal time in the therapeutic range.

3.8. Rhythm or rate control therapy

All SI patients have their heart rhythm and rate closely monitored and the definition for optimal rate control based on a combination of regularity of ventricular contraction, quality of life, symptom reduction and reduction in the development of cardiomyopathy. Standardised, target ventricular rates between 60 and 80 beats per minute at rest and between 90 and 115 beats per minute during moderate exercise will be applied unless specifically varied by the treating clinician [22]. An average ventricular rate of ≤90 beats per minute for at least 75% of Holter monitoring time (i.e. >18 h over 24 h) will be considered as “rate controlled” [22].

3.9. Patient follow-up

Multiple follow-up assessments of therapeutic targets and management will include:

- A home visit schedule which includes developing a personal and individualised management plan at the first home visit (7–14 days post-discharge) with input from the patient (and their family and/or carer if present), and review of this plan to understand if the patient is achieving their health goals, remaining (or becoming) clinically stable and is appropriately taking and utilising the medications prescribed to them. The patient’s knowledge on AF will also be informally assessed and education provided if necessary.
- Brief checks of cardiac rate and rhythm control at the baseline home visit, 1 month, 3 months (optional) and 6 months using a hand-held device (Omron HCG-801 HeartScan- Portable, cordless, single-channel ECG Monitor) or 12-lead ECG recording.
- Review following any unplanned admission to hospital.
- Patient initiated contacts with the cardiac nurse (when required).

3.10. Usual care

In accordance with our previous disease management studies [33,35,36], no restrictions on discharge planning and post-discharge follow-up will be imposed on those randomised to UC. Patients’ GPs and specialist physicians will be asked to apply their usual pattern of patient visits and treatment strategies to achieve optimal AF management.

3.11. Study power

Based on a combination of pilot data [19,33] and results from contemporary clinical trials [31] we estimated that 60% of patients randomised to UC in SAFETY will suffer a recurrent hospitalisation or fatal event during 18–36 months follow-up. Assuming an alpha of 0.05 with a total of 320 patients (160 in each group) we will have 85% power to detect a 25% relative difference in the primary endpoint (45% in the SI group) and >90% power to detect a 30% difference (42% in the SI group). In the ATHENA study [31], the composite primary endpoint of all-cause mortality or a cardiovascular event occurred in 40% of AF patients treated with placebo during a mean of 21 months follow-up. Assuming the same rate of underlying events in our study cohort, we will still have >80% power to detect a 33% difference in this composite outcome.

3.12. Prospective sub-studies

Given the importance of further delineating thrombotic risk in patients with AF with the potential for an important role for a combination of underlying oxidative stress, endothelial dysfunction and platelet activation, a sub-study of these factors in >100 study patients will be performed. Similarly, given the central importance of rate control (and risk due to rate-related negative inotropic effects of treatment) a sub-study of the utility of advanced echocardiography (in intervention patients only) will be performed.

4. Discussion

The burden and consequences imposed by a modern epidemic of chronic forms of AF in our ageing populations in whom pre-existing risk factors and established heart disease are prevalent requires an urgent response. A rising epidemic of CHF was similarly addressed. Part of the current response has to focus not only on developing new therapeutic options that shift the benefit-to-risk ratio of treatment into much safer territory, but also developing cost-effective management programmes that can reduce morbidity and prolong survival. SAFETY represents a new generation of studies focusing on the potential benefits of AF-specific management. Arising from a
favourable evidence base (in the context of CHF [33,36]) and positive pilot data, this important study will potentially provide the foundation for the same type of cost-effective services (most probably integrated) applied in relation to CHF management. Results from the study are expected to be released in early 2014.

Acknowledgements

The SAFETY study is funded by a National Health and Medical Research Council of Australia Program Grant (519823). In addition, MC, JB and SS are supported by the National Health and Medical Research Council of Australia. This research is supported in part by the Victorian Government’s Operational Infrastructure Support Program.

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

References

Summary

The historical development of now gold-standard multi-disciplinary management programs of care to apply effective modern therapeutics, reduce recurrent hospitalisations and prolong survival in those affected by CHF provides a clear pathway to similar programs for those affected by chronic AF. There is obvious urgency required to control the emerging AF epidemic that was highlighted in Chapter 3 and disease management is likely to be effective in this clinical context. SAFETY represents an AF-specific approach to understanding if this is possible.

With regard to the aims of the current research program, SAFETY is an appropriate research framework. It provides the platform from which enhanced strategies of risk delineation in patients with AF can effectively be assessed. Whether these methods positively influence a reduction in AF-related re-hospitalisations, morbidity and mortality will be determined at a later date and is beyond the scope of this thesis. However, the identification of enhanced risk delineation approaches and the implementation of these to direct patient management may prove important to the immediate post-discharge management of hospitalised patients with AF and provide the strong potential for longer-term health benefits.

The antecedent risks of AF identified in Chapter 3 were incorporated into the design of SAFETY and form the following two chapters of this thesis; gender as an inherent risk factor is assessed in Chapter 5 and mild cognitive impairment (MCI) as an acquired risk factor is analysed in Chapter 6. Both Chapters 5 and 6 report on data collected on all patients (usual care and intervention patients) at the baseline time point (during index hospitalisation). Detailed assessment of post-discharge AF management (effective rate versus rhythm control) is undertaken in Chapter 7 and reports on data collected from intervention patients only at both the baseline time point and during the baseline home visit delivered by a cardiac intervention nurse at 7 – 14 days post-hospital discharge. The specific methodological details of each SAFETY sub-study conducted as part of this research is described in the published/submitted manuscripts that form the chapters contained within this thesis.
Postscript

During the completion of this research, the evolving collection of published reports contributing to the AF literature was continually reviewed. One specific report, written by the AF-Clinic investigators and colleagues, suggested that the systematic interdisciplinary approach required for effective AF management should be supported by a dedicated software program and should be conducted within a clinic environment (see Appendix II) [Berti et al., 2013a]. Furthermore, it was stated that effectiveness studies of AF nurse-led management interventions are scarce, with only publications produced by the AF-Clinic investigators being referenced. Neither the pilot study data of Inglis et al. [Inglis et al., 2004] nor the SAFETY rationale and design manuscript [Carrington et al., 2013] were acknowledged. Therefore, the following Letter-to-the-Editor was submitted in response, prompting a subsequent reply from Berti et al. (see Appendix III) [Berti et al., 2013b].
A new or old solution to an old problem?

Jocasta Ball, B.Biomed.Sci(Hons) Melinda J. Carrington, Simon Stewart
IHMRC Centre of Research Excellence to Reduce Inequality in Heart Disease,
Preventative Health, Bake

Re: "A proposal for interdisciplinary, nurse-coordinated atrial fibrillation expert programmes as a way to structure daily practice" Berti, et al., doi:10.1093/eurheartj/ehb096

Re: "A proposal for interdisciplinary, nurse-coordinated atrial fibrillation expert programmes as a way to structure daily practice" (Berti et al., doi:10.1093/eurheartj/ehb096)

Dear Editor,

We read with interest, the European Heart Journal article by Berti et al. recently published online (1). We acknowledge the recommendations made by the authors for complete and accurate implementation of interdisciplinary, nurse-coordinated atrial fibrillation (AF) management with the aim of improving patient outcomes and we also support the call for a concerted effort to reduce the global burden of AF. We too are strong advocates of nurse-led disease management and know the benefits of this model of care (2-4). Testament to this, our group first flagged the need and potential value of AF-specific management programs almost a decade ago (5).

As with the development of heart failure management programs, where there appears to be differential value of an outreach versus clinic-based approach to management depending on the typical age and profile of individuals (4), we would advocate caution in proposing that the AF-Clinic (6) represents a panacea in terms of optimal AF management; particularly given the advanced age, gender profiles and complexity of typical cases (i.e. unlike those enrolled in clinical trials). In this respect, one of a number of interdisciplinary disease management trials within our ongoing program of research, the Standard versus Atrial Fibrillation specific management study (SAFETY), represents a nurse-led, multi-centre randomised controlled trial (7) that builds on our pioneering report in 2004 (5) and solid evidence-base for AF-specific, individualised management programs. SAFETY has or will (when completed in early 2014) address all the factors the authors state are specifically required for an effective systematic, interdisciplinary AF management program - comprehensive assessment, systematisation of medical care, education, coordination of care and evaluation of care plan execution. In addition, SAFETY assesses the many facets (functional, behavioural, psychosocial, knowledge-based, self-management and education requirements) involved in receiving a diagnosis of AF. Further to this, we are using the study as a platform for developing novel tools that allow further risk delineation and optimal delivery of care (8).

Generalisation of the recommendations made by the authors (clearly based on their experience of the AF-Clinic), is potentially precarious. Their study cohort mainly comprised younger males with paroxysmal AF and patients with serious comorbidities were excluded. It is widely acknowledged in the literature that patients with AF are older with multiple comorbidities (both cardiac and non-cardiac) and are often prescribed multiple pharmacotherapies. There are clear gender differences in presentation, functional and cognitive decline is common and the rate of AF-related complications is high. We have taken all of these factors into consideration in the...
SAFETY trial which consists of elderly individuals (mean age 72 years), equal numbers of men and women with chronic forms of AF and a high level of mild cognitive impairment (MCI) that can have serious adverse effects on the implementation of highly complex disease management programs (9). AF itself is a highly heterogeneous and inherently complex condition even before a management plan is developed and this needs to be factored into community-delivered management programs, which should not be generically prescriptive. It could be argued the SAFETY cohort more accurately reflects the "real world" AF patient population where the median age is approximately 75 years and absolute numbers are roughly gender-equal (10). At this stage, therefore, it is perhaps premature to present the AF-Clinic as the potential gold-standard of nurse-coordinated AF patient assessment and management. We look forward to adding our own experiences in attempting to improve AF-related outcomes with that of Berli and colleagues, although it is possible that our endeavor may prove to be difficult to implement due to the complexity of the patient cohort. However, we will welcome the day when we finally develop an evidence-rich basis for optimising the care of an increasing number of (predominantly older) individuals with AF.

REFERENCES


Chapter 5

Gender – an inherent factor with the potential for use in risk delineation
Chapter 5 explores potentially important differences in the risk profile of men and women admitted to hospital with chronic AF. The influence of these differences on future health outcomes for women compared to men with AF is discussed from the perspective of providing individualised disease management.

This chapter includes the following peer-reviewed and published report:

Declaration for Thesis Chapter 5

Declaration by candidate

In the case of Chapter 5, the nature and extent of my contribution to the work was the following:

<table>
<thead>
<tr>
<th>Nature of contribution</th>
<th>Extent of contribution (%)</th>
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</thead>
<tbody>
<tr>
<td>Conception and design, acquisition of data, analysis and interpretation of data; drafting of the article and revision; final approval of the version to be published.</td>
<td>65%</td>
</tr>
</tbody>
</table>

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

<table>
<thead>
<tr>
<th>Name</th>
<th>Nature of contribution</th>
<th>Extent of contribution (%) for student co-authors only</th>
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<tr>
<td>Dr Melinda J. Carrington</td>
<td>Conception and design, interpretation of data; drafting of the article and revision; final approval of the version to be published.</td>
<td>N/A</td>
</tr>
<tr>
<td>Dr Kathryn A. Wood</td>
<td>Interpretation of data; drafting of the article and revision; final approval of the version to be published.</td>
<td>N/A</td>
</tr>
<tr>
<td>Professor Simon Stewart</td>
<td>Conception and design, interpretation of data; drafting of the article and revision; final approval of the version to be published.</td>
<td>N/A</td>
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</table>
Chapter 5: Gender – an inherent factor with the potential for use in risk delineation

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate’s and co-authors’ contributions to this work.

<table>
<thead>
<tr>
<th>Candidate’s Signature</th>
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<tr>
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<td>29&lt;sup&gt;th&lt;/sup&gt; November, 2013</td>
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<th>Main Supervisor’s Signature</th>
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Preface

It is well known that important clinical differences exist between females and males who suffer from CVD in all its forms, representing a constant challenge for treating clinicians [Go et al., 2013]. Gender, in any patient group, is the most basic factor by which to stratify risk. However, it is inherent and non-modifiable. As with other cardiovascular conditions, the absolute number of women affected by AF is higher than the number of affected men [Benjamin et al., 1994; Go et al., 2001]. Caution must be taken in the evaluation and application of clinical trial results of new therapeutics, as the proportion of representative women versus men is often not equal, with vastly more men represented in trial cohorts [McAlister et al., 2004; Melloni et al., 2010]. Therefore, ready application to all patients who are matched in all other risk factors aside from gender may not be accurate or safe. This has potential implications for current clinical practice (i.e. “real world” practice) in which new therapeutics are constantly evolving and introduced to market. The development and trials of therapeutics for use in the management of patients with AF has been most prolific in recent years, with the introduction of novel anti-thrombotic and anti-arrhythmic therapies and the assessment of the foremost combination of pharmacological strategies (see Table 5).

In order to optimise the management of patients with AF, the impact of gender-specific differences on both pharmacologic and non-pharmacologic management should be assessed. Gender-specific differences have previously been identified in patients with AF, although the extent to which this affects clinical management is yet to be fully elucidated. It was on this basis that detailed clinical phenotyping of the high risk, hospitalised patients of the SAFETY trial cohort was undertaken to understand if differences existed in the clinical presentation, thrombo-embolic risk and therapeutic management of women versus men with chronic AF. Further to this, the use of gender as a method for delineating risk in patients with AF in an attempt to better direct individual AF-specific management was assessed.
Women Versus Men with Chronic Atrial Fibrillation: Insights from the Standard Versus Atrial Fibrillation spEcific managemenT studY (SAFETY)

Jocasta Ball1,2, Melinda J. Carrington1,2, Kathryn A. Wood2, Simon Stewart1,2*, on behalf of the SAFETY Investigators

1 Centre of Research Excellence to Reduce Inequality in Heart Disease, Preventative Health, Baker IDI Heart and Diabetes Institute, Melbourne, Australia, 2 Department of Epidemiology and Preventative Medicine, Monash University, Melbourne, Australia, 3 School of Nursing, Duke University, Durham, North Carolina, United States of America

Abstract

Background: Gender-based clinical differences are increasingly being identified as having significant influence on the outcomes of patients with cardiovascular disease (CVD), including atrial fibrillation (AF).

Objective: To perform detailed clinical phenotyping on a cohort of hospitalised patients with chronic forms of AF to understand if gender-based differences exist in the clinical presentation, thrombo-embolic risk and therapeutic management of high risk patients hospitalised with chronic AF.

Methods: We are undertaking the Standard versus Atrial Fibrillation spEcific managemenT studY (SAFETY) - a multi-centre, randomised controlled trial of an AF-specific management intervention versus usual care. Extensive baseline profiling of recruited patients was undertaken to identify gender-specific differences for risk delineation.

Results: We screened 2,438 patients with AF and recruited 335 into SAFETY. Of these, 48.1% were women who were, on average, 5 years older than their male counterparts. Women and men displayed divergent antecedent profiles, with women having a higher thrombo-embolic risk but being prescribed similar treatment regimens. More women than men presented to hospital with co-morbid thyroid dysfunction, depression, renal impairment and obesity. In contrast, more men presented with coronary artery disease (CAD) and/or chronic obstructive pulmonary disease (COPD). Even when data was age-adjusted, women were more likely to live alone (odds ratio [OR] 2.33; 95% confidence interval [CI] 1.47 to 3.69), have non-tertiary education (OR 2.69; 95% CI 1.61 to 4.48) and be symptomatic (OR 1.93; 95% CI 1.06 to 3.52).

Conclusion: Health care providers should be cognisant of gender-specific differences in an attempt to individualise and, hence, optimise the management of patients with chronic AF and reduce potential morbidity and mortality.

Introduction

Combating cardiovascular disease (CVD) in women, in all its forms, represents an ongoing challenge [1] – from acknowledging its wider impact from a population burden perspective (it remains the single largest cause of death in women [1]) to formulating a robust evidence-base for those affected. In both low-to-middle [2,3] and high-income countries [3], the natural history of CVD and age profile of affected women are typically different from their male counterparts. This requires careful interpretation of key clinical trials of new treatment strategies where women are almost always in the minority [4,5]. Underlying gender-based differences in the pattern and outcomes of CVD presentations are complex; ranging from intrinsic drivers such as anatomic, physiological and genetic factors, to differences in health behaviours, delays in recognising and responding to symptoms, to critical health care factors such as under-utilisation of gold-standard diagnostic tests and treatments [6–8]. The current description of “typical” cardiac symptoms is based primarily on white, middle-aged men and has contributed to misconceptions in clinicians and lay individuals, leading to inaccurate diagnosis and a delay in women seeking treatment [9].

The conundrum of ensuring gender-based equity in outcomes is becoming increasingly evident in relation to atrial fibrillation (AF). Predicted to be the next CVD-related epidemic due to the progressive ageing of the population and successful treatment of
many of its antecedents, it is the most common cardiac arrhythmia observed in clinical practice and accounts for approximately one third of hospitalisations for all arrhythmias [10]. With a current overall population prevalence of 2% to 3%, age-adjusted prevalence rates are higher in males than females [10]. However, the absolute number of women with AF exceeds that of men due to their greater longevity [11,12]. Indeed, after 75 years of age (the median age of AF diagnosis) approximately 60% of individuals with AF are women [13]. Known clinically relevant differences between women and men with AF currently relate only to the prevalence, presentation and outcomes [14–17]. However, fundamental biological differences between women and men relating to the underlying pathogenesis of AF have only just begun to be elucidated.

Study aims

Consistent with the development of chronic heart failure (CHF) management programs to support the application of gold-standard therapeutics, with more equitable recruitment of women into key clinical trials of the same [4], we are applying a systematic approach to risk delineation and optimising management of hospitalised patients with chronic forms of AF. As such, we are undertaking the Standard versus Atrial Fibrillation spEcific managementT study (SAFETY) [18]. We prospectively hypothesised that gender-based differences would exist in the clinical presentation, thrombo-embolic risk and therapeutic management within the cohort of high risk patients hospitalised with a diagnosis of chronic AF screened for and subsequently recruited into SAFETY. We further hypothesised that subject to detailed clinical phenotyping, these differences would have important clinical implications in respect to disease management requirements.

Methods

Ethics statement

Ethics approval was obtained from the Central Northern Adelaide Health Service Ethics of Human Research Committee, Metro South Health Service District Human Research Ethics Committee, Melbourne Health Human Research Ethics Committee, Western Health Office for Research and the ACT Health Directorate Human Research Ethics Committee. Written informed consent was obtained from each study participant prior to study procedures being conducted.

Study setting

The overall purpose and design of SAFETY has been described in greater detail previously [18]. In brief, 335 hospital in-patients with chronic forms of AF were recruited from three tertiary hospitals in Australia. All were subject to comprehensive baseline profiling. Patients were randomised to either usual post-discharge care or a home-based, multidisciplinary, AF-specific intervention designed to reduce morbidity and mortality.

Study participants

A systematic screening program to identify eligible inpatients was conducted at each participating hospital. Patients were approached for recruitment if they were English-speaking, had a documented diagnosis of recurrent paroxysmal (i.e. recurrent episodes by history as documented on ECG), persistent or permanent AF; were living independently in the community or their own home post-hospitalisation; and were able and willing to provide written informed consent to participate. Patients were excluded if they were aged less than 45 years, had a primary diagnosis of valvular heart disease, were scheduled for catheter ablation of their AF, had pre-existing CHF as evidenced by the combination of symptoms indicative of NYHA Class III-IV with a documented left ventricular ejection fraction (LVEF) less than 45%, or had a transient form of AF. Patients with dementia, as assessed on routine evaluations conducted by hospital clinical teams, were also excluded as were patients who were too unwell at the time when testing was attempted.

Data Collection

Baseline profiling

Comprehensive profiling of each patient subsequently enrolled in SAFETY involved the collection of basic socio-demographic, past medical history and current admission data. In addition, questionnaires were administered at the time of recruitment (wherever feasible) to assess lifestyle (i.e. cigarette and alcohol consumption, exercise and sleep habits), health-related quality-of-life (HRQoL – via EuroQol 5-dimension scale [EQ-5D] [19] and Short Form 12 [SF-12] [20]), depression status (via the ARROLL [21] ≥ Centre for Epidemiological Studies Depression Scale [CES-D] [22]) and cognitive function (via the Montreal Cognitive Assessment [MoCA] [23]). Furthermore, a comprehensive profile of each patient’s experiences with AF was derived, including subtype classification, patient-reported symptoms, patient-reported triggers, patient awareness (of AF episodes, symptoms and triggers), previous and current treatment plans. The CHA2DS2-VASc score was used as a risk stratification tool to assess requirements for antithrombotic therapy [24]. For the current research, the CHA2DS2-VASc score was scored from 0-8 (not 0–9 as is the norm) due to the exclusion of patients with chronic heart failure. All questionnaire data were collected prospectively during face-to-face semi-structured interview by trained personnel according to standardised criteria. Self-reported AF profile data was collected utilising an investigator designed interview guide that specifically asked about symptoms experienced and triggers associated with episodes.

Statistical analyses

Where appropriate, descriptive values are presented as mean (± standard deviation [SD]) for continuous variables or a proportion for categorical variables. Differences between women and men were assessed using the chi-square (X²) test for dichotomous variables and independent t-test for normally distributed continuous variables. Age-adjusted comparisons of the socio-demographic, risk and clinical profile of patients were examined with a simple regression model. Only statistically significant odds ratios (ORs) are presented. Data were analysed using SPSS, V.20. A probability value of p<0.05 (two-sided) was considered statistically significant.

Results

Patient screening and recruitment

Figure 1 shows the profile of screened and recruited patients according to gender. Overall, of the 2,438 patients with AF (as a primary or secondary diagnosis) screened for entry into SAFETY across the three hospital study sites, n = 335 (13.7%) were enrolled. Of these, 1,167 (47.9%) were women and 1,271 (52.1%) were men. The mean age of these patients who presented to hospital with AF was 75 years ± 13 years. Women presented, on average, 4 years older than men (77 years ± 13 years versus 73 years ± 13 years, respectively).
Socio-demographic profile
As shown in Table 1, 161 (48.1%) recruited patients were women aged, on average, 5 years older than their male counterparts. Over half of these women were aged 75 years or more compared to just over a third of men in the same age group. In addition, more than half of female patients were currently living alone (as a result of being divorced/separated [4.8%], having been widowed [17.6%] or never being married [2.1%]; *p* < 0.001). Further, the proportion of women who had formal education at a tertiary level was less than half that of male participants.

AF antecedents
As shown in Table 1, women demonstrated a higher mean body mass index (BMI) than men reflecting that, on average, women were classified as “obese” and men as “overweight”. Just over one third of women undertook the recommended levels (specifically for older individuals) of exercise in Australia [25] compared to over half of their male counterparts. Only a minority of women (6%) consumed alcohol at “high risk” levels (considered more than two standard drinks on any one occasion [26]), compared to a quarter of male patients. A similar proportion of women reported currently smoking cigarettes. Over double the proportion of men compared to women reported current cigarette smoking. Self-reported average sleep quality was “poor” according to one third of the female patients; however, the same reports were made by 22% of their male counterparts (*p* = 0.037).

AF-specific profile
Women and men showed a similar pattern of basic AF characteristics (Table 1). Future thrombo-embolic risk, as calculated via the CHA2DS2-VASc score was significantly higher in women than men.

Co-morbidity profile
Gender-based differences in the co-morbidity of the study cohort were also evident (Table 1). Both concomitant coronary artery disease (CAD) and chronic obstructive pulmonary disease (COPD) was more common in men (41.4% versus 24.8% and 20.1% versus 11.2%, respectively). Conversely, it was significantly more common for women to present with co-morbid thyroid dysfunction (previously ruled out as the cause of AF), depression, renal impairment and obesity. Women had more preserved cardiac function as reflected by a higher mean LVEF than men (61.4% ± 10.3% versus 54.4% ± 13.0%; *p* = 0.005). With respect to HRQoL, the only difference was that women had more overall physical limitations (as determined by a lower composite score of the SF-12; *p* < 0.001).
Table 1. Baseline characteristics of females and males hospitalised with chronic AF.

<table>
<thead>
<tr>
<th></th>
<th>Females (n = 161)</th>
<th>Males (n = 174)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Socio-demographic profile</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>74.0±10.3</td>
<td>69.3±11.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥75 years</td>
<td>81 (50.3%)</td>
<td>64 (38.8%)</td>
<td>0.013</td>
</tr>
<tr>
<td>Living alone (%)</td>
<td>82 (50.9%)</td>
<td>50 (28.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tertiary level education obtained (%)*</td>
<td>30 (19.0%)</td>
<td>68 (40.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Employed in unskilled/semi-skilled occupation (%)</td>
<td>89 (71.8%)</td>
<td>73 (48.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>AF-specific profile</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxysmal AF diagnosis (%)</td>
<td>4 (2.5%)</td>
<td>9 (5.2%)</td>
<td>0.203</td>
</tr>
<tr>
<td>Persistent AF diagnosis (%)</td>
<td>140 (87.0%)</td>
<td>149 (85.6%)</td>
<td>0.725</td>
</tr>
<tr>
<td>Permanent AF diagnosis (%)</td>
<td>17 (10.6%)</td>
<td>16 (9.2%)</td>
<td>0.676</td>
</tr>
<tr>
<td>Rate Control (%)</td>
<td>102 (63.4%)</td>
<td>112 (64.4%)</td>
<td>0.847</td>
</tr>
<tr>
<td>Rhythm Control (%)</td>
<td>59 (36.6%)</td>
<td>62 (35.6%)</td>
<td>0.847</td>
</tr>
<tr>
<td>Mean CHA2DS2-VASc score</td>
<td>4±2</td>
<td>3±2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Antecedents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean HR on admission (bpm)</td>
<td>101±34</td>
<td>97±33</td>
<td>0.268</td>
</tr>
<tr>
<td>Mean HR at discharge (bpm)</td>
<td>74±15</td>
<td>75±17</td>
<td>0.883</td>
</tr>
<tr>
<td>Mean BMI (kg/m²)*</td>
<td>30.5±7.9</td>
<td>28.8±5.3</td>
<td>0.033</td>
</tr>
<tr>
<td>Total serum cholesterol (mmol/L)</td>
<td>4.3±1.2</td>
<td>4.1±1.1</td>
<td>0.097</td>
</tr>
<tr>
<td>At least 150 mins moderate intensity exercise per week (%)</td>
<td>58 (36.7%)</td>
<td>95 (55.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>“High risk” alcohol intake (%)</td>
<td>9 (5.9%)</td>
<td>41 (25.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>“Poor” sleep quality (%)</td>
<td>51 (32.3%)</td>
<td>37 (22.0%)</td>
<td>0.037</td>
</tr>
<tr>
<td>Current cigarette smoker (%)</td>
<td>112 (7.6%)</td>
<td>32 (18.8%)</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td><strong>Co-morbidity profile</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>123 (76.4%)</td>
<td>117 (67.2%)</td>
<td>0.063</td>
</tr>
<tr>
<td>CAD (%)</td>
<td>40 (24.8%)</td>
<td>72 (41.4%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Type 2 diabetes (%)</td>
<td>45 (28.0%)</td>
<td>51 (29.3%)</td>
<td>0.783</td>
</tr>
<tr>
<td>Stroke/Systemic Embolism/TIA (%)</td>
<td>21 (13.0%)</td>
<td>31 (17.8%)</td>
<td>0.228</td>
</tr>
<tr>
<td>COPD (%)</td>
<td>19 (11.8%)</td>
<td>35 (20.1%)</td>
<td>0.039</td>
</tr>
<tr>
<td>Thyroid dysfunction (%)</td>
<td>18 (11.2%)</td>
<td>8 (4.6%)</td>
<td>0.024</td>
</tr>
<tr>
<td>Depression (%)</td>
<td>56 (34.8%)</td>
<td>40 (23.0%)</td>
<td>0.017</td>
</tr>
<tr>
<td>Renal Impairment (eGFR&lt;60 mL/min/1.73 m², %)</td>
<td>70 (43.8%)</td>
<td>47 (27.2%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Obesity (BMI ≥30 kg/m², %)**</td>
<td>69 (49.6%)</td>
<td>59 (37.3%)</td>
<td>0.033</td>
</tr>
<tr>
<td>Mean LVEF (%)</td>
<td>61.4±10.3%</td>
<td>54.4±13.0%</td>
<td>0.005</td>
</tr>
<tr>
<td>Mean MoCA score</td>
<td>23±4</td>
<td>23±4</td>
<td>0.828</td>
</tr>
<tr>
<td>Mean SF-12 HRQoL PCS</td>
<td>34.7±11.5</td>
<td>40.6±11.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean EQ-5D PCS</td>
<td>49.3±11.9</td>
<td>50.7±10.8</td>
<td>0.264</td>
</tr>
<tr>
<td><strong>Treatment profile</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta Blocker (%)</td>
<td>77 (47.8%)</td>
<td>88 (50.6%)</td>
<td>0.615</td>
</tr>
<tr>
<td>Digoxin (%)</td>
<td>64 (39.8%)</td>
<td>53 (30.5%)</td>
<td>0.075</td>
</tr>
<tr>
<td>Anti-arrhythmic (%)</td>
<td>51 (31.7%)</td>
<td>50 (28.7%)</td>
<td>0.558</td>
</tr>
<tr>
<td>Diuretic (%)</td>
<td>84 (52.2%)</td>
<td>55 (31.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Warfarin (%)</td>
<td>87 (54.0%)</td>
<td>99 (56.9%)</td>
<td>0.599</td>
</tr>
<tr>
<td>Aspirin only (%)</td>
<td>75 (46.6%)</td>
<td>86 (49.4%)</td>
<td>0.603</td>
</tr>
<tr>
<td>Aspirin plus Clopidogrel (%)</td>
<td>29 (18.0%)</td>
<td>33 (19.0%)</td>
<td>0.822</td>
</tr>
<tr>
<td>Premature discontinuation of anti-thrombotic therapy (%)</td>
<td>40 (24.8%)</td>
<td>45 (25.9%)</td>
<td>0.831</td>
</tr>
</tbody>
</table>

*Assessed in n=325 patients; † Assessed in n=276 patients; ‡ Assessed in n=297 patients; § Assessed in n=328 patients; * defined as consumption of >2 standard drinks on any occasion (on average).

AF = Atrial Fibrillation; CHA2DS2-VASc score definition: C = congestive heart failure/LV dysfunction (1 point), H = hypertension (even if treated; 1 point), A2 = age ≥75 years (2 points), D = diabetes mellitus (1 point), S2 = stroke/SE/TIA (2 points), V = vascular disease (1 point), A = age 65–74 years (1 point), Sc = sex category (female sex; 1 point).
Table 1. Cont.

| Point | HR = Heart Rate; bpm = beats per minute; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; BMI = Body Mass Index; HDL = High Density Lipoprotein; LDL = Low Density Lipoprotein; CAD = Coronary Artery Disease; PVD = Peripheral Vascular Disease; TIA = Transient Ischaemic Attack; COPD = Chronic Obstructive Pulmonary Disease; eGFR = estimated Glomerular Filtration Rate; LVEF = Left Ventricular Ejection Fraction; MoCA = Montreal Cognitive Assessment; SF-12 = Short Form 12 Items questionnaire; HRQoL = Health-Related Quality of Life; PCS = Physical Composite Score; MCS = Mental Composite Score; EQ-SD = EuroQol Five-Dimensional questionnaire; INR = International Normalised Ratio.

Discussion

Given parallel issues relating to high levels of morbidity and mortality, there remains a paucity of studies examining the potential impact of AF-specific management programs with the potential to deliver equivalent improvements in health outcomes similar to those applied to patients with CHF [4]. Like the seminal trials of CHF management programs, there is the potential to address critical gender imbalances in developing evidence-based therapeutics; via the same pattern of recruiting older, more complex and more gender-balanced study cohorts who more accurately reflect real-world patient populations. With the notable exception of the earliest report of AF-specific management from our group [27], and the largest AF-specific management trial to date (involving 712 patients) [28], SAFETY represents one of the largest studies of its kind. In this detailed examination of the SAFETY cohort from a gender-specific perspective, we can not only confirm a more even balance of men and women consistent with the broad epidemiology of AF that contrasts with key clinical trials, but some important differences that will likely influence individualised management. As represented by Figure 3, the “typical” demographic and clinical profile of female and male patients in the SAFETY cohort (and by inference the wider AF patient population) is markedly different. Of particular interest, in our cohort, typically older women were more socially isolated and less educated. While this is not surprising given the social history of Australia (as with many other countries), these factors have potentially important implications for disease-specific knowledge, symptom recognition and seeking medical assistance. Furthermore, we have recently highlighted the critical importance of mild cognitive impairment in older individuals with AF, recommending systematic screening to determine those at risk and/or requiring modification to any educational programs, although this applies equally to women and men [29].

Our findings are consistent with those of other studies reporting that women with AF were older, had a higher symptom burden, had poorer HRQoL, were more likely to be treated with diuretics, had an increased prevalence of hypertension, and that men with AF had a higher prevalence of CAD [14-17]. The Symptom Mitigation in Atrial fibrillation (SMART) Study by Goli et al. showed that patients with severe AF symptoms were more likely to be female and less educated [30]. The current study provides an extension to previous data by identifying additional socio-demographic, lifestyle, clinical and therapeutic factors of potential importance to longer-term health outcomes and individualised management. When considering AF-specific management studies, some potentially influential differences between the cohorts exist. Age profiles of the nurse-led care and usual care cohorts of the AF-Clinic study conducted by Hendriks et al. comprising 44.7% and 37.9% females, were 66±13 years and 67±12 years, respectively [28]. Female and male patients in the current study were 7–8 years and 2–3 years older than participants of AF-Clinic, respectively. Furthermore, patients of the current research were high-risk, hospitalised patients unlike the healthier participants recruited by Hendriks et al. within primary care clinics [26].

Treatment profile

Nominate rate or rhythm control of underlying AF was similar for men and women (approximately 64% for rate and 36% for rhythm, p=0.047 for both) and this was reflected in the most commonly prescribed medications (beta blockers, digoxin or anti-arrhythmic) to achieve therapeutic goals in AF. Despite increased thrombo-embolic risk in women, there were no discernible differences in anti-thrombotic use (warfarin, aspirin alone or in combination with clopidogrel) between the sexes. When anti-thrombotic therapy was further assessed, approximately 25% of both sexes reported permanent and persistent treatment discontinuation due to, most commonly, a procedure requiring therapy withdrawal (7.5% versus 12.1% for women versus men; p=0.157), their physician’s decision (6.2% versus 5.7%; p=0.858) or a bleeding episode (6.8% versus 4.0%; p=0.255). Finally, it was significantly more common for women to be prescribed diuretic therapy than for men (52.2% versus 31.6%; p<0.001).

Symptom and trigger profile

There were gender-related differences present in AF symptoms self-reported by patients. Of the more typical symptoms commonly described by patients relating to the presence of AF (or rapid AF) for those with permanent AF, significantly more women than men reported fatigue or lethargy (56.5% versus 44.3%; p=0.025), palpitations or “fluttering” (63.4% versus 38.5%; p<0.001) and weakness (43.5% versus 29.9%; p=0.010). Alternatively, no gender-based differences were observed in respect to self-reported triggers of AF (stress, overexertion, illness, medications or alcohol).

Age-adjusted comparisons of women and men

Figure 2 provides a summary of age-adjusted comparisons of the demographic and clinical characteristics of women and men. From a demographic perspective, women were more than twice as likely to live alone and were nearly six times more likely to be a widow. In addition, women were almost three times more likely to have non-formal tertiary education and to have worked in an unskilled/semi-skilled occupation (i.e. clerical/ administration/ community worker/ personal/ customer service/ labourer). Clinically, women were approximately twice as likely to experience symptomatic AF (particularly palpitations, weakness and fatigue), have a high thrombo-embolic risk (indicated by a CHA2DS2-VASc score of 3 or more), be classified as obese and have renal impairment, but no medical history of CAD or COPD. Furthermore, stress was the most likely trigger of an episode of AF (or rapid AF) in double the proportion of women to men. With regard to lifestyle factors, women were almost 4.5 times more likely to consume alcohol at “low risk” levels, twice as likely to be a non-smoker and twice as likely to be receiving diuretic therapy.
Common identification of gender-related diversity may potentially reflect different pathways of development and/or promotion of AF between the sexes. From the current data, it appears that the pathway to AF in men is related to CAD and/or ischaemic heart disease. However, for women, AF was more commonly associated with co-morbid conditions (hypertension, obesity, thyroid and renal dysfunction). It is also possible that women experience AF differently to their male counterparts. Historically, oestrogen was implicated as the cause of the gender-related diversity in CVD and extensive observational data supported this theory. However, recent prospective clinical trials have shown that oestrogen therapy alone or in combination with progestin does not protect from CVD or stroke and may even be harmful [31,32]. Electrophysiological differences throughout the atrial tissue (e.g. in the atrial effective refractory period) and hormonal differences are now suggested as potential mechanisms [6]. More broadly, differences in serum cholesterol, BMI and diabetes prevalence being responsible for approximately 50% of the gender-related disparity between women and men with CVD have also been described [33]; a similar relationship could be assumed for AF. The

![Figure 2. Age-adjusted differences in the profile of women (versus men) recruited into SAFETY. doi:10.1371/journal.pone.0065795.g002](image-url)
prescription of evidence-based treatment strategies may also be influenced by the gender of the presenting individual [6]. Here, we have described the influence of gender on gold-standard antithrombotic AF-treatment; women are at higher thrombo-embolic risk, yet treatment regimens remain no different to those of men. Further, women experience a greater symptom burden, indicating that standards for rate (or rhythm) control may also show gender inequality. It is also possible that the involved therapeutic regimens required for AF management may be too complex to be optimised for typically less educated women with a small (if existent) support network.

The differences identified in the current research have important clinical implications for the management of patients with AF based on their gender. Utilising more specific factors to formulate and deliver individualised disease management programs may enable improvement of clinical outcomes. A higher symptom burden identified in women suggests the need for increased education into symptom recognition and clinical impact, ensuring that help is sought as early as possible before major deterioration. To this end, design and delivery of educational programs targeted at assisting patients to develop an inventory of skills relating to when to seek medical attention is essential. Women are at greater risk of AF-related complications due to being older at presentation, more clinically complex and at greater thrombo-embolic risk than their male counterparts within the context of similar prescription and delivery of AF-specific therapeutic regimens. Difficulty in interpreting the severity of symptoms of acute coronary syndrome was shown to be most predictive in female patients who delay seeking care [34]. Confusion in symptom identification, interpretation and perception and their vulnerability to heart disease by women and health care professionals has led to a delay in seeking care for cardiac problems that can reduce the success of treatment or prevent the use of some interventions [35]. Increasing knowledge of different patients’ experiences of AF would allow for education to be adjusted accordingly with the ultimate aim of preventing readmissions and longer-term morbidity and mortality.

Awareness of specific gender-related differences is critical when applying disease management programs that include examining the effectiveness of newly developed therapeutics for the medical management of chronic diseases. As clinical trials inform the advancement of clinical practice, it is useful to understand the ready application of results from recent positive trials in patients with AF to patients in “real world” clinical practice. Comparison of “real world” AF patients with clinical trial cohorts shows that clinical differences may have implications for balancing benefit and risk when applying standardised therapies to high risk AF patients. Differing from recent clinical trial cohorts, SAFETY is most reflective of the true ratio of high risk women to men with AF who present to hospital [see Table 2]. It is likely that gender-based differences in AF will be exacerbated in the next decade or more; for example, in Australia it is predicted that there will be equal

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**Figure 3. Typical socio-demographic and risk profiles of women versus men with chronic AF in the SAFETY cohort.**

doi:10.1371/journal.pone.0065795.g003
numbers of females aged <5 years as those >80 years (far outnumbering equivalent aged men). Much research is still required to complete the picture of the physiology behind gender-specific differences in patients with AF; the current research contributes somewhat to its elucidation. It will also be important to learn if these differences extend beyond hospitalisation. Confirmation of gender-specific differences in patients with chronic AF highlights a need to identify and accommodate differences into disease management programs. Otherwise, clinical outcomes may be compromised. Awareness of key gender-specific differences in AF allows for formulation and delivery of a safer, more effective and individualised approach to clinical management with patient stratification into well-known risk groups.

There are a number of limitations that require comment. Firstly, the respective cohorts of women and men analysed are relatively small and focused only on those who are high risk and have been hospitalised in Australia (with its hybrid universal health/private health care system). Therefore, findings from the current research may not be readily applicable to all women and men with AF in different countries and health care settings. Further, the cohort consists of those who are acutely ill, potentially exaggerating clinical stability and affecting generalisability of the findings. Exclusion of non-English speaking individuals into the study may have introduced selection bias, although English competency is necessary for comprehensive understanding of the many questionnaires administered. Furthermore, the often chaotic acute clinical setting under which the initial comprehensive assessment was conducted in addition to the patients’ altered health state may not represent an ideal testing situation. Despite the selection of a “real world” cohort, we cannot discount the possibility of bias in study selection (perhaps still under-representing females despite screening data) and these data may not readily apply to other hospitalised cohorts.

Whether observed differences in this cohort (particularly in respect to treatment) translate to differential health outcomes is still unknown (study follow-up will be complete in late 2013). Despite these limitations, these data have important clinical implications for the post-discharge management of patients with chronic AF.

**Conclusion**

Gender differences identified in high risk individuals hospitalised with chronic AF must be recognised as valid stratifying features for the treatment and prevention of poorer health outcomes in this patient group. Health care providers should be cognisant of these defining features in an attempt to individualise and, hence, optimise the management of patients with chronic AF and reduce potential morbidity and mortality.

**Author Contributions**

Conceived and designed the experiments: JB MJC SS. Performed the experiments: JB MJC SS. Analyzed the data: JB MJC SS. Contributed reagents/materials/analysis tools: JB MJC SS. Wrote the paper: JB MJC KAW SS.

**References**


Chapter 5: Gender – an inherent factor with the potential for use in risk delineation

Summary

The research findings presented in this peer-reviewed manuscript have important implications for the requirements of disease management of patients with chronic AF. Specific gender-based differences in the clinical presentation, thrombo-embolic risk and therapeutic management have been identified that are critical to implementing effective management strategies. Women with AF in this cohort (and by inference, the wider AF population) appear to be socially, clinically and treatment disadvantaged. In this cohort at least, they were less educated, had smaller (if any) social networks that can aid management practices, were older, and more clinically complex than their male counterparts. Perhaps reflecting the male bias of clinical trials of anti-thrombotic agents, despite elevated risk of thrombo-embolism, women were more likely to be treated less intensively and according to current gold-standards. There were also higher levels of depression and lower HR-QoL identified in the women of this cohort; both of which, if true in the wider AF population, can adversely impact disease-specific knowledge, symptom recognition and poorer health outcomes. Women affected by chronic AF, therefore, may require specifically designed educational programs as a component of management in addition to increased surveillance and support. This research also reinforces the potential of SAFETY to address key gender disparities by recruiting a more gender-balanced cohort that reflects the real-world patient population and allows for the successful assessment of an AF-specific management program which includes examining the effectiveness of new therapeutics.

Specific biological and physiological differences between women and men relating to the pathogenesis of AF still remain to be fully elucidated. It must be noted, therefore, that when analysing the demographic and co-morbidity profile of patients with AF, it is difficult to determine the influence of each identified gender-specific factor on the development and progression of AF. It is also difficult to determine whether AF is the cause or the result of these factors.

In conclusion, these data remind clinicians to be cognisant of potentially important gender-specific differences when treating patients with chronic AF. Furthermore, assessment of certain factors identified should be undertaken in order to enhance
profiling of patient risk and allow the classification of female and male patients into known risk categories to individualise and, therefore, optimise AF management. Disregarding gender-based differences in patients with AF or failing to adjust management according to identified diversity could potentially result in poorer patient outcomes.
Chapter 6

Mild cognitive impairment (MCI) in chronic AF – an acquired factor with the potential for use in risk delineation
Chapter 6 describes high levels of mild cognitive impairment (MCI), in the SAFETY cohort of typically old individuals hospitalised with a chronic form of AF. MCI may not be readily recognisable but can have significant influence on patient self-management and health outcomes. The role of cognitive profiling as an important method for enhancing risk delineation in patients with chronic AF is also discussed: this includes the application of the easy-to-use Montreal Cognitive Assessment (MoCA) as a screening tool for all patients hospitalised with chronic AF.

This chapter includes the following peer-reviewed and published report and Letter-to-the-Editor:


Declaration for Thesis Chapter 6

Declaration by candidate

In the case of Chapter 6, the nature and extent of my contribution to the work was the following:

<table>
<thead>
<tr>
<th>Nature of contribution</th>
<th>Extent of contribution (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conception and design, acquisition of data, analysis and interpretation of data; drafting of the article and revision; final approval of the version to be published.</td>
<td>65%</td>
</tr>
</tbody>
</table>

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

<table>
<thead>
<tr>
<th>Name</th>
<th>Nature of contribution</th>
<th>Extent of contribution (%) for student co-authors only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Melinda J. Carrington</td>
<td>Conception and design, interpretation of data; drafting of the article and revision; final approval of the version to be published.</td>
<td>N/A</td>
</tr>
<tr>
<td>Professor Simon Stewart</td>
<td>Conception and design, interpretation of data; drafting of the article and revision; final approval of the version to be published.</td>
<td>N/A</td>
</tr>
</tbody>
</table>
The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate’s and co-authors’ contributions to this work.

<table>
<thead>
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Preface

It is well-known that mild cognitive impairment (MCI) is common over a wide spectrum of cardiovascular disorders, including AF, and has important clinical implications [Eggermont et al., 2012]. The most common deficit detected is in executive functioning (a cognitive process that allows the organisation of thoughts and activities, prioritisation, efficient time-management and decision making) which is crucial for the self-management of chronic diseases [Naik et al., 2009; Eggermont et al., 2012]. AF has been identified as an independent predictor of cognitive impairment in a number of research studies [Ott et al., 1997; Kilander et al., 1998; Knecht et al., 2008]. However, the burden and potential impact of MCI is often disregarded in patients with AF, due to the non-specific nature of signs and symptoms and particularly if patients have not experienced a related cerebrovascular event. Overlooking cognitive impairment in these patients may potentially result in poorer outcomes, as AF is a heterogenous condition requiring strict compliance to complex treatment regimens. Furthermore, patients with MCI may have difficulty in the ability to undertake effective self-management. This is concerning given the heavy reliance on appropriate patient self-care for the successful management of AF. In addition, inadequate self-care has previously been identified as a major contributor to hospital readmissions and poorer outcomes of cardiac patients [Schwarz & Elman, 2003].

Although it is difficult to define cause and effect of AF and MCI, it is important to understand patient cognitive status and the consequences that can result from an altered cognitive state. AF-specific interventions can, therefore, be designed to focus on strengthening or accommodating the areas of cognition that are most commonly affected. In the shorter term, if cognitive dysfunction is identified, increased patient surveillance and immediate support can be triggered. To this end, the value of MCI screening as an enhanced risk delineation strategy for the assessment of hospitalised patients with AF was investigated as part of this research program. The extent of MCI in the SAFETY trial cohort (comprising non-demented patients) using the Montreal Cognitive Assessment (MoCA) tool [Nasreddine et al., 2005] (see Appendix IV) was determined and the value of integrating MCI screening into AF management programs
to inform individual requirements for post-discharge care was evaluated. Independent predictors of MCI were also identified.
Mild cognitive impairment in high-risk patients with chronic atrial fibrillation: a forgotten component of clinical management?

Jocasta Ball,1,2 Melinda Jane Carrington,1,2 Simon Stewart,1,2

ORIGINAL ARTICLE

ABSTRACT

Objective We examined cognitive function in older hospitalised patients with chronic atrial fibrillation (AF).

Design A prospective substudy of a multicentre randomised trial of an AF-specific disease management intervention (the Standard versus Atrial Fibrillation specific management study; SAFETY).

Setting Three tertiary referral hospitals within Australia.

Patients A total of 260 patients with chronic AF: mean age 72±11 years; 53% men; mean CHA2DS2-VASc score 4±2.

Interventions Cognitive function was assessed at baseline (during inpatient stay) using the Montreal Cognitive Assessment (MoCA).

Main Outcome Measures The extent of mild cognitive impairment (MCI—defined as a MoCA score <26) in AF patients and identification of independent predictors of MCI.

Results Overall, 169 patients (65%, 95% CI 59% to 71%) were found to have MCI at baseline (mean MoCA score 21±3). Multiple deficits in cognitive domains were identified, most notably in executive functioning, visuospatial abilities and short-term memory. Predictors of MCI (age and sex-adjusted) were lower education level (technical/trade school level OR 6.00, 95% CI 2.07 to 17.42; <8 years school education OR 5.29, 95% CI 1.95 to 14.36 vs 8–13 years), higher CHA2DS2-VASc score (OR 1.46, 95% CI 1.23 to 1.74) and prescribed digoxin (OR 2.19, 95% CI 1.17 to 4.10).

Conclusions MCI is highly prevalent amongst typically older high-risk patients hospitalised with AF. Routine assessment of cognitive function with adjustment of clinical management is indicated for this patient group.

BACKGROUND

With a reported population prevalence of 1–2%, atrial fibrillation (AF) is the most common sustained cardiac arrhythmia seen in clinical practice.1 The numbers of cases are predicted at least to double by 20502 as the key pathways to AF (including advancing age, chronic forms of cardiovascular disease, hypertension and obesity/metabolic disorders) reach historically high levels. From an individual perspective, AF (in all its forms) confers an independent 1.5–fold risk of death in the longer term2 with close links to ischaemic stroke (3–5-fold risk),3 heart failure (up to 50% develop AF)4 and acute coronary syndromes (AF (usually paroxysmal) is documented in almost 25% of patients who present to hospital during ischaemic/postischaemic episodes).5 As such, there is a challenge to improve clinical management and subsequent health outcomes.

Despite a growing body of literature, an often forgotten component of the burden of AF, with important clinical implications, is cognitive impairment and vascular dementia. In fact, the prevalence and influence of cognitive impairment is considerable across a wide spectrum of cardiac diseases, with deficits most notably identified in execution functioning.6 A number of studies (predominantly using the mini-mental state examination; MMSE) have identified AF as an independent predictor of cognitive impairment.7–9 Moreover, the prevalence of cognitive impairment in both community dwelling and hospitalised individuals with AF is reported to be approximately 26–51%.8–9 Although the pathways to cognitive impairment in AF are not fully understood, in those individuals with AF suffering from concurrent stroke or transient ischaemic attack (TIA), 15–26% have signs of one or more silent cerebral infarcts on computed tomography.10–11 Furthermore, AF is regarded as a common cause of white matter low attenuation, most likely due to cerebral hypoperfusion.12 In comparison, population-based studies of ‘healthy’ individuals aged 60–64 years suggest the underlying prevalence of cognitive impairment is a far lower figure of approximately 4%.13 In healthy individuals older than 65 years of age, equivalent prevalence estimates rise to 10–20%.14

Due to the clinical heterogeneity and treatment complexities of AF, careful and balanced management is required to prevent known adverse effects. Individuals with AF and even forms of mild cognitive impairment (MCI) should be considered at higher risk of poorer health outcomes due to the potentially complex requirements of self-managing therapies with narrow therapeutic margins. As such, strict and effective adherence to clinical routines and required treatments is influenced by MCI, potentially impairing a patient’s capacity to plan, sequence and carry out tasks associated with AF management/self-care, diminishing a patient’s ability to participate in decisions surrounding their medical care and/or determine if they are at high risk of a serious clinical event (eg, a haemorrhagic stroke).

STUDY OBJECTIVE

We sought to determine the extent of MCI in a cohort of typically older and non-demented
patients hospitalised with a diagnosis of chronic AF. We hypothesised that the prevalence of MCI would be high in this cohort.

METHODS
Study setting
As part of a systematic approach to risk delineation and optimising the management of hospitalised patients with chronic forms of AF, we are undertaking the Standard versus Atrial Fibrillation speCific managemenT studY (SAFETY). The overall purpose and design of SAFETY has been described in greater detail previously. In brief, 335 non-demented patients with chronic forms of AF (see table 1) were randomly assigned into this study and all were subject to comprehensive baseline profiling. Patients were randomly assigned to either usual post-discharge care or a home-based, multidisciplinary, AF-specific intervention designed to reduce morbidity and mortality.

Wherever feasible, we prospectively measured cognitive function using the Montreal Cognitive Assessment (MoCA) tool that was designed to be more sensitive and specific to MCI. The MoCA was applied at the point of recruitment in hospital to all eligible patients. Ethics approval was obtained from the Central Northern Adelaide Health Service Ethics of Human Research Committee, Metro South Health Service District Human Research Ethics Committee, Melbourne Health Human Research Ethics Committee, Western Health Office for Research and the ACT Health Directorate Human Research Ethics Committee. Written informed consent was obtained from each study participant before study procedures were conducted.

Participants
A systematic screening programme to identify eligible inpatients was conducted at each participating hospital. Patients were approached for recruitment if they had a documented diagnosis of recurrent paroxysmal (ie, recurrent episodes by history as documented on ECG), persistent or permanent AF; were living independently in the community or their own home post-hospitalisation; and were able and willing to provide written informed consent to participate. Patients were excluded if they were aged less than 45 years, had a primary diagnosis of valvular heart disease, were scheduled for catheter ablation, had pre-existing chronic heart failure (CHF) as evidenced by the combination of symptoms indicative of New York Heart Association class III–IV with a documented left ventricular ejection fraction less than 45%, or had a transient form of AF. Patients determined to be demented, as assessed on routine evaluations conducted by hospital clinical teams, were also excluded.

Data collection
Baseline profiling
A comprehensive range of sociodemographic and clinical data were collected at baseline. This included basic demographic characteristics (age and sex), education (level of education completed and number of years), subtype of AF, comorbid conditions and CHA2DS2-VASc score to identify those at very high thromboembolic risk (with a score ≥3). The CHA2DS2-VASc score is validated risk stratification tool used to assess the thromboembolic risk of individuals with AF and indicates antithrombotic therapy requirements. The scoring of eight criteria contributes to the final score of 0–9. Each criterion accounts for one or two points: congestive heart failure or left ventricular dysfunction (one point); hypertension (one point); age 75 years or greater (two points); diabetes mellitus (one point); stroke/TIA/systemic embolism (two points); vascular disease (one point); age 65–74 years (one point); sex category (one point if a woman). Assessment of cognitive function
The MoCA is a validated screening tool for cognitive dysfunction that is administered during in-person interview in the clinical setting. The MoCA is designed to delineate MCI patients from those with normal cognition with a greater predictive value than the MMSE. Scoring ranges from 0 to 30 and a score of less than 26 is indicative of MCI. Six domains of cognitive function are assessed using the MoCA: executive functioning, visuospatial abilities, language abilities, short-term memory, sustained attention and orientation. Adjustment is made for obtaining a formal education of 12 years or less. Personnel conducting the MoCA were trained according to standardised

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Summary of cognitive function in SAFETY participants at baseline (in hospital)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (n=260)</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>72±11</td>
</tr>
<tr>
<td>Aged &lt;65 years (%)</td>
<td>68 (26%)</td>
</tr>
<tr>
<td>Aged 65–74 years (%)</td>
<td>79 (30%)</td>
</tr>
<tr>
<td>Aged ≥75 years (%)</td>
<td>113 (44%)</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>137 (53%)</td>
</tr>
<tr>
<td>Mean CHA2DS2-VASc score (±SD)</td>
<td>4±2</td>
</tr>
<tr>
<td>Education &lt; secondary school*</td>
<td>80 (31%)</td>
</tr>
<tr>
<td>Mean MoCA score (±SD)</td>
<td>23±4</td>
</tr>
<tr>
<td>AF subtype</td>
<td>Paroxysmal (%)</td>
</tr>
<tr>
<td>Persistent (%)</td>
<td>224 (86%)</td>
</tr>
<tr>
<td>Permanent (%)</td>
<td>26 (10%)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>Hypertension (%)</td>
</tr>
<tr>
<td>CAD (%)</td>
<td>84 (32%)</td>
</tr>
<tr>
<td>Type 2 diabetes (%)</td>
<td>67 (26%)</td>
</tr>
<tr>
<td>Stroke/TIA (%)</td>
<td>41 (16%)</td>
</tr>
<tr>
<td>Vascular disease (%)</td>
<td>15 (6%)</td>
</tr>
<tr>
<td>Excessive alcohol intake (%)†</td>
<td>43 (17%)</td>
</tr>
<tr>
<td>CHA2DS2-VASc score ≥3 (%)†</td>
<td>185 (71%)</td>
</tr>
<tr>
<td>Prescribed therapies</td>
<td>Anti-coagulant (%)</td>
</tr>
<tr>
<td>Clopidogrel+aspirin (%)</td>
<td>46 (18%)</td>
</tr>
<tr>
<td>Aspirin only (%)</td>
<td>126 (49%)</td>
</tr>
<tr>
<td>Diblozin (%)</td>
<td>92 (35%)</td>
</tr>
<tr>
<td>β-Blocker (%)</td>
<td>130 (50%)</td>
</tr>
<tr>
<td>Anti-arrhythmic (%)</td>
<td>69 (27%)</td>
</tr>
</tbody>
</table>

For the current research, the CHA2DS2-VASc score is scored from 0 to 8 (not to 9 as is the norm) due to the exclusion of patients with chronic heart failure.

*Assessed in n=257; †More than two standard drinks on any occasion. Assessed in n=250 patients.

AF, atrial fibrillation; CAD, coronary artery disease; MCI, mild cognitive impairment; MoCA, Montreal Cognitive Assessment; SAFETY, Standard versus Atrial Fibrillation speCific managemenT studY; SE, systemic embolism; TIA, transient ischaemic attack.

criteria relating to questionnaire administration, question delivery and scoring. Given recent suggestions that a MoCA score less than 24 increases specificity for MCI without impacting on sensitivity (albeit in a younger cohort of individuals with a much lower prevalence of MCI than expected in the SAFETY cohort), we compared the two cut-off scores (<26 vs <24) to generate a more conservative prevalence estimate in this cohort.

From a total of 335 SAFETY participants, 260 (78%) were administered the MoCA at baseline (during inpatient stay) to assess cognitive function. For the purpose of this substudy, individuals whose primary language was not English (n=17, 5%) were excluded on the basis of language proficiency affecting MoCA responses, and those who were too unwell at the time when testing was attempted were also excluded (n=58, 17%).

Statistical analyses
Descriptive values are presented as mean (±SD) for continuous variables or a proportion for categorical variables. Unadjusted odds ratios (ORs) with 95% confidence intervals (CIs) compared education, AF subtype and comorbidities between patients with and without MCI. Multivariate analyses to determine independent correlates of MCI (referred to here as predictors) were examined with a stepwise linear regression model and adjusted for age, sex, AF subtype, high-risk alcohol use, comorbid conditions (hypertension, type 2 diabetes, cerebrovascular disease, coronary artery disease; CAD) and ‘new AF’ diagnosis (ie, first diagnosis of a chronic form of AF (recurrent paroxysmal, persistent or permanent) not related to a transient physiological state). Further categorisation and analysis of CHA2DS2-V ASc scores was undertaken to understand which score(s) confers the independent association with MCI. Data were analysed using SPSS, V20. A probability value of p<0.05 (two-sided) was considered statistically significant.

RESULTS
Baseline profile
The baseline patient profile (n=260) is presented in table 1 according to the presence/absence of MCI (cut-off MoCA score <26). Overall, 137 (53%) participants were men with a mean age of 72±11 years (more patients with MCI were aged ≥75 years; p<0.01) and 80 (31%) had 12 years or less of formal education. The majority of participants assessed for MCI had persistent AF (n=224; 86%) with 185 (71%) recording a CHA2DS2-V ASc score of 3 or greater, indicating a high inherent risk of stroke. The comorbid profile of these patients was extensive: 188 (72%), 84 (32%) and 67 (26%) had hypertension, CAD and type 2 diabetes, respectively. A previous history of stroke/systemic embolism/TIA was present in 41 (16%) patients. AF-specific therapies were prescribed in similar proportions. However, digoxin was significantly more likely to be prescribed to patients displaying MCI (p=0.01).

Baseline cognitive function
The overall mean MoCA score at baseline (prehospital discharge) in this cohort was 23±4; equivalent scores being 21±3 versus 27±1 in those with and without identified MCI, respectively. Overall, 169 patients (65%, 95% CI 59% to 71%), of which 53% were men, recorded a MoCA score less than 26. As shown in table 1, on an unadjusted basis, those with MCI were on average 6 years older than those without MCI (74±10 years vs 68±12 years, p<0.001). A higher proportion of individuals with MCI had less than 12 years of formal education (despite correction for education level). Those classified with MCI also had an increased likelihood of concurrent hypertension (OR 1.61, 95% CI 0.92 to 2.82), CAD (OR 1.67, 95% CI 0.95 to 2.95), type 2 diabetes (OR 1.83, 95% CI 0.98 to 3.41) and stroke/systemic embolism/TIA (OR 1.82, 95% CI 0.85 to 3.91). Consequently, those classified as having MCI also had a higher risk of thromboembolic events with a 2-fold increased likelihood of a higher CHA2DS2-V ASc score of 3 or greater (OR 2.18, 95% CI 1.26 to 3.79).

MoCA sensitivity analyses
When applying a lower (more stringent) MoCA cut-off score of less than 24, the proportion of those classified as MCI fell from 65% (95% CI 59% to 71%; cut-off <26) to 49% (95% CI 43% to 55%). Patients classified with MCI on this basis had a mean age of 75±10 years (only slightly older than the original MCI group) and a mean MoCA score of 20±3 compared to 69±12 years and 27±2 for those without MCI, respectively. In both MCI groups, 53% were men.

Affected cognitive domains
Tables 2 and 3 outline the proportion of patients in each group (with or without MCI) demonstrating paired deficits in each affected cognitive domain at the time of testing, as measured by the MoCA. In both groups, high levels of dysfunction were identified in almost all cognitive domains (most notably in executive functioning, visuospatial and short-term memory domains); however, dysfunction in orientation was only seen in 25% and 2% of individuals with and without MCI, respectively. Overall, deficits were more extensive in those with MCI. In total, only 11 individuals obtained a ‘perfect’ MoCA score of 30.

Predictors of MCI
Table 4 shows the independent predictors of MCI. MCI was more likely in those reporting lower levels of education (including <8 years education or trade qualifications) and in those with a higher CHA2DS2-V ASc score. The odds of MCI increased by 46% for every unit increase in the CHA2DS2-V ASc score. In addition, those prescribed digoxin were more likely to demonstrate MCI. Further analysis of a subgroup of patients (n=32) who had digoxin levels tested at the time of MoCA administration revealed a (non-significant) trend towards those with MCI having, on average, a lower body mass index (28.5±6.6 kg/m²) but higher serum digoxin levels (0.96±0.34 μg/l) in contrast to those without MCI who had, on average, a higher body mass index (30.0±5.7 kg/m²) and lower serum digoxin levels (0.45±0.08 μg/l). Figure 1 shows a more detailed description of the relationship between the CHA2DS2-V ASc score and MCI. An incremental decrease in the MoCA score (ie, an increased likelihood of demonstrating MCI) with higher CHA2DS2-V ASc scores was shown.

DISCUSSION
Consistent with the high potential for cognitive decline and vascular dementia in a typical cohort of 260 older individuals hospitalised with chronic AF, we found that a high proportion of our study cohort (approximately two-thirds) displayed concurrent MCI. Even with a more stringent definition (ie, lowering the qualifying MoCA score to <24) the underlying prevalence of MCI was approximately half. Deficits in executive functioning, visuospatial abilities and short-term memory were common, as were overlapping deficits across multiple cognitive domains. Those found to have MCI were more likely to have lower education levels and the highest thromboembolic risk (primarily calculated on the basis of more advanced age and cardiovascular risk factors) in this cohort was 23±4; equivalent scores being 21±3 versus 27±1 in those with and without identified MCI, respectively. Overall, 169 patients (65%, 95% CI 59% to 71%), of which 53% were men, recorded a MoCA score less than 26. As shown in table 1, on an unadjusted basis, those with MCI were on average 6 years older than those without MCI (74±10 years vs 68±12 years, p<0.001). A higher proportion of individuals with MCI had less than 12 years of formal education (despite correction for education level). Those classified with MCI also had an increased likelihood of concurrent hypertension (OR 1.61, 95% CI 0.92 to 2.82), CAD (OR 1.67, 95% CI 0.95 to 2.95), type 2 diabetes (OR 1.83, 95% CI 0.98 to 3.41) and stroke/systemic embolism/TIA (OR 1.82, 95% CI 0.85 to 3.91). Consequently, those classified as having MCI also had a higher risk of thromboembolic events with a 2-fold increased likelihood of a higher CHA2DS2-V ASc score of 3 or greater (OR 2.18, 95% CI 1.26 to 3.79).
As such, these data confirm previous studies suggesting high levels of cognitive dysfunction in those with AF.8,9 They also represent an important clinical warning, particularly given that the risk factors we identified are frequently seen in those being treated for AF. The role of digoxin, a commonly prescribed drug in the presence of AF, but with clear potential for toxicity, has also been found to occur at levels of serum antifibrinogen.8 They also impair functioning and lower mortality.21 However, cognitive impairment has also been found to occur at levels of serum digoxin that are within the therapeutic range.20,21 In the current study, those with MCI and concurrent digoxin levels had lower body weight but greater digoxin levels, potentially reflecting higher tissue saturation and, thus, digoxin toxicity albeit at a therapeutic level. Recommendations have been made outlining the need for digoxin withdrawal in any patient displaying cognitive symptoms, even when the serum digoxin level is within the normal therapeutic range.20

Our findings are of obvious clinical concern in AF due to the heavy reliance on self-care behaviours crucial to managing this complex chronic disease successfully. Inadequate self-care has been identified as a major contributor to hospital readmission and to the poor outcomes associated with heart failure;23 the same can be assumed for AF. Cause and effect is difficult to delineate, however. Individuals with MCI may have problems performing complex tasks such as preparing meals or paying bills while still being able to perform activities of daily living (and thus maintain a sense of independence).24 The ability to learn and acquire knowledge is also influenced by MCI, and lack of knowledge about chronic disease and self-care has been shown to result in poor self-care maintenance and management behaviours.24 Intact executive functions have been identified as crucial for the management of chronic conditions.26 Impaired executive functioning limits an individual’s ability to recognize symptoms and make decisions related to symptom management.27 These were all factors that influenced the subsequent management of those allocated to the intervention arm of SAFETY—with incremental surveillance and support applied according to a traffic-light classification system28 that ‘titrates’ post-discharge support in this context using more than just clinical parameters to determine an increased risk of suboptimal health outcomes. In this case, the presence of MCI signified a need to modify expectations of ‘self-care’ and increase the role of caregivers and other healthcare providers (eg, incremental community pharmacist support and/or use of medicine reminder tools). Whether this was sufficiently robust in terms of additional support will be a major factor in determining the overall success of the home-based, nurse-led intervention being compared to usual post-discharge care.15

Beyond the impact of the SAFETY intervention, these data have immediate clinical implications. Screening of MCI can and should be used as a risk delineation strategy to add to the suite of risk stratification tools available for the assessment of patients with AF. Pitfalls of therapy, clinical lability or adverse behaviours can be identified and highlighted, triggering increased patient surveillance for those at high risk of instability or events. Increased surveillance is often required to promote treatment adherence and self-care management. In addition, education focussed on addressing peripheral risk factors can be tailored according to individual needs. Furthermore, AF-specific interventions should be focused on strengthening the areas of cognition most commonly affected. In their recent systematic review,

### Table 2
Proportion of patients with MCI (n=169) demonstrating deficits within each cognitive domain

<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>Executive functioning</th>
<th>Visualspatial abilities</th>
<th>Language abilities</th>
<th>Short-term memory</th>
<th>Sustained attention</th>
<th>Orientation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Executive functioning n=155 (92%)</td>
<td>155/155 (100%)</td>
<td>142/155 (85%)</td>
<td>107/155 (63%)</td>
<td>169/169 (100%)</td>
<td>116/169 (69%)</td>
<td>42/42 (100%)</td>
</tr>
<tr>
<td>Visualspatial abilities n=142 (84%)</td>
<td>142/142 (100%)</td>
<td>94/142 (66%)</td>
<td>107/107 (100%)</td>
<td>169/169 (100%)</td>
<td>116/169 (69%)</td>
<td>42/42 (100%)</td>
</tr>
<tr>
<td>Language abilities n=107 (63%)</td>
<td>94/107 (87%)</td>
<td>107/107 (100%)</td>
<td>116/169 (69%)</td>
<td>116/169 (100%)</td>
<td>116/169 (69%)</td>
<td>42/42 (100%)</td>
</tr>
<tr>
<td>Short-term memory n=169 (100%)</td>
<td>107/107 (100%)</td>
<td>75/107 (70%)</td>
<td>116/169 (69%)</td>
<td>116/169 (100%)</td>
<td>116/169 (69%)</td>
<td>42/42 (100%)</td>
</tr>
<tr>
<td>Sustained attention n=116 (69%)</td>
<td>103/142 (73%)</td>
<td>75/107 (70%)</td>
<td>116/169 (69%)</td>
<td>116/169 (100%)</td>
<td>116/169 (69%)</td>
<td>42/42 (100%)</td>
</tr>
<tr>
<td>Orientation n=42 (25%)</td>
<td>32/142 (23%)</td>
<td>30/107 (28%)</td>
<td>42/169 (25%)</td>
<td>42/169 (25%)</td>
<td>42/169 (25%)</td>
<td>42/42 (100%)</td>
</tr>
</tbody>
</table>

The denominator for each cell is the total number of affected individuals displaying deficits in the top domain (column) in addition to displaying deficits in the intersecting domain (row).

MCI, mild cognitive impairment.

### Table 3
Proportion of patients without MCI (n=91) demonstrating deficits within each cognitive domain

<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>Executive functioning</th>
<th>Visualspatial abilities</th>
<th>Language abilities</th>
<th>Short-term memory</th>
<th>Sustained attention</th>
<th>Orientation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Executive functioning n=45 (49%)</td>
<td>45/45 (100%)</td>
<td>36/36 (100%)</td>
<td>6/36 (17%)</td>
<td>27/27 (100%)</td>
<td>16/16 (100%)</td>
<td>1/45 (2%)</td>
</tr>
<tr>
<td>Visualspatial abilities n=36 (40%)</td>
<td>36/36 (100%)</td>
<td>24/36 (67%)</td>
<td>21/27 (78%)</td>
<td>68/68 (100%)</td>
<td>16/16 (100%)</td>
<td>2/36 (67%)</td>
</tr>
<tr>
<td>Language abilities n=27 (30%)</td>
<td>24/36 (67%)</td>
<td>6/36 (17%)</td>
<td>7/27 (26%)</td>
<td>11/68 (16%)</td>
<td>16/16 (100%)</td>
<td>2/27 (26%)</td>
</tr>
<tr>
<td>Short-term memory n=68 (75%)</td>
<td>21/27 (78%)</td>
<td>6/36 (17%)</td>
<td>7/27 (26%)</td>
<td>11/68 (16%)</td>
<td>16/16 (100%)</td>
<td>2/27 (26%)</td>
</tr>
<tr>
<td>Sustained attention n=16 (18%)</td>
<td>10/45 (22%)</td>
<td>0/36 (0%)</td>
<td>0/27 (0%)</td>
<td>2/68 (3%)</td>
<td>0/16 (0%)</td>
<td>2/27 (26%)</td>
</tr>
<tr>
<td>Orientation n=2 (2%)</td>
<td>1/45 (2%)</td>
<td>0/36 (0%)</td>
<td>0/27 (0%)</td>
<td>2/68 (3%)</td>
<td>0/16 (0%)</td>
<td>2/27 (26%)</td>
</tr>
</tbody>
</table>

The denominator for each cell is the total number of affected individuals displaying deficits in the top domain (column) in addition to displaying deficits in the intersecting domain (row).

MCI, mild cognitive impairment.
Table 4  Independent predictors of MCI (age and sex adjusted)

<table>
<thead>
<tr>
<th>Variable</th>
<th>p Value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education level overall</td>
<td>&lt;0.01</td>
<td>1.46</td>
<td>1.33 to 1.60</td>
</tr>
<tr>
<td>Tertiary education (reference)</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary school</td>
<td>0.11</td>
<td>1.79</td>
<td>0.88 to 3.64</td>
</tr>
<tr>
<td>Technical/trade school</td>
<td>&lt;0.01</td>
<td>2.57</td>
<td>1.48 to 4.46</td>
</tr>
<tr>
<td>Primary school</td>
<td>&lt;0.01</td>
<td>1.19</td>
<td>1.15 to 1.24</td>
</tr>
<tr>
<td>CHA2DS2-VASc score (per unit increment)</td>
<td>&lt;0.001</td>
<td>1.46</td>
<td>1.33 to 1.60</td>
</tr>
<tr>
<td>Digoxin treatment vs rest</td>
<td>0.01</td>
<td>1.01</td>
<td>0.97 to 1.05</td>
</tr>
<tr>
<td>Age</td>
<td>0.69</td>
<td>1.01</td>
<td>0.97 to 1.04</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.20</td>
<td>1.49</td>
<td>0.81 to 2.73</td>
</tr>
</tbody>
</table>

MCI, mild cognitive impairment.

Figure 1  Correlation between CHA2DS2-VASc and Montreal Cognitive Assessment (MoCA) scores. This figure is only reproduced in colour in the online version.

Eggermont et al6 suggested that MCI may be addressed simply by optimising cardiac treatment. The incorporation of physical activity programmes into interventions has also been suggested due to positive improvements in cognition observed in patients with CAD and chronic heart failure.6 29 In addition to the screening and detection of MCI, identifying associated independent predictors of lower education level, higher thromboembolic risk and the use of digoxin allows the potential to address or increase surveillance on these peripheral factors in an attempt to prevent the development of MCI and vascular dementia in those who present with AF.

There are a number of limitations that require comment. First, we applied only one clinical assessment tool to assess cognitive function. While the MoCA has been shown to be more sensitive and specific at discerning cognitive deficits than the MMSE, more extensive psychometric testing in addition to the testing of functional capacity would be required to confirm the presence of MCI.18 However, the MoCA could reasonably constitute an initial screening of MCI due to its short length (approximately 10 min) and ease of administration. It is also publicly available for use. The decision to use less than 26 as the cut-off score for defining MCI also influences this research, particularly when such a large decrease in the proportion of classified MCI within this population was observed in the sensitivity analysis. Whether a more stringent cut-off of less than 24 is required for more specific determination of the prevalence in these patients should be the subject of further research. The exclusion of non-English-speaking individuals may have introduced selection bias, although English competency is necessary for comprehensive understanding of the test questions. Furthermore, the often chaotic acute clinical setting under which the MoCA was conducted in addition to the patients’ altered health state may not represent an ideal testing situation. Moreover, the duration and cause of MCI is not known and cannot be distinguished in this cohort. Finally, despite the selection of a ‘real world’ cohort, we cannot discount the possibility of bias in study selection and these data may not readily apply to other hospitalised cohorts.

Despite these limitations, these data have important clinical implications for the post-discharge management of patients with chronic AF. We found that MCI is highly prevalent in typically older patients who have been hospitalised with chronic AF before discharge. Overall, cognitive deficits are abundant in this population. Beyond education levels, MCI correlated with increasing thromboembolic risk and the use of digoxin. In addition, residual levels of MCI remain high in these individuals post-discharge. Therefore, we would recommend that patients with AF should be routinely screened for MCI (as a potential source of risk delineation), and subsequent disease management programmes implemented in the setting of AF (as has been recommended in relation to heart failure management)10 should be modulated if MCI is detected.

CONCLUSION

MCI is common in high-risk patients hospitalised with chronic AF and is potentially related to poorer health outcomes. Assessment of patients with chronic AF should include MCI screening using the MoCA, an easily administered and effective tool that identifies patients for whom more intensive surveillance is required to maintain clinical stability and optimise management.

Contributors All authors contributed to the study design, data analysis, manuscript writing, reviewing and editing.

Funding The SAFETY study is funded by a National Health and Medical Research Council of Australia Programme Grant (519823). In addition, JH, MJC and SS are supported by the National Health and Medical Research Council of Australia. The study was supported in part by the Victorian government’s operational infrastructure support programme. The National Health and Medical Research Council of Australia and the Victorian Government had no involvement in the study design; data collection, analysis and interpretation; or writing or preparation of this manuscript for publication.

Competing interests None.

Ethics approval This study was approved by the human research ethics committee(s) associated with each of the study sites (hospitals).

Patient consent Obtained.

Provenance and peer review Not commissioned; internally peer reviewed.

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Heart rhythm disorders

11 Carrington MJ, Ball J, Horowitz JD, et al. Navigating the fine line between benefit and risk in chronic atrial fibrillation: Rationale and design of the Standard versus Atrial Fibrillation speCific managementT study (SAFETY). Int J Cardiol 2011; In Press.


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Summary

The research findings presented in this peer-reviewed manuscript serve as a critical reminder of the multi-factorial complexity of AF and the consequences that even mild forms of cognitive dysfunction can have on patient management. In analysing the baseline characteristics of high risk patients hospitalised with chronic forms of AF, the prevalence of MCI was extensive (49%-65%) with deficits demonstrated in multiple cognitive domains. These findings confirm data from previous studies assessing cognitive function in AF patients [Kilander et al., 1998; Knecht et al., 2008]. Most notably in the current study, those displaying MCI were less educated (a potential confounder but still of critical importance) and at the highest thrombo-embolic risk. A further important finding was that those with MCI were more likely to be prescribed digoxin – a commonly used therapeutic in the setting of AF. Digoxin toxicity has previously been shown to be associated with mental confusion in older patients [Wofford & Ettinger, 1991; Bauman, Didomenico & Galanter, 2006]. Pertaining to this, in a subset of SAFETY patients for whom digoxin levels were assessed, those with MCI demonstrated higher digoxin levels but lower body weight, potentially indicating digoxin toxicity, albeit at so-called therapeutic levels. However, further research to confirm this finding and establish a physiological mechanism is required. The limitations of this study, beyond the potential confounding of educational status in completing the MoCA, must also be acknowledged, particularly the exclusion of non-English speaking individuals and the less than ideal, often chaotic acute clinical setting under which the MoCA was conducted at baseline. Furthermore, only the MoCA was used as a cognitive function screening tool which is not diagnostic and requires the addition of extended psychometric and functional testing to confirm the presence of MCI.

Abilities such as learning and acquiring knowledge are influenced by MCI. In addition, impaired executive functioning can limit the recognition of symptoms and hinder symptom management decision-making. Due to the known consequences of MCI on disease management and patient outcomes, it is recommended that patients are screened. Therefore, management interventions can be individually developed,
directed and delivered with the awareness of patient cognitive capacity. Furthermore, interventions with the potential for positive improvements in cognition (as described in patients with CAD and CHF [Carles et al., 2007; Eggermont et al., 2012]) can be incorporated into AF-specific programs. For AF patients with intact cognition, the identification of factors associated with MCI and the management of these provides the potential to prevent (or delay) its development. Therefore, screening for MCI in addition to associated peripheral factors may assist in optimising the management of patients with AF via these enhanced methods of risk delineation.

**Postscript**

Online publication (prior to printing) of the manuscript resulting from this research brought awareness to the clinical implications of MCI for AF patients and stimulated significant interest in its findings. Multiple media outlets reported the results and requested comments and interviews with Professor Simon Stewart (SAFETY Principal Investigator). The manuscript was selected as the “Editor’s Choice” for the month of April in *Heart* and a podcast was recorded with Professor Stewart to supplement the publication. Study findings were also discussed as part of an extensive segment on Norman Swan’s Health Report on ABC Radio. Furthermore, an independent and external Letter-to-the-Editor of *Heart* was written in correspondence that questioned the results and selection of the MoCA as an MCI screening tool (see Appendix V). The right-of-reply was provided by the Journal’s editors and the following Letter-to-the-Editor was written and published in response.
We thank O’Caoimh and Molloy for their interest in our recent article published in *Heart.*

We appreciate their support of systematic screening for mild cognitive impairment (MCI) in patients affected by chronic disease in order to best tailor their support and management. Identifying the best and most cost-effective clinical tool in this regard remains a challenge. We note that the authors are intimately involved in developing the Quick MCI Screen (*Qmci*), a tool they suggest is potentially more accurate in diagnosing MCI than the Montreal Cognitive Assessment (MoCA) or even the Mini-Mental State Examination (MMSE).

We certainly welcome alternatives to the MoCA (our main interest being in accurately identifying cognitive impairment in non-demented patients) to improve clinical management. However, we believe from original reports that the *Qmci* requires further development (an acknowledgement also made by the authors themselves) given the methods used to validate the tool (comparison of sensitivity and specificity only) and in specific cohorts used to do so (aged over 55 years with no depression attending the memory clinic setting with convenience sampling used to select controls with ‘normal’ cognition). As acknowledged, there is no gold-standard for diagnosing MCI, although the MoCA and MMSE have been proven to be equal in MCI diagnostic utility in the memory clinic setting.

From a clinical perspective, we know that apparent MCI (as detected via the MMSE) adversely influences health outcomes in chronic heart failure and we suspect the same in atrial fibrillation (regardless of definitive cognitive status). We employ the MoCA because it offers advantages to the MMSE (more sensitive to even mild deficits and more specific) and demonstrates superiority to the MMSE in post-stroke populations.

We have extensive experience in using the MoCA and have found it extremely useful in guiding our disease management programmes as well as determining that MCI is highest among our patients with atrial fibrillation. Our finding of a clear gradient in MoCA scores relative to thrombo-embolic risk is potentially crucial for anti-coagulation management of these patients. As the authors highlight, and as we outlined in the limitations of this research, the acute hospital setting is not ideal to assess MCI in this patient population; however, we have definitive data indicating that MCI (as detected by the MoCA) persists once patients return home as an extension to the current data. Among 132 patients visited at home 7–14 days post-discharge, mean MoCA scores had slightly improved from in-patient assessment (23±4 during hospital visit to 24±4 postdischarge,
p<0.01). Of these patients, 58% (95% CI 50–66%) still displayed MCI at this time-point (MoCA cut-off <26), impacting disease management. Further, self-care was found to be significantly lower in those with MCI than in those without (p<0.05). We will watch with interest the scrutiny of MCI diagnosis and will certainly investigate the use of the Qmci when development is complete. As SAFETY continues, we will be performing repeat measures to assess MCI and determine its prognostic importance and the influence of MCI on optimising the management of patients with atrial fibrillation.

Jocasta Ball,1,2 Melinda J Carrington,1,2 Simon Stewart,1,2 on behalf of the SAFETY investigators

1NHMRC Centre of Research Excellence to Reduce Inequality in Heart Disease, Preventative Health, Baker IDI Heart and Diabetes Institute, Melbourne, Victoria, Australia
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Contributors All authors have contributed to the conception and design, drafting of the text and final approval for submission.

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Competing interests None.

Ethics approval South Australia, Victoria, ACT.

Provenance and peer review Not commissioned; internally peer reviewed.

More definitive determination of rate and rhythm control in AF
Chapter 7 discusses the use of ECG Holter monitoring as a method of further extending risk assessment and delineation of high-risk patients with AF who have recently experienced an acute hospitalisation due to the arrhythmia. A comparison of intended with detected rate and rhythm control post-discharge is undertaken and three potentially predictive phenotypes of heart rate variability are identified. The characteristics of patients in each of these three groups are described.

This chapter includes the following manuscript submitted for peer-review:

Ball J, Carrington MJ, Thompson DR, Horowitz JD, Stewart S. Post-discharge ECG Holter monitoring in recently hospitalised individuals with chronic atrial fibrillation to enhance therapeutic monitoring and identify potentially high risk phenotypes. Submitted 14th November, 2013 to Europace (IF: 2.765).
Declaration for Thesis Chapter 7

Declaration by candidate

In the case of Chapter 7, the nature and extent of my contribution to the work was the following:

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<tr>
<th>Nature of contribution</th>
<th>Extent of contribution (%)</th>
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<tr>
<td>Conception and design, acquisition of data, analysis and interpretation of data; drafting of the article and revision; final approval of the version to be published.</td>
<td>65%</td>
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The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

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<th>Name</th>
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<tr>
<td>Dr Melinda J. Carrington</td>
<td>Conception and design, interpretation of data; drafting of the article and revision; final approval of the version to be published.</td>
<td>N/A</td>
</tr>
<tr>
<td>Professor David R. Thompson</td>
<td>Interpretation of data; drafting of the article and revision; final approval of the version to be published.</td>
<td>N/A</td>
</tr>
<tr>
<td>Professor John D. Horowitz</td>
<td>Interpretation of data; drafting of the article and revision; final approval of the version to be published.</td>
<td>N/A</td>
</tr>
<tr>
<td>Professor Simon Stewart</td>
<td>Conception and design, interpretation of data; drafting of the article and revision; final approval of the version to be published.</td>
<td>N/A</td>
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The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate’s and co-authors’ contributions to this work*.

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Preface

In current medical practice, the continuous ECG Holter monitor is employed as a tool for use in the diagnosis of cardiac arrhythmias. Its use is triggered by symptoms described by a patient presenting to their physician. However, Holter monitoring has the additional potential for extended use as a management tool for cardiac patients with known arrhythmias, including patients with AF, to provide more definitive determination of their rhythm status and success/failure of their treatment plan. It is perhaps most useful (and most cost-effective) in those at high risk for future events or hospitalisation (e.g. patients with a recent hospitalisation related to their arrhythmia). Frequent monitoring of AF rate and/or rhythm control and determination of therapeutic target achievement in AF patients is not routinely undertaken. Often, rate and rhythm control is assessed via standard 12-lead ECG during a follow-up appointment. Holter monitoring can provide extended and detailed information on a patient’s cardiac rhythm and in turn quantify AF burden. This clinical information is particularly useful for a patient’s health care team in the immediate post-discharge period and may alert a treating physician to any adverse events, for example a sustained uncontrolled heart rate.

As part of the comprehensive home visit conducted in all intervention patients within the SAFETY trial cohort at 7 – 14 days post-hospital discharge, a Holter monitor was attached to patients to record cardiac activity for a period of 24 hours. The rationale behind the use of the Holter monitor for this research was to identify whether the intended therapeutic target of rate or rhythm control (nominated during hospitalisation) was being achieved and to identify patients requiring therapeutic intervention or clinical re-assessment if stability was not being achieved. In addition, those who were clinically unstable would be identified sooner, potentially preventing re-presentation to hospital.

For this research, the extent of rate/rhythm achievement (or treatment failure) was determined within the SAFETY intervention cohort. Furthermore, quantification of AF burden and heart rate variability was undertaken. Quantitative assessment of the recordings was also used to develop a novel method for extended risk delineation with
the aim of stratifying patients at different levels of risk and utilising the information to improve patient management.
Post-discharge ECG Holter monitoring in recently hospitalised individuals with chronic atrial fibrillation to enhance therapeutic monitoring and identify potentially high risk phenotypes

Jocasta Ball\textsuperscript{a,b}, Melinda J Carrington\textsuperscript{a,b}, David R Thompson\textsuperscript{c}, John D Horowitz\textsuperscript{d}, Simon Stewart\textsuperscript{a,b}\textsuperscript{*} on behalf of the SAFETY Investigators

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WORD COUNT: 3,528 words (abstract 247 words)
ABSTRACT

Aims: To determine the value of post-discharge ECG Holter monitoring to enhance the management of patients with atrial fibrillation (AF).

Methods: Prospective sub-study of a multicentre randomised controlled trial comparing AF-specific management with usual post-discharge care. Continuous 24-hour ECG Holter monitoring was undertaken in 133 patients 7-14 days post-discharge. Intended rate and rhythm control was compared to ECG Holter data. Analysis of the frequency distribution of mean hour-to-hour differences was also used to identify those with particularly labile heart rates (HR).

Results: Mean age was 71 ± 10 years, 67 (50%) were male and mean hourly HR was 72±14 bpm. Most patients (89%) had persistent AF (median time in AF - 39%, IQR 0, 100%). Uncontrolled HR (>90bpm for >10% of recording) occurred in 35 (26%) patients and 49 (37%) patients did not achieve their intended rate (n=26) or rhythm control (n=23). Those patients in the upper quartile of mean hour-to-hour HR variability were identified as persistently labile (n=33). A further group (n=22) with periodically labile HRs (17%) predominantly during the day were identified. On an adjusted basis, those with coronary artery disease (OR 0.34; 95% CI 0.13 to 0.91, p=0.033) or renal disease/dysfunction (OR 0.24; 95% CI 0.06 to 0.98, p=0.047) were less likely to demonstrate stable HR control (n=78).

Conclusion: Post-discharge ECG Holter monitoring of AF patients represents a valuable tool to identify deviations in intended rhythm/rate control and adjust therapeutic management accordingly. It may also identify particularly high risk individuals who demonstrate labile HRs.

Key words: Atrial fibrillation; Holter monitoring; risk delineation; disease management
**What’s new?**

- ECG Holter monitoring revealed that intended AF rhythm or rate control at hospital discharge was often not maintained within 7-14 days post-discharge, with therapeutic implications for patient management.

- Three distinct Holter phenotypes of variable heart rate control were identified which showed a tendency for patients with a history of coronary artery disease or renal disease to demonstrate more labile heart rate levels over 24 hours.
INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia diagnosed and managed in clinical practice. Previously estimated to affect 1% to 2% of adult populations, recent systematic reviews of published data suggest this figure is actually between 2.5% and 3.5%\(^1\) and potentially as high as 4.0%\(^2\). Moreover, the number of affected adults aged >55 years in Europe is projected to double from 8.8 million to 17.9 million by 2060\(^3\) with a similar increase in the United States\(^4\). Given the well-established impact of AF on future cardiovascular morbidity and mortality\(^5-8\), these projections have major public health implications; particularly if, as reported in large patient populations\(^9\) real-world management often falls short of therapeutic targets. Apart from providing adequate (and safe) protection from future thromboembolic events, the cornerstone of AF management is the attainment of heart rate control or sinus rhythm (rhythm control)\(^10\). Irrespective of the treatment strategy chosen and regardless of underlying AF or sinus rhythm, some form of rate control is required in the setting of chronic AF\(^10\). No survival advantage has been demonstrated by the use of one control strategy over the other\(^10\); however, it is still important to select one of these strategies based on the clinical profile of the individual. Rhythm control is the preferred option for younger patients, those who are symptomatic, for new-onset AF and for AF secondary to a treated/corrected precipitant\(^10\). Alternatively, rate control is an option used for older individuals, those unsuitable for anti-arrhythmic therapeutics or cardioversion and patients without cardiac dysfunction\(^10\).

Electrocardiogram (ECG) Holter monitoring is routinely applied in the diagnostic evaluation of patients with suspected AF according to ESC/EHRA guidelines (i.e. paroxysmal, persistent or permanent AF)\(^10\). Although the prognostic value of Holter monitoring has been questioned\(^11\), there are some data to support its use as a management tool\(^12-14\). In this regard, the well-known negative consequences of increased heart rate variability and lability must be considered when making clinical decisions to control demonstrated heart rates and rhythms\(^15\). Regardless of its prognostic value, the Holter monitor is a sensitive and specific tool (particularly with recent technological advances) in identifying arrhythmias in different patient populations.

Study aims

As part of a systematic program of research to improve risk-delineation and management of hospitalised patients with chronic forms of AF\(^16\), we postulated that ECG Holter monitoring would provide important therapeutic data in respect to intended
rate or rhythm control. Specifically, we hypothesised that in the immediate post-discharge period, we would identify a clinically significant proportion of individuals who demonstrated a marked variation from physician designated rate or rhythm control and would require therapeutic intervention. We further postulated that identifying distinct phenotypes in heart rate control would identify individuals at greater risk (beyond standard clinical profiling) of future events, particularly those relating to thrombo-embolism and progressive cardiac dysfunction.

METHODS

Study setting

This was a prospectively designed, sub-study of the multi-centre, randomised Standard versus Atrial Fibrillation spEcific managemenT studY (SAFETY). The overall purpose and design of SAFETY that conforms to CONSORT standards for pragmatic trials has been described in greater detail previously (ANZCTR: 12610000221055). In brief, 335 hospital in-patients with chronic forms of AF were recruited from three tertiary hospitals in Australia and randomised to usual post-discharge care (n=167) or a home-based, multidisciplinary, AF-specific intervention designed to reduce morbidity and mortality (n=168). This study complies with the Declaration of Helsinki and ethics approval was obtained from the relevant ethics committees. Written informed consent was obtained from each participant prior to study procedures being conducted.

Baseline profiling during hospital admission

Comprehensive profiling of patients was undertaken during the index hospital admission (including socio-demographic profile, past medical history and current admission data). Questionnaires were also administered to assess lifestyle (i.e. cigarette and alcohol consumption, exercise and sleep habits), depression status (via the ARROLL and Centre for Epidemiological Studies Depression Scale [CES-D]) and cognitive function (via the Montreal Cognitive Assessment [MoCA]). The CHA2DS2-VASc score was used as a risk stratification tool to assess requirements for antithrombotic therapy.

Post-discharge home visit

As part of the study intervention, a comprehensive home visit was conducted 7 to 14 days post-discharge by a nurse with postgraduate cardiac training. During the visit, each patient’s cardiac risk profile was assessed and a brief clinical assessment conducted. Wherever possible, a continuous ECG Holter monitor (Lifecard CF Digital Holter Recorder; Spacelabs Healthcare, Washington USA) was attached to record...
heart rate and rhythm for 24 hours. Clinical findings informed the individualised, AF-specific intervention applied in the 12 months post-index hospitalisation.

**Holter data**

Holter monitoring data were downloaded at a central laboratory and subject to beat-to-beat analysis including removal of all artifact and classification of events (e.g. supraventricular tachycardia runs, bradycardia, etc.) by a specifically trained technician using the Impresario Solo Holter analysis software (version 3.07.0158; Spacelabs Healthcare, Washington USA). A total of 141 baseline recordings were collected; rules were applied to each recording in a blinded (to clinical management) and prospective manner to obtain the most accurate data set for reported analysis. Recordings that contained >10 hours of artifact-free data and a minimum of 2000 beats per hour were eligible for analyses (n=8 excluded). Therefore, a total of 133 Holter recordings were suitable for analyses. Day time was defined as 7:00am to 11:00pm and night time as 11:01pm to 6:59am.

**Rhythm versus rate control**

A key component of the SAFETY trial intervention was determination of intended (nominated during the index admission) versus detected (post-discharge) rate versus rhythm control. Assessment of rhythm and rate control was undertaken via 24-hour Holter monitoring applied at the home visit and the following determined on a blinded (to all clinical and demographic profile data) basis:

1. Presence or absence of AF - if present the percentage of recording time in AF was calculated.
2. Rhythm control - defined as sinus rhythm for >90% of recording time.
3. Rate control - defined as a mean hourly heart rate <90 beats per minute [bpm] for >90% of recording time.

The type of control (rhythm or rate) nominated by each patient’s treating physician at the index hospitalisation was then compared to that detected on the Holter recording.

**Heart rate analyses/phenotypes**

Visual assessment of all 24-hour heart rate plots suggested distinct patterns of variability. Inter-individual variability in heart rate was quantified according to hour-to-hour differences in heart rate values (absolute scores). These differences were then averaged over 24-hours, during day time hours (7:00am to 11:00pm) and during night time hours (11:01pm to 6:59am). Patients in the upper quartile of the 24-hour heart rate variability frequency distribution (cut-off 4.22 bpm) were classified as “labile” (i.e.
greatest variability in heart rate during the entirety of Holter monitoring comprising day and night periods). The remainder of patients not identified in the upper quartiles of either the 24 hour, day or night distributions were classified as potentially stable (relative to the labile group). To confirm this status, the frequency distribution of heart rate variability (using the same methods) were discretely analysed for the day and night periods. Those individuals with the same cut-off for 24 hour heart rate lability but occurring only during one of the two time periods were designated as “periodically labile”. The remainder were designated as “stable” relative to the other two groups. All individual heart rate plots were then reviewed (blinded to group allocation) to determine the veracity of detecting sustained and periodic lability with >90% agreement between statistical and visual coding.

**Statistical analyses**

Data are presented as mean (+ standard deviation [SD]) or median (interquartile range [IQR]) for continuous variables (depending on dispersion) or as a proportion for categorical variables. Differences between two groups were assessed using the chi-square ($\chi^2$) test for dichotomous variables and independent t-test for normally distributed continuous variables. Analyses of data comparing three groups was conducted using one-way Analysis of Variance (ANOVA) involving the Dunnett’s t-test for post-hoc significance testing for normally distributed continuous variables and $\chi^2$ for nominal variables. Differences between median values of non-Gaussian data were assessed using the independent samples non-parametric Kruskal-Wallis one-way ANOVA. Multiple logistic regression models (backward stepwise method with univariate entry at a p value of <0.1 and retention if p <0.05) were used to determine independent correlates of rhythm/rate control and stability with adjustment for the variables summarised in Table 1. Data were analysed using SPSS, V.20. A probability value of p<0.05 (two-sided) was considered statistically significant.

**RESULTS**

**Study cohort**

Table 1 summarises the baseline characteristics of the study cohort (n=133) according to intended rhythm or rate control. Mean age was 71 years and there were approximately equal numbers of men and women. Two thirds of patients had underlying hypertension and approximately one third had coronary artery disease, type 2 diabetes and depression. The majority of patients had preserved systolic function but high thrombo-embolic risk according to the CHA2DS2-VASc score.
Table 1: Characteristics of SAFETY intervention Holter cohort according to intended rate or rhythm control

<table>
<thead>
<tr>
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<th>ALL (n = 133)</th>
<th>Intended Rate Control (n = 89)</th>
<th>Intended Rhythm Control (n = 44)</th>
<th>p value</th>
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<td><strong>Socio-demographic profile</strong></td>
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<tr>
<td>Age (years)</td>
<td>71 ± 10</td>
<td>73 ± 10</td>
<td>68 ± 10</td>
<td>0.010</td>
</tr>
<tr>
<td>Male sex</td>
<td>67 (50%)</td>
<td>47 (53%)</td>
<td>20 (46%)</td>
<td>0.465</td>
</tr>
<tr>
<td>Living alone</td>
<td>49 (37%)</td>
<td>34 (38%)</td>
<td>15 (34%)</td>
<td>0.705</td>
</tr>
<tr>
<td><strong>Heart rate/rhythm profile</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-hour heart rate (bpm)</td>
<td>72 ± 14</td>
<td>74 ± 14</td>
<td>67 ± 12</td>
<td>0.004</td>
</tr>
<tr>
<td>Recording time in AF (%)</td>
<td>39 (0, 100)</td>
<td>86 (1, 100)</td>
<td>2 (0, 100)</td>
<td>0.016</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>18 (14%)</td>
<td>13 (15%)</td>
<td>5 (11%)</td>
<td>0.789</td>
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<tr>
<td><strong>AF-specific profile</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic AF</td>
<td>109 (82%)</td>
<td>74 (83%)</td>
<td>35 (80%)</td>
<td>0.637</td>
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<tr>
<td>New AF</td>
<td>33 (25%)</td>
<td>25 (28%)</td>
<td>8 (18%)</td>
<td>0.287</td>
</tr>
<tr>
<td>Persistent AF</td>
<td>118 (89%)</td>
<td>75 (84%)</td>
<td>43 (98%)</td>
<td>0.021</td>
</tr>
<tr>
<td>Permanent AF</td>
<td>15 (11%)</td>
<td>14 (16%)</td>
<td>1 (2%)</td>
<td>0.021</td>
</tr>
<tr>
<td>CHA₂DS₂-VASc score*</td>
<td>4 ± 2</td>
<td>4 ± 2</td>
<td>3 ± 2</td>
<td>0.001</td>
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<tr>
<td><strong>Clinical presentation</strong></td>
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<tr>
<td>Dyspnoea</td>
<td>68 (51%)</td>
<td>48 (54%)</td>
<td>20 (46%)</td>
<td>0.461</td>
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<td>Chest pain</td>
<td>61 (46%)</td>
<td>43 (48%)</td>
<td>18 (41%)</td>
<td>0.463</td>
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<tr>
<td>Palpitations</td>
<td>48 (36%)</td>
<td>29 (33%)</td>
<td>19 (43%)</td>
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<tr>
<td>Heart rate (bpm)</td>
<td>103 ± 35</td>
<td>101 ± 34</td>
<td>105 ± 37</td>
<td>0.571</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>136 ± 23</td>
<td>138 ± 24</td>
<td>131 ± 22</td>
<td>0.129</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>78 ± 16</td>
<td>78 ± 17</td>
<td>78 ± 15</td>
<td>0.999</td>
</tr>
<tr>
<td>AF on ECG</td>
<td>109 (82%)</td>
<td>74 (83%)</td>
<td>35 (80%)</td>
<td>0.637</td>
</tr>
<tr>
<td>Current smoker</td>
<td>15 (11%)</td>
<td>11 (12%)</td>
<td>4 (9%)</td>
<td>0.773</td>
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<tr>
<td>High-risk alcohol use</td>
<td>19 (14%)</td>
<td>14 (16%)</td>
<td>5 (11%)</td>
<td>0.604</td>
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<tr>
<td>Moderate exercise</td>
<td>59 (44%)</td>
<td>39 (44%)</td>
<td>20 (46%)</td>
<td>1.000</td>
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<td><strong>Co-morbidity profile</strong></td>
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<tr>
<td>Hypertension</td>
<td>98 (74%)</td>
<td>70 (79%)</td>
<td>28 (64%)</td>
<td>0.093</td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>45 (34%)</td>
<td>35 (39%)</td>
<td>10 (23%)</td>
<td>0.079</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>39 (29%)</td>
<td>27 (30%)</td>
<td>12 (27%)</td>
<td>0.840</td>
</tr>
<tr>
<td>Prior cerebrovascular event</td>
<td>20 (15%)</td>
<td>17 (19%)</td>
<td>3 (7%)</td>
<td>0.074</td>
</tr>
<tr>
<td>Chronic Airways Limitation</td>
<td>20 (15%)</td>
<td>20 (23%)</td>
<td>0 (0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>57 ± 9</td>
<td>56 ± 10</td>
<td>59 ± 6</td>
<td>0.066</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>12 (9%)</td>
<td>10 (11%)</td>
<td>2 (5%)</td>
<td>0.336</td>
</tr>
<tr>
<td>Obesity</td>
<td>55 (42%)</td>
<td>37 (42%)</td>
<td>18 (41%)</td>
<td>1.000</td>
</tr>
<tr>
<td>“Poor” sleep quality</td>
<td>47 (36%)</td>
<td>37 (42%)</td>
<td>10 (23%)</td>
<td>0.036</td>
</tr>
<tr>
<td>Depression</td>
<td>40 (30%)</td>
<td>31 (35%)</td>
<td>9 (21%)</td>
<td>0.109</td>
</tr>
<tr>
<td>Mild cognitive impairment</td>
<td>68 (51%)</td>
<td>53 (60%)</td>
<td>15 (34%)</td>
<td>0.009</td>
</tr>
<tr>
<td>Valve disease</td>
<td>4 (3%)</td>
<td>4 (5%)</td>
<td>0 (0%)</td>
<td>0.302</td>
</tr>
<tr>
<td>Renal disease</td>
<td>15 (11%)</td>
<td>13 (15%)</td>
<td>2 (5%)</td>
<td>0.143</td>
</tr>
<tr>
<td>Charlson Index score</td>
<td>4 ± 2</td>
<td>5 ± 2</td>
<td>3 ± 2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Discharge profile</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>73 ± 15</td>
<td>75 ± 14</td>
<td>70 ± 16</td>
<td>0.042</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>128 ± 18</td>
<td>132 ± 18</td>
<td>120 ± 16</td>
<td>0.001</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>72 ± 12</td>
<td>73 ± 12</td>
<td>68 ± 10</td>
<td>0.014</td>
</tr>
<tr>
<td>Warfarin</td>
<td>76 (57%)</td>
<td>51 (57%)</td>
<td>25 (57%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Aspirin only</td>
<td>70 (53%)</td>
<td>49 (55%)</td>
<td>21 (48%)</td>
<td>0.464</td>
</tr>
<tr>
<td>Clopidogrel + Aspirin</td>
<td>26 (20%)</td>
<td>17 (19%)</td>
<td>9 (21%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Beta-Blocker</td>
<td>65 (49%)</td>
<td>58 (65%)</td>
<td>7 (16%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>41 (31%)</td>
<td>38 (43%)</td>
<td>3 (7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atenolol</td>
<td>14 (11%)</td>
<td>10 (11%)</td>
<td>4 (9%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Digoxin</td>
<td>54 (41%)</td>
<td>47 (53%)</td>
<td>7 (16%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
### Calcium Channel Blocker

<table>
<thead>
<tr>
<th>Blocker</th>
<th>Number / (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Verapamil</strong></td>
<td>9 (7%)</td>
</tr>
<tr>
<td><strong>Diltiazem</strong></td>
<td>7 (5%)</td>
</tr>
<tr>
<td><strong>Amlodipine</strong></td>
<td>10 (8%)</td>
</tr>
<tr>
<td><strong>Amiodarone</strong></td>
<td>8 (6%)</td>
</tr>
<tr>
<td><strong>Flecainide</strong></td>
<td>6 (5%)</td>
</tr>
<tr>
<td><strong>Sotalol</strong></td>
<td>21 (16%)</td>
</tr>
<tr>
<td><strong>Diuretic (%)</strong></td>
<td>56 (42%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blocker</th>
<th>Number / (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Calcium Channel Blocker</strong></td>
<td>34 (26%)</td>
</tr>
<tr>
<td>27 (30%)</td>
<td>7 (16%)</td>
</tr>
<tr>
<td><strong>Verapamil</strong></td>
<td>9 (7%)</td>
</tr>
<tr>
<td>9 (10%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Diltiazem</strong></td>
<td>5 (6%)</td>
</tr>
<tr>
<td>2 (5%)</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>Amlodipine</strong></td>
<td>1 (1%)</td>
</tr>
<tr>
<td>5 (11%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Amiodarone</strong></td>
<td>8 (6%)</td>
</tr>
<tr>
<td>1 (1%)</td>
<td>7 (16%)</td>
</tr>
<tr>
<td><strong>Flecainide</strong></td>
<td>6 (5%)</td>
</tr>
<tr>
<td>1 (1%)</td>
<td>5 (11%)</td>
</tr>
<tr>
<td><strong>Sotalol</strong></td>
<td>21 (16%)</td>
</tr>
<tr>
<td>1 (1%)</td>
<td>20 (46%)</td>
</tr>
<tr>
<td><strong>Diuretic (%)</strong></td>
<td>56 (42%)</td>
</tr>
<tr>
<td>44 (49%)</td>
<td>12 (27%)</td>
</tr>
</tbody>
</table>

*CHADS2-VASc score definition: C = congestive heart failure/LV dysfunction (1 point), H = hypertension (even if treated; 1 point), A2 = age ≥75 years (2 points), D = diabetes mellitus (1 point), S2 = stroke/SE/TIA (2 points), V = vascular disease (1 point), A = age 65-74 years (1 point), Sc = sex category (female sex; 1 point); bpm = beats per minute; BP = blood pressure; mmHg = millimeters of mercury; LVEF = left ventricular ejection fraction

**NOTE:** For the current research, the CHA2DS2-VASc score is scored from 0-8 (not 0-9 as is the norm) due to the exclusion of patients with chronic heart failure.

### Intended versus detected rhythm and rate control

Overall, 44 patients (33%) were nominated for rhythm control and the remaining 89 patients for rate control at hospital discharge (see Table 1). As expected, rhythm control patients were significantly younger and there were proportionally more males in this group although this difference did not reach statistical significance. Intended rate control patients were significantly more clinically complex than rhythm control patients; they had a higher thrombo-embolic risk (as indicated by a higher mean CHA2DS2-VASc score), more chronic airways limitation, poorer sleep quality, higher levels of mild cognitive impairment and a higher Charlson index of co-morbidity score. Therapeutic differences were also apparent within the cohort with more intended rate control patients prescribed beta-blockers, digoxin, verapamil and diuretics and more intended rhythm control patients prescribed amiodarone, flecainide and sotalol. Consistent with the intended therapeutic target, those nominated for rate control were recorded in AF far longer than rhythm control patients (86% [IQR 1, 100] versus 2% [0, 100], p=0.016). However, there were some important disparities between intended and detected rate and rhythm control.

**Rhythm control group:** Overall 19 patients intended for rhythm control (43%) were in AF >10% of the recording time. Of these, 14 (32%) were in AF for 100% of the time. Transient AF (≤10% of recording time) was detected in 4 patients (9%). Complete absence of AF was, therefore, detected in 21 (48%) patients (i.e. complete rhythm control). The majority of patients (n=35, 80%) demonstrated rate control; of whom 15 (43%) were in AF and the remainder (57%) in sinus rhythm.
**Rate control group:** Overall, 63 (71%) patients with intended rate control actually achieved this target and one quarter of patients (n=22) were in sinus rhythm for the entire recording.

**Table 2:** Independent correlates of rhythm and rate control detected on post-discharge Holter monitoring

<table>
<thead>
<tr>
<th>Correlates of post-discharge rhythm control</th>
<th>p value</th>
<th>Adjusted OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior cerebrovascular event</td>
<td>0.037</td>
<td>9.09</td>
<td>1.15 to 100.00</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.006</td>
<td>10.00</td>
<td>1.96 to 50.00</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>0.024</td>
<td>1.19</td>
<td>1.02 to 1.38</td>
</tr>
<tr>
<td>CHA2DS2-VASc score (per unit increase)</td>
<td>&lt;0.001</td>
<td>0.39</td>
<td>0.23 to 0.68</td>
</tr>
<tr>
<td>Palpitations on presentation</td>
<td>0.003</td>
<td>5.56</td>
<td>1.79 to 16.67</td>
</tr>
<tr>
<td>Heart rate on admission (bpm)</td>
<td>0.004</td>
<td>1.03</td>
<td>1.01 to 1.05</td>
</tr>
<tr>
<td>Sinus rhythm on presentation ECG</td>
<td>&lt;0.001</td>
<td>54.61</td>
<td>9.42 to 316.42</td>
</tr>
<tr>
<td>Diastolic blood pressure on admission (mmHg)</td>
<td>0.005</td>
<td>0.95</td>
<td>0.91 to 0.98</td>
</tr>
<tr>
<td>Prescribed digoxin</td>
<td>0.009</td>
<td>0.23</td>
<td>0.08 to 0.69</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Correlates of post-discharge rate control</th>
<th>p value</th>
<th>Adjusted OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>0.002</td>
<td>5.56</td>
<td>1.85 to 16.67</td>
</tr>
<tr>
<td>Dyspnoea on presentation</td>
<td>0.001</td>
<td>0.17</td>
<td>0.06 to 0.49</td>
</tr>
<tr>
<td>Diastolic blood pressure on admission (mmHg)</td>
<td>0.004</td>
<td>0.95</td>
<td>0.92 to 0.98</td>
</tr>
<tr>
<td>Heart rate on discharge (bpm)</td>
<td>0.034</td>
<td>0.97</td>
<td>0.94 to 1.00</td>
</tr>
<tr>
<td>Prescribed anticoagulant</td>
<td>0.006</td>
<td>0.22</td>
<td>0.07 to 0.65</td>
</tr>
<tr>
<td>Prescribed anti-arrhythmic agent</td>
<td>0.018</td>
<td>4.55</td>
<td>1.30 to 16.67</td>
</tr>
</tbody>
</table>

**Table 2** shows the independent correlates of detected rhythm (n=43) and rate (n=98) control detected on post-discharge Holter monitoring (39 being included in both analyses). Patients with underlying hypertension were far more likely to be recorded in both sinus rhythm and rate controlled; noting that 39 patients (29%) achieved both targets and, of these, 31 (80%) had a history of hypertension. Patients with a prior cerebrovascular event, more preserved cardiac function, palpitations, a higher initial heart rate and (not surprisingly) sinus rhythm on initial presentation were also more likely to be rhythm controlled. Alternatively, patients predominantly in sinus rhythm had a lower CHA2DS2-VASc score and initial diastolic BP and were prescribed digoxin. Not surprisingly, those prescribed an anti-arrhythmic agent were far more likely to be truly
rate controlled. Alternatively, those presenting in NHYHA Class II, III or IV, had a lower initial diastolic BP or lower heart rate on discharge and were prescribed an anti-coagulant were less likely to be rate controlled. Two additional borderline correlates associated with diminished and enhanced rate control, respectively, was increased body mass index (adjusted OR 0.94, 95% CI 0.87 to 1.01 per kg/m²) and diuretic therapy (OR 2.94, 95% 0.94 to 9.09).

**Heart rate control phenotypes**

Based on our prospective criteria, 78 patients (59%) were classified as displaying relatively “stable” heart rate variability, 22 patients (16%) as “periodically labile” and the remaining 33 patients (25%) “persistently labile”. As shown in Figure 1, there was an expected gradient in the degree of variability across these groups. All three groups showed the well known increase in heart rate variability with morning awakening, which was more pronounced in the periodically and persistently labile groups.
Figure 1: Mean hour-to-hour heart rate over 24 hours of patients in the three identified phenotypic groups (stable, periodically labile and persistently labile)
Figure 2A-C displays the hour-to-hour difference in mean hourly heart rate plots of all patients in each of the groups. Regardless of group, variation is displayed over the 24-hour period, with the greatest variations (particularly day time) demonstrated in the persistently labile group.

Figure 2: Heart rate plots of all patients in the three identified phenotypic groups (A: stable; B: periodically labile; C: persistently labile)

A: Stable
Table 3 summarises the baseline characteristics of patients according to the three distinct phenotypes with not unexpected differences according to pharmacotherapy, absolute heart rate and underlying rhythm. Notably, more patients in the periodically labile group drank alcohol at high-risk levels (OR 2.5; 95% CI 1.2 to 5.2, p=0.035).
Table 3: Characteristics of SAFETY intervention Holter cohort according to identified heart rate phenotypes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Stable (n = 78)</th>
<th>Periodically Labile (n = 22)</th>
<th>Persistently Labile (n = 33)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Socio-demographic profile</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>71 ± 10</td>
<td>71 ± 12</td>
<td>70 ± 10</td>
<td>0.850</td>
</tr>
<tr>
<td>Male sex</td>
<td>37 (47%)</td>
<td>10 (46%)</td>
<td>20 (61%)</td>
<td>0.394</td>
</tr>
<tr>
<td><strong>Heart rate/rhythm profile</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-hour heart rate (bpm)</td>
<td>67 ± 12</td>
<td>72 ± 12</td>
<td>82 ± 14***</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>“Uncontrolled” 24-hour HR</td>
<td>7 (9%)</td>
<td>4 (18%)</td>
<td>24 (73%)***</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recording time in AF (%)</td>
<td>13 (0, 100)</td>
<td>13 (0, 100)</td>
<td>100 (27, 100)**</td>
<td>0.017</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>16 (21%)</td>
<td>0 (0%)*</td>
<td>2 (6%)</td>
<td>0.016</td>
</tr>
<tr>
<td><strong>AF-specific profile</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic AF</td>
<td>62 (80%)</td>
<td>18 (82%)</td>
<td>29 (88%)</td>
<td>0.576</td>
</tr>
<tr>
<td>New AF</td>
<td>20 (26%)</td>
<td>6 (27%)</td>
<td>7 (21%)</td>
<td>0.848</td>
</tr>
<tr>
<td>Persistent AF</td>
<td>68 (87%)</td>
<td>21 (95%)</td>
<td>29 (88%)</td>
<td>0.547</td>
</tr>
<tr>
<td>Permanent AF</td>
<td>10 (13%)</td>
<td>1 (5%)</td>
<td>4 (12%)</td>
<td>0.547</td>
</tr>
<tr>
<td>Nominated rate control</td>
<td>45 (58%)</td>
<td>19 (86%)*</td>
<td>25 (76%)</td>
<td>0.019</td>
</tr>
<tr>
<td>Nominated rhythm control</td>
<td>33 (42%)</td>
<td>3 (14%)*</td>
<td>8 (24%)</td>
<td>0.019</td>
</tr>
<tr>
<td>CHA2DS2-VASc score</td>
<td>4 ± 2</td>
<td>4 ± 2</td>
<td>3 ± 2</td>
<td>0.338</td>
</tr>
<tr>
<td><strong>Clinical presentation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>33 (42%)</td>
<td>11 (50%)</td>
<td>24 (73%)*</td>
<td>0.014</td>
</tr>
<tr>
<td>Chest pain</td>
<td>33 (42%)</td>
<td>11 (50%)</td>
<td>17 (52%)</td>
<td>0.615</td>
</tr>
<tr>
<td>Palpitations</td>
<td>28 (36%)</td>
<td>9 (41%)</td>
<td>11 (33%)</td>
<td>0.847</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>101 ± 35</td>
<td>104 ± 39</td>
<td>105 ± 33</td>
<td>0.818</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>138 ± 22</td>
<td>132 ± 29</td>
<td>134 ± 23</td>
<td>0.508</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>77 ± 14</td>
<td>76 ± 21</td>
<td>83 ± 17</td>
<td>0.169</td>
</tr>
<tr>
<td>AF on ECG</td>
<td>61 (78%)</td>
<td>18 (82%)</td>
<td>30 (91%)</td>
<td>0.282</td>
</tr>
<tr>
<td>Current smoker</td>
<td>8 (10%)</td>
<td>1 (5%)</td>
<td>6 (18%)</td>
<td>0.266</td>
</tr>
<tr>
<td>High-risk alcohol use</td>
<td>7 (9%)</td>
<td>6 (27%)*</td>
<td>6 (18%)</td>
<td>0.073</td>
</tr>
<tr>
<td><strong>Co-morbidity profile</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>59 (76%)</td>
<td>18 (82%)</td>
<td>21 (64%)</td>
<td>0.269</td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>23 (30%)</td>
<td>9 (41%)</td>
<td>13 (39%)</td>
<td>0.448</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>24 (31%)</td>
<td>6 (27%)</td>
<td>9 (27%)</td>
<td>0.909</td>
</tr>
<tr>
<td>Prior cerebrovascular event</td>
<td>11 (14%)</td>
<td>5 (23%)</td>
<td>4 (12%)</td>
<td>0.524</td>
</tr>
<tr>
<td>Chronic Airways Limitation</td>
<td>10 (13%)</td>
<td>4 (18%)</td>
<td>6 (18%)</td>
<td>0.696</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>58 ± 9</td>
<td>58 ± 9</td>
<td>54 ± 10</td>
<td>0.217</td>
</tr>
<tr>
<td>Obesity</td>
<td>30 (39%)</td>
<td>10 (46%)</td>
<td>15 (46%)</td>
<td>0.722</td>
</tr>
<tr>
<td>Renal disease/dysfunction</td>
<td>6 (8%)</td>
<td>4 (18%)</td>
<td>5 (15%)</td>
<td>0.285</td>
</tr>
<tr>
<td>Depression</td>
<td>23 (30%)</td>
<td>6 (27%)</td>
<td>11 (33%)</td>
<td>0.877</td>
</tr>
<tr>
<td><strong>Discharge profile</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>72 ± 14</td>
<td>74 ± 15</td>
<td>78 ± 16</td>
<td>0.161</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>126 ± 18</td>
<td>131 ± 21</td>
<td>131 ± 18</td>
<td>0.349</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>71 ± 13</td>
<td>73 ± 15</td>
<td>73 ± 8</td>
<td>0.449</td>
</tr>
<tr>
<td>Warfarin</td>
<td>45 (58%)</td>
<td>11 (50%)</td>
<td>20 (61%)</td>
<td>0.730</td>
</tr>
<tr>
<td>Aspirin only</td>
<td>38 (49%)</td>
<td>14 (64%)</td>
<td>18 (55%)</td>
<td>0.450</td>
</tr>
<tr>
<td>Clopidogrel + Aspirin</td>
<td>14 (18%)</td>
<td>4 (18%)</td>
<td>8 (24%)</td>
<td>0.735</td>
</tr>
<tr>
<td>Beta-Blocker</td>
<td>33 (42%)</td>
<td>17 (77%)**</td>
<td>15 (46%)</td>
<td>0.014</td>
</tr>
<tr>
<td>Digoxin</td>
<td>32 (41%)</td>
<td>8 (36%)</td>
<td>14 (42%)</td>
<td>0.898</td>
</tr>
<tr>
<td>Calcium Channel Blocker</td>
<td>22 (28%)</td>
<td>3 (14%)</td>
<td>9 (27%)</td>
<td>0.371</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>5 (6%)</td>
<td>2 (9%)</td>
<td>1 (3%)</td>
<td>0.635</td>
</tr>
<tr>
<td>Flecanide</td>
<td>4 (5%)</td>
<td>1 (5%)</td>
<td>1 (3%)</td>
<td>0.888</td>
</tr>
<tr>
<td>Sotalol</td>
<td>17 (22%)</td>
<td>0 (0%)*</td>
<td>4 (12%)</td>
<td>0.037</td>
</tr>
<tr>
<td>Diuretic (%)</td>
<td>36 (46%)</td>
<td>10 (46%)</td>
<td>10 (30%)</td>
<td>0.285</td>
</tr>
</tbody>
</table>

Legend: * <0.05; ** <0.01; *** <0.001
On an adjusted basis, both intended (OR 3.64; 95% CI 1.31 to 10.0, p=0.013) and actual rate control (OR 12.0; 95% CI 3.57 to 40.0, p<0.001) was correlated with a *stable* heart rate profile. Other positive correlates of such stability were an implanted pacemaker (OR 7.39; 95% CI 1.34 to 40.8, p=0.022) or presence of a permanent form of AF (10/15 - OR 5.76; 95% CI 1.23 to 27.0, p=0.026). Alternatively, those with coronary artery disease (OR 0.34; 95% CI 0.13 to 0.91, p=0.033) or renal disease/dysfunction (OR 0.24; 95% CI 0.06 to 0.98, p=0.047) were less likely to be classified as *stable* and, therefore, more likely to contribute to the labile groups.

**DISCUSSION**

To our knowledge, this is the first study that has specifically employed Holter monitoring to quantify and identify achievement (or failure) of AF control treatment targets and utilise these data as potential predictors of patient outcomes. Importantly, this was a typically old and fragile patient cohort with chronic AF and the results are likely to be generalisable to other settings. Notably, we identified potentially important disparities between physician intended therapeutic targets and actual clinical status shortly following an acute hospitalisation. We found that over half (52%) of those nominated for rhythm control displayed AF on recording. Furthermore, almost one third (29%) of nominated rate controlled patients demonstrated an uncontrolled heart rate and a further 20% of intended rhythm control patients were also not rate controlled. Overall, 49 (37%) patients did not achieve the therapeutic target at the point of Holter monitoring (either rhythm or rate control) and, regardless of actual rhythm or intended target, 35 (26%) were not rate controlled. Beyond traditional Holter data quantification and reporting, we identified and then quantified potentially important phenotypes (*stable, periodically labile* and *persistently labile*) according to underlying heart rate variations that may well have some prognostic importance. Patients suffering from coronary heart disease or renal disease were less likely to demonstrate heart rate stability whilst, not surprisingly, the presence of a pacemaker correlated with greater stability. Overall, these data and the reports we were able to generate for treating clinicians, provide strong preliminary support for the application of post-discharge Holter monitoring in such high risk patients; particularly if technological advances facilitate easier and longer data acquisition and synthesis. Reported health outcomes from the SAFETY cohort (in addition to repeat monitoring in all study patients at 12 months) may help to elucidate this further (particularly from a cost perspective).

These findings should probably come as no surprise given therapeutic management of AF is often complicated by a disparity between discernible clinical stability and
electrophysiological efficiency and underscores the potential value of these data. Despite this, these findings highlight the need for improved surveillance and constant monitoring of patients with AF to identify inconsistencies and stimulate reassessment of management targets in order to achieve more favourable outcomes. We hypothesise that the identified heart rate variability phenotypes may well prove to be important determinants of longer-term health outcomes (both in terms of risk of future thromboembolic events and, perhaps, more importantly progressive cardiac dysfunction linked to tachycardia-induced cardiomyopathy). On a more fundamental level, these data reconfirm the difficulty of achieving what might be perceived as a simple therapeutic goal for AF management – either rhythm or rate control. In two key studies assessing the benefits of rate versus rhythm control, sinus rhythm was maintained in only 40% and 23% of rhythm controlled patients, respectively. Even in trials in which amiodarone was proven to be the most successful pharmaceutical agent to maintain sinus rhythm, AF recurred in 35% of patients. In the recently published nurse-led AF-Clinic trial, approximately 20% of the 712 recruited patients demonstrated an uncontrolled heart rate and the investigators stated that, in clinical practice, it is difficult to attain an optimal heart rate in AF patients. Furthermore, it was reported that rhythm control is often nominated and applied when it is not indicated. Potentially supporting the current finding that rate control is more likely to result in clinical stability, a meta-analysis conducted by de Denus and colleagues suggested that mortality was lower in rate controlled patients than in rhythm controlled patients (p=0.09).

Notwithstanding the likely treatment response to our findings (during longer-term follow-up we will be able to quantify the therapeutic response to our reports), clear disparities between intended and detected rate or rhythm control are significant when considering the potential to subsequently improve health outcomes; much in the same way patients with AF are monitored to determined time spent in a therapeutic INR range when being treated with warfarin. This cohort will be monitored closely as part of the long-term follow-up of the SAFETY cohort to determine if therapeutic change was initiated (as intended) and if this contributes to improved morbidity and survival relative to usual care. These data also have important implications when evaluating clinical trials that specifically assessed the effectiveness of rate versus rhythm control or have compared the two methods as a means of assessing patient outcomes and have demonstrated no incremental benefits accordingly. In this cohort, individuals with a more clinically complex profile and who were symptomatic at presentation but had preserved cardiac function were more likely to achieve true rhythm control post-discharge, possibly due to the need to achieve clinical stability. Alternatively, patients
who were less clinically complex, appropriately treated but at higher thrombo-embolic risk were more likely to achieve true rate control following hospital discharge. The clinical complexity of patients under nominated rhythm control is supported by the findings of Badheka and colleagues (2013) who found that all-cause mortality was higher in these patients. The indication from the current analyses is that lability detected on Holter monitoring may be risk defining and has the potential for inclusion in risk profiling of AF patients (i.e. to enhance delineation), as these aspects of risk may not be detected otherwise. The SAFETY Holter cohort is a high-risk group (as evidenced by factors such as high thrombo-embolic risk) that has demonstrated a high proportion of rhythm and rate control crossover. Evaluating the rate and rhythm of AF patients using Holter monitoring is important, not only because there appears to be a relationship between the phenotypes and severity of AF but because findings may also reflect the status of the overall cardiac function, e.g. the haemodynamic consequences of functional impairment. Additionally, the finding that lability is more evident in those with coronary artery disease or renal dysfunction may highlight a further high-risk group of patients requiring increased surveillance due to the potential indication of a failing heart due to neurohormonal activation resulting in the inability to sustain tissue metabolic requirements and renal perfusion.

A number of limitations of this work require comment. The Holter monitors were employed for a 24-hour period which may not have been long enough to obtain a comprehensive rhythm/rate picture of these AF patients. We observed inherent and spontaneous variability of normal rhythm as well as during arrhythmias caused by day-to-day variations in heart rate and adrenergic drive, potentially causing an overestimation of lability. Although all recordings were reviewed and analysed by trained personnel, initial classification of beats and rhythms was via an electronic classification system, which itself has inherent limitations. It cannot be discounted that misclassification occurred, although, due to the comprehensive analysis of each recording undertaken, this was minimised. Data obtained from the Holter monitor database was provided in hourly epochs, meaning that more comprehensive minute-to-minute evaluation was not possible. As noted previously, our findings did prompt a treatment response (these will be described in subsequent reports) and determining the true prognostic value of the identified phenotypes will be difficult to determine (although, as part of the SAFETY trial, we will be passively collecting Holter data on patients randomised to the control group).
Despite these limitations, these data, derived from a more proactive use of post-discharge Holter monitoring, are promising in respect to extending risk delineation and optimising definitive management of chronic AF by capturing potentially important differentials between therapeutic intention and clinical outcomes in the short-term. These clinical disparities may well prove to be important determinants of longer-term outcomes in patients with chronic AF and further clarify why no clear differences between rhythm and rate control have been found.

**FUNDING**

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Summary

The research findings presented in this manuscript which has been submitted for peer reviewed publication have potentially positive implications for the delineation of risk in patients with AF. The 24-hour Holter monitor recordings of 133 patients within the SAFETY intervention cohort captured 7 – 14 days post-discharge were analysed. Initial assessment of these recordings revealed that a large proportion of patients who were assumed to be stable following AF-related hospitalisation were otherwise unstable or had not reached their intended therapeutic target. Of those patients who were intended for rhythm control, 43% were detected in AF for >10% of the recording time and 32% of these were actually in AF for 100% of the time. Of those patients intended for rate control, 29% did not achieve this target. Independent correlates of detected rhythm and rate control were determined and patients who were more clinically complex (with hypertension and a prior cerebrovascular event) but with a lower thrombo-embolic risk and lower initial diastolic blood pressure were more likely to be rhythm controlled (i.e. detected in sinus rhythm). These patients were also more likely to be symptomatic and demonstrate a higher heart rate at hospital presentation. Patients prescribed an anti-arrhythmic were more likely to be rate controlled on Holter monitoring.

Three distinct (and to our knowledge unique) heart rate phenotypes were also identified as being displayed on Holter monitoring and correlates of each group were determined. Classification of patients into persistently labile (25%), periodically labile (16%) or stable (59%) groups was performed which may provide an extended risk delineation strategy for AF patients with the potential for predicting those at greatest risk for future events and/or re-hospitalisation (i.e. those in the labile groups). Both intended (odds ratio [OR] 3.64; 95% CI 1.31 to 10.0, p=0.013) and detected (OR 12.0; 95% CI 3.57 to 40.0, p<0.001) rate control, an implanted pacemaker (OR 7.39; 95% CI 1.34 to 40.8, p=0.022) and the presence of permanent AF (OR 5.76; 95% CI 1.23 to 27.0, p=0.026) were positively correlated with the stable heart rate phenotype. However, patients with coronary artery disease (OR 0.34; 95% CI 0.13 to 0.91, p=0.033) or renal disease/dysfunction (OR 0.24; 95% CI 0.06 to 0.98, p=0.047) were less likely to be classified as stable. The true predictive ability of these phenotypes and their use as an extended risk delineation tool remains to be fully elucidated and this will only be
determined following the conclusion of the SAFETY trial and analysis of morbidity and mortality data. However, this research goes somewhat towards providing justification for the extended use of Holter monitoring as a tool to assist with and optimise AF management.
Chapter 8

General Discussion and Conclusions
Chapter 8 summarises the contents of this thesis and provides a general discussion on the methods employed, major findings and clinical implications. The limitations of this body of work are also discussed and future research directions are outlined.
Thesis summary
The primary focus of the research presented and discussed in this thesis was to identify or extend new methods of risk delineation (over and above standard risk stratification processes) that may facilitate more specifically directed AF patient management and, in turn, better patient outcomes. True to this aim, this thesis provided a snapshot of contemporary AF management and the potential value of individualised risk delineation in the setting of AF as a means to positively influence health outcomes. It demonstrated some clinically important and under-reported management issues in a “real-world” cohort of high-risk patients with chronic forms of AF.

Firstly, in order to better quantify and synthesise the current literature to accurately project the burden of AF within our ageing populations, a systematic review of epidemiological and population-based data was undertaken. The clinical and societal implications of these published findings (described in Chapter 3) with new, more accurate estimates of the population prevalence of AF are discussed below. These include potentially important insights into the future burden of AF and any attempts to attenuate a prolonged epidemic of AF and associated morbidity/mortality within our ageing populations. Focusing more specifically on contemporary clinical conundrums surrounding the management of typically older patients admitted to hospital with chronic forms of AF, Chapter 4 described a multi-centre trial of AF-specific management in a typically older and clinically complex cohort of individuals. The clinical implications of published data from this study focusing on gender-specific issues (Chapter 5), the high prevalence of often undiagnosed mild cognitive impairment (Chapter 6) and a novel classification system of post-discharge ECG Holter monitoring (Chapter 7) to determine future risk of clinical events are also described in more detail below.

Research findings
The status of the epidemiology and the size of the global burden of AF in a comprehensive review of the current literature were presented in Chapter 3. The burden of AF on individuals, societies and health care systems was described. The
findings of this published research report provided firm evidence that the consequences of AF are damaging and the number of affected individuals shows no signs of abating, with at least a doubling of the number of affected individuals expected by the year 2050 worldwide [Go et al., 2001; Miyasaka et al., 2006; Naccarelli et al., 2009]. This is particularly true if current methods of clinical management and secondary prevention continue to be employed without consideration of the clinical conundrums that complicate day-to-day management of AF in the real-world setting. Perhaps most notably, the population prevalence of AF was found to be between 2.5% and 3.5%, which is substantially greater than commonly reported (1.0% to 2.0% [Go et al., 2001]). The economic consequences were equally large, with up to 2.5% of health care costs in Europe, North America and Australia spent on AF alone. AF also has a detrimental influence on overall health, with multiple adverse consequences that are individually and economically costly. Therefore, more concentrated multi-disciplinary action is required with a particular focus on patient-specific risk profiles and individualised AF management in an effort to curb the predicted exponential increase in its prevalence. Identification of enhanced risk delineation strategies accompanied by appropriate treatment and management may go somewhat towards achieving this goal.

The future burden of AF will be largely defined by a growing number of older individuals living with multiple (but successfully managed/treated) co-morbidities. There is a clear need, therefore, for pragmatic trials to be conducted and results of clinical trials to be confirmed with effectiveness studies of interventions in “real world” populations. This, in fact, closely mirrors the scenario over the last few decades to address a growing epidemic of CHF that subsequently led to the development and implementation of heart failure management programs [McAlister et al., 2004]. It is likely that a similar effort employed to address the AF epidemic may result in equally effective management programs leading to improvements in patient outcomes and a reduction in AF-related re-hospitalisations. Therefore, in response to the need for the development and evaluation of such programs, we designed the Standard versus Atrial Fibrillation spEcific managemenT studY (SAFETY). SAFETY is a pragmatic, multi-centre, prospective randomised controlled trial assessing the effectiveness of a
Chapter 8: General Discussion and Conclusions

nurse-led, AF-specific disease management program in a cohort of recently hospitalised patients with chronic forms of AF versus usual post-discharge care for patients with the same. With a primary endpoint of all-cause mortality and/or unplanned hospital re-admission, follow-up is between 18 and 36 months. Chapter 4 of this thesis described the rationale and methodology of SAFETY, the platform from which the current research was conducted. SAFETY is presently ongoing, with results due in mid-to-late 2014. Baseline data collected from the patients recruited into SAFETY were used for the current research; addressing some of the clinical conundrums that surround the clinical management of AF.

In light of the well-known influence of gender-based differences on the outcomes of patients with CVD including AF [Go et al., 2013], we conducted a detailed evaluation of gender-specific differences within the SAFETY cohort and a published research report was presented in Chapter 5. Here, gender was analysed as a factor by which risk delineation can be carried out. Gender differences in clinical presentation, thromboembolic risk and therapeutic management were assessed. Women within this cohort were disadvantaged socially, clinically and according to treatment guidelines. They were older and more clinically complex than their male counterparts. Furthermore, women were more likely to have depression and lower HR-QoL which can have negative implications for knowledge, symptom recognition and health outcomes. As noted in Chapter 3, a gender-specific burden of AF exists whereby men are 1.5 times at greater risk of AF although the absolute number of women exceeds that of men due to the greater longevity of women overall [Benjamin et al., 1994]. Additionally, gender influences the presence or absence of certain risk factors for AF [Benjamin et al., 1994; Feinberg et al., 1995; Stewart et al., 2001]. Gender balance is maintained within the SAFETY cohort with an even proportion of women and men consistent with the epidemiology of AF. It should be noted, however, that clinical trials of pharmacological agents typical involve the recruitment of younger males primarily from high income countries which results in incomplete evaluation of inherent gender-based differences. This is reflected in the recent trials assessing the efficacy and effectiveness of novel therapeutics for the management of AF [Connolly et al., 2009; Granger et al., 2011; Patel et al., 2011].
The findings of this sub-study are consistent with previous research reporting that women with AF are older with a higher symptom burden, poorer HR-QoL and different co-morbidity and treatment profiles than their male counterparts [Benjamin et al., 1998; Levy et al., 1999; Humphries et al., 2001; Rienstra et al., 2005; Goli et al., 2012]. These findings also imply that women with AF should be more carefully assessed and potentially require a higher level of surveillance and support. As a component of AF disease management, women may also have inherently different educational requirements to overcome these identified disparities.

We also identified the importance of cognitive impairment assessment in the setting of AF with up to 65% of patients demonstrating MCI within the high-risk SAFETY cohort. Chapter 6 of this thesis, therefore, presented a published research report that explored the prevalence of MCI and discussed the implications for effective patient self-care and self-management. MCI detected in the hospital setting was found to persist within 7-14 days of hospital discharge. Furthermore, deficits in multiple cognitive domains (therefore affecting multiple thought processes such as learning, acquiring knowledge and task prioritisation) were identified. Those with identified MCI were less educated but at higher thrombo-embolic risk. Furthermore, patients displaying MCI were more likely to be prescribed digoxin. In addition, these patients were more likely to demonstrate higher digoxin levels but be of lower body weight, potentially indicating a form of digoxin toxicity, although further research to confirm these findings is required. Given the typical age and comorbid profile of individuals hospitalised with AF, it is not unexpected that patients will experience some difficulties with cognitive as well as physical processes. Our findings support previous research that MCI is a well-known concomitant condition in AF patients and a common consequence of vascular dementia [Eggermont et al., 2012]. In addition, AF is a known independent predictor of cognitive impairment [Ott et al., 1997; Kilander et al., 1998; Knecht et al., 2008]. However, MCI (and its assessment) is often overlooked in patients with AF, which has the potential to result in poorer clinical outcomes due to the complexity of AF treatment regimens and the need for constant self-monitoring. This research reinforces the need for implementation of patient- and disease-specific management interventions.
that can incorporate patient cognitive status in considering the best methods to employ for education delivery, stimulation of appropriate self-care practices and increased support requirements.

Both the systematic review of AF-related outcomes (described in Chapter 3) and initial profiling of the SAFETY trial cohort confirmed the potential to address high levels of morbidity and mortality in typically older individuals with chronic AF. Given the scope of the problem, there is an urgent need to find cost-effective ways to further risk-stratify affected individuals beyond traditional methods. In Chapter 7, a new application for ECG Holter monitoring as a means of assessing the success or failure of achieving therapeutic targets was described. When AF patients are discharged from hospital, a therapeutic target of rhythm or rate control is nominated for achievement and/or maintenance in order to minimise future clinical events and re-hospitalisation. However, minimal follow-up is carried out post-discharge to understand if these targets are being met. Continuous ECG Holter monitoring is usually applied for diagnostic purposes when patients have had a clinical event (e.g. stroke) or are experiencing symptoms (e.g. palpitations or syncope). The current research, however, applied Holter monitoring as a method of enhanced risk delineation.

A considerable number of patients who were not meeting their physician-nominated AF control target were identified (34%). Notably, 43% of nominated rhythm control patients had reverted back to AF post-discharge. Furthermore, an uncontrolled heart rate (sustained at >90bpm for >10% of recording time) was identified in 26% of all patients. A novel method for describing heart rate control in AF patients was determined and three distinct heart rate phenotypes were described; stable, periodically labile and persistently labile. In addition, correlates of true rhythm and rate control were identified. Patients with a lower thrombo-embolic risk (as determined by the CHA$_2$DS$_2$-VASc score), a lower diastolic blood pressure at hospital presentation and those prescribed digoxin were less likely to be classified as truly rhythm controlled. Those prescribed an anti-arrhythmic (as expected) were more likely to be truly rate controlled. Correlates of stability were also identified, the most important being that patients who were more clinically complex with diagnosed CAD and/or
renal disease were less likely to display heart rate stability. These phenotypes are potentially predictive of clinical stability, patient outcomes and re-hospitalisation, although analysis of this predictive value is beyond the scope of this thesis and these will be prospectively tested once follow-up (with blinded adjudication of all events) of the SAFETY cohort is completed. The identified correlates have the potential to be used as additional factors with which to direct individual patient management and stratify patients into different risk categories, if the identified phenotypes prove to be truly predictive.

The findings of this thesis provide insights into optimising the management of patients with AF using enhanced risk delineation strategies. Specific AF management issues and sub-groups were identified that require additional surveillance and support during active management, i.e. women, patients with MCI, patients not achieving intended rate or rhythm control and those represented in the persistently labile or permanently labile groups.

Within this dissertation, it has been acknowledged that the spectrum of risk displayed by AF patients is expansive, diverse and variable (between and within patients). We have also demonstrated that employing enhanced delineation methods to assess risk on an individual basis can provide critical clinical information, prompting the initiation of action plans to achieve or re-establish clinical stability in the short-term and optimal outcomes in the longer-term.

**Limitations**

The broad limitations of the current research program require acknowledgement. Firstly, the respective cohort of patients with AF comprised only those at high risk who have been hospitalised in Australia (with its hybrid universal health/private health care system). Additionally, in the analysis of gender-specific differences, the sample sizes of women and men are relatively small. Therefore, findings from the current research program may not be readily applicable to all patients with AF in different countries and health care settings.
In the assessment of MCI in patients with AF, we applied only one clinical assessment tool. Furthermore, the duration and cause of MCI is not known and cannot be distinguished in this cohort. Although the MoCA has been shown to be sensitive and specific, more extensive psychometric testing in addition to testing of functional capacity would be required to confirm the presence of MCI. However, the MoCA could reasonably constitute an initial screening of MCI due to its short length (approximately 10 minutes) and ease of administration.

In the analysis of heart rhythm/rate control, Holter monitoring was employed for a 24-hour period which may not have been long enough to obtain a comprehensive picture of rate and rhythm in these AF patients. Overestimation of lability may also have been possible due to observed inherent and spontaneous variability of normal rhythm as well as during arrhythmias caused by day-to-day variations in heart rate and adrenergic drive. Although all recordings were reviewed and analysed by trained personnel, initial classification of beats and rhythms was via an electronic classification system, which itself has inherent limitations. It cannot be discounted, therefore, that misclassification occurred, although this was minimised by the comprehensive analysis undertaken. Furthermore, data obtained from the Holter monitor database was only provided in hourly epochs restricting more comprehensive minute-to-minute evaluation. Initial findings did prompt a treatment response and determining the true prognostic value of the identified phenotypes may prove difficult to determine.

More generally, the overall cohort consists of patients who are acutely ill, potentially exaggerating clinical instability. Exclusion of non-English speaking individuals into the study may have introduced selection bias, although English competency is necessary for comprehensive understanding of the many questionnaires administered. In addition, selected validated tools were utilised in data collection. Assessment tools have inherent limitations and the use of single tools may over- or under-estimate the conditions or health states assessed within this cohort. Furthermore, the often chaotic acute clinical setting under which the initial comprehensive assessment was conducted in addition to the patients’ altered health state may not represent an ideal testing
situation. Despite the selection of a “real world” cohort, we cannot discount the possibility of bias in study selection and perhaps the under-representation of certain groups of patients (e.g. females). Therefore, these data may not readily apply to other hospitalised cohorts.

Whether observed differences in this cohort translate to differential health outcomes is still unknown. Despite these limitations, these data have important clinical implications for the post-discharge management of patients with chronic AF.

**Future Research**

The major short-term objective for continued research into optimising AF patient management is the successful completion of the SAFETY trial and the collection and interpretation of primary and secondary outcome data. With the pre-specified number of participants recruited and mandatory 24 month follow-up (with acquisition of 12 and 24 month clinical data) near complete in late 2013, the primary outcomes from SAFETY will be reported in mid-to-late 2014. The effectiveness and influence of the AF-specific management intervention on unplanned re-hospitalisations and mortality (both related and unrelated to AF) will be assessed at this point. Furthermore, cost-effectiveness evaluation of the intervention and individualised AF management will be undertaken.

An evident extension of the current research should involve understanding the value of each of the methods identified for extended risk delineation in the management of AF, particularly on patient outcomes. The simplest method of delineation examined here was by gender and analysis of outcomes should be assessed separately in females compared to males. We also found a considerable level of MCI present in hospitalised patients with AF (extending into the post-discharge period) and the influence of cognitive impairment on patient management and intervention implementation should be determined. If the presence of MCI leads to confounding of management, it is potentially practical to undertake a prospective sub-analysis of outcomes according to the presence or absence of MCI. Further research must also be undertaken to confirm
the predictive power of the Holter monitoring heart rate phenotypes classified within the current body of work. With the comparison of Holter monitoring data obtained at 12 months post-discharge and interim data on patient outcomes collected at the same time point, the predictive ability of this method of enhanced risk delineation can be ascertained. Additionally, there may be a potential need for refinement of the phenotype classifications, providing further extension to the delineation of risk in patients with AF to optimise management.

Due to the complexity and heterogeneity of AF, there also remain many more patient-specific factors (e.g. the presence of certain co-morbidities or the prescription of certain therapies) that have the potential for use in enhanced risk delineation strategies. Future research efforts should be employed to identify these. Additionally, elements of AF-specific management interventions that address the risk defining factors identified in this dissertation should be developed and tested in future cohorts of AF patients. These elements could include more extensive clinical assessment whilst an in-patient to trigger more (or less) intensive pathways (according to requirements) for post-discharge care, education programs specifically designed for patients with MCI, screening tools to more definitively assess self-care in the context AF or the ongoing use of Holter monitoring for continuous assessment, re-evaluation and re-direction of therapeutic management targets. Of course, there are cost implications and resourcing requirements for these suggestions which must be taken into consideration. However, the influences of these elements on both short- and longer-term patient outcomes and clinical stability should be assessed in future prospective randomised controlled intervention trials. Whether these elements are also predictive of longer-term patient outcomes must also be understood.

**Conclusions**

The burden of AF is larger than widely reported, which has important implications for individuals, societies and health care systems worldwide. This research program assessed the true size of this burden which highlighted the critical need for multi-disciplinary action to curtail the potentially devastating influences of this increasingly
common condition. Furthermore, the effectiveness of enhanced delineation methods to assess individual patient risk was examined. Current management practices do not appear to be reducing the frequency of poor outcomes associated with an AF-related hospitalisation and it is a critical time to intervene in an attempt to optimise patient management. There is the potential for the methods of extended stratification assessed in the current research program to be integrated into future AF management practices or become the basis for AF-specific rehabilitation programs that would operate in a similar manner to current cardiac rehabilitation programs.

Overall, the hypotheses at the foundations of this thesis were supported by the findings of this research. Risk profiles of patients with AF are evidently diverse with different risk factors influencing the effectiveness of management programs and/or patient outcomes with different intensity. With further investigation and integration into current management practices, the enhanced methods of risk delineation highlighted in this thesis may improve expected outcomes and optimise the management of patients with AF.
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Supplementary data (Appendix 3) for:


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Appendix II
A proposal for interdisciplinary, nurse-coordinated atrial fibrillation expert programmes as a way to structure daily practice

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Introduction

Atrial fibrillation (AF) is a frequently occurring arrhythmia that is independently related to increased morbidity and mortality. In particular, AF is associated with complications such as ischaemic stroke, systemic thrombo-embolism, and heart failure, leading to increased hospitalizations.1 Atrial fibrillation, therefore, has a major impact on healthcare systems, which is likely to expand in an ageing population.1 – 3

Although AF can occur asymptomatically, two-thirds of the patients experience symptoms. The management of AF is, besides stroke prevention, predominantly focused on controlling symptoms and on improving quality of life (QOL).1,2,4 Symptom profile and burden can vary over time, both within and between patients. Consistent symptom assessment and follow-up are therefore important. Moreover, evidence-based guidelines facilitate clinicians in obtaining positive patient outcomes.1,2,4,8 Nonetheless, guideline adherence in practice is often poor,1 leading to suboptimal symptomatic control, reduced benefit from proven treatments on morbidity and mortality, and inappropriate healthcare resource use.

Recognizing that symptom management and improving guideline adherence are important both for patients individually and for the impact on healthcare systems globally, it is mandatory to develop and implement more efficient ways to deal with AF.6,8,9 However, the best model for implementing AF care is still unclear. This article presents our viewpoint regarding optimized AF management by comprehensively addressing (i) the main goals to be achieved; (ii) the related requirements for AF management programmes to achieve those goals; (iii) our position that nurses should have an important coordinating role in such programmes; (iv) the implementation of such programme in practice; and (v) which outcomes should be targeted to evaluate effective deployment.

What do we aim to achieve in atrial fibrillation management?

Atrial fibrillation care should be organized to achieve clearly defined outcomes.10 As AF management is aimed at reducing symptoms and preventing severe complications,2 care should primarily focus on outcomes such as lower symptom burden, increased QOL, and decreased morbidity and mortality. However, healthcare system factors should also be targeted, e.g. optimizing access for patients despite limited physician time, or preventing unplanned hospitalizations, readmissions, and emergency care visits.

Hence, the ideal strategy should commit to a continuous improvement in delivering care by focusing on all relevant AF management outcomes and thus achieving the best possible effect of care. Effectiveness, cost-effectiveness, and impact of delivered service should be assessed by measuring outcomes in practice, to make evaluation and continuous adjustments possible.

What are requirements of an atrial fibrillation management programme to tackle the atrial fibrillation epidemic?

Implementation of evidence-based guidelines is critical. The term ‘implementation’ is often used to indicate ‘dissemination’, i.e. the
process of reaching professionals. Real implementation, however, means conversion of guidelines into practical workflow models that guarantee their application in individual patient care. The latter is usually not addressed in a systematic way, but forms the focus of the AF management programmes that we describe here.

The most effective way to accomplish systematic implementation of guidelines into daily care is still unclear. Other areas in cardiology, like heart failure clinics, have developed experience in dedicated comprehensive disease management programmes. We believe that such a programme, in which different professionals collaborate, is also essential to provide guideline-based AF management. An AF programme can integrate protocolized diagnostics, management of anticoagulation, rate and rhythm control, and treatment of co-morbidities. Throughout, patients are educated, empowered, trained, and provided with self-management counselling, which contributes to improved outcomes in terms of cardiovascular hospitalization and death.

Such a systematic interdisciplinary AF approach should address the following specific requirements to be effective: comprehensive assessment, systematization of medical care, education, coordination of care, and evaluation of care plan execution (Figure 1). These five cornerstones can be supported by a dedicated software program.

**Advocacy for nurse-coordinated atrial fibrillation management**

Many components of an integrated management approach are not purely medical, but consist of communication and education. Physician time is limited and expensive, often focusing on essential aspects of diagnosis and treatment but less on non-medical aspects, leading to suboptimal guideline implementation. A dedicated person is needed to coordinate all aspects of care. First experiences with AF programmes show that a devoted Clinical Nurse Specialist (CNS) can play a critical role in coordinating interdisciplinary practice. Clinical Nurse Specialists in heart failure clinics have proved to be effective. Nurse-coordinated care allows better to systematically assess patients and implement the multifaceted approach adherent with guidelines. Clinical Nurse Specialists have more time for patients than physicians and are more easily accessible, and thus constitute the natural pivot of communication. Clinical Nurse Specialists, frequently Masters-trained, can act more than in an executive role but also as change agent, because they have research skills and knowledge of healthcare improvement processes. They are capable of coordinating multidisciplinary teams in developing, implementing, and evaluating new strategies that meet the expectations of healthcare entities.

**A ‘nurse-coordinated atrial fibrillation expert programme’ addresses five cornerstones in practice**

**Comprehensive assessment**

Detailed assessment is critical for patient stratification and allocation towards an appropriate and tailored management plan. The CNS can perform a global cardiovascular risk assessment and can check for systematic screening of underlying diseases. Awareness of symptoms is not a good discriminator of presence or severity of AF and therefore difficult to use as a risk-related predictor of complications. The latter should be based on the CHA2DS2-VASc score for stroke and HAS-BLED bleeding risk score. Nevertheless, symptom control is a separate ‘driver’ of AF management and a key factor for patients’ QOL. Relation between symptoms and AF, however, is not always obvious, because other cardiovascular conditions and AF risk factors can cause similar symptoms. Changing AF patterns also contributes to the complexity of its assessment. Hence, sound symptom assessment is needed to determine whether therapies aimed at reducing symptoms are needed and effective. Atrial fibrillation-specific tools to systematically assess patient symptoms should be developed, evaluated, and integrated. Implementing risk and symptom scoring tools in a software decision support system could further improve application of guideline recommendations, as discussed below.

**Systematization of medical care**

The entire assessment, coordinating diagnostic work-up, treatment plan developing, and setting up proper follow-up are time-consuming. Systemization is critical to avoid unnecessary or unwanted variability in care provision. On the basis of comprehensive assessment and in dialogue with the supervising physician, CNSs can define and propose an interdisciplinary guideline-based management plan. To systemize the whole AF management process, CNSs can develop and use evidence-based practice protocols adapted to a specific healthcare institution. Furthermore, (digital) clinical pathways should be developed and implemented into the
hospital information system, both for outpatient and in-hospital patients, to support the disease management programme and to enhance the quality of care by improving outcomes, promoting safety, increasing satisfaction, and optimizing the use of resources. Clinical pathways attempt to increase efficiency by organizing the care-delivery process into analysable steps and are one means of supporting the systematic use of evidence-based recommendations. Implementation in hospitalized heart failure patients showed better guideline-adherence, decreased mortality rates, shorter hospital stays, and less readmission after discharge. The CNS can play a key role in development and execution of such pathways, as full advantage can only be taken if the process is governed by a ‘process care taker’. Pathways allow continuous surveillance of clinical outcome indicators and can be used for auditing, standardizing, and improving the organization of care.16

Education
Better patient education is needed. At least one-quarter of patients does not understand and cannot explain AF. One in four physicians experiences lack of time to educate the patients.17 Nevertheless, education is effective since it leads to active patient participation and improved outcomes.7 Clinical Nurse Specialist may be the best guarantee that education is provided. Clinical Nurse Specialists have the competence to assess patients’ educational needs, and can provide personalized education about pathophysiology of AF, treatment options, and action plan, including addressing psychosocial challenges. As education is not a one-way process, assessing whether a patient is receptive is important. ‘Testing knowledge’ and ‘adaptation of education level’ should therefore be integrated in the AF care programme. By the CNS competence to use evidence-based education strategies and to create a learning environment that facilitates patients’ self-reflection and self-management, the programme will obtain positive behavioural changes. The CNS can direct patients to existing educational materials using a variety of formats including written and interactive computer applications. Group education sessions can also be efficient to inform and facilitate peer support. Furthermore, to pursue continuous quality improvement, the CNS commits to lifelong learning and uses feedbacks to improve effectiveness of the educator role.18

Coordination of care
Physicians consider AF difficult and time-consuming to manage. Cardiologists rated AF as the third most demanding and the second most difficult condition to manage.17 Even for a trained specialist, many aspects of assessment and communication are time-consuming. Failure to address those aspects may negatively affect the quality of care.7

Therefore, an AF programme may be more effectively and efficiently organized by a CNS, who coordinates implementation of the management plan by being a liaison between patient, family, referring physicians, and other caregivers. The CNS can plan and coordinate concerted action by various caregivers, and can provide education, information, and specific instructions regarding their responsibilities. As a central contact person, the CNS can be reached concerning management questions by both in- and outpatient caregivers and patients themselves, leading to improved access.

Evaluation of care plan execution
A critical aspect should be evaluation of care plan execution. The CNS can be responsible for continuous follow-up of the management plan, focusing mainly on compliance issues, adherence to follow-up, changes in risk profiles, symptom improvement, and on satisfaction. Monitoring predefined outcomes pertinent to the care plan can serve as an ideal evaluation method to check whether it is effective and well implemented. On the basis of these outcomes, care plan adjustments can be made.

Overall importance of software and clinical pathways
Using a software program containing guideline-based management advice is recommended, as it can be a meaningful tool to support the five cornerstones. It guides physicians and CNSs through the care process. Moreover, it serves as an electronic patient record (medical history, diagnostic tests, etc.), is able to determine an individual patient profile (based on type of AF, stroke risk, bleeding risk, symptoms, etc.), and proposes the most appropriate guideline-based management plan to implement. It is, however, important to adapt it to local practice, both medically and logistically, to optimize its impact. At both the University Hospitals of Maastricht and Leuven, such a software program, which directs medical therapy based upon patient’s profile and clinical guidelines, has been implemented and shown to effectively increase guideline-adherence both by physicians and by CNSs.9,12,13

Interdisciplinary clinical pathways put the whole care process (from comprehensive assessment to evaluation of care plan execution) into concrete terms and translate it into actual care. It is known for its ability to expedite patient care while optimizing healthcare resources. Moreover, a digital clinical pathway with full integration of nursing and physician documents reduces variations in clinical practice, improves standard of care, and facilitates guideline implementation by medical teams. It prevents duplication and allows physicians and nurses to spend more time on disease management. Such personalized care also improves patient satisfaction.16

How can nurse-coordinated atrial fibrillation expert programmes be structured?
It is our position that the CNS should be a central contact person in AF patient care under the supervision of a cardiologist or electrophysiologist. Figure 2 displays how different disciplines could be structured around the patient. The CNS could act as recipient for intra- and extramural consultation requests and could see patients in preparation of clinic visit evaluation by the physician (‘nurse-coordinated’: upper panel). Alternatively, the evaluating physician delegates tasks to the CNS in the work-up and management of a patient (‘nurse-assisted’: lower panel). The supervising physician defines guideline-based management plan, in collaboration with a CNS and a patient. This usually is finalized during a clinic visit.
The CNS is responsible for plan implementation, patient education, and coordination of care and follow-up in conjunction with the referring physician.

Inspired by earlier work,8,12,13,19 we developed a flowchart detailing assessment and care process of patients in the AF programme, from consultation request until follow-up (Figure 3). This flowchart should be seen as a blueprint, a starting guide for development and implementation of AF programmes. It should be adapted according to institutional needs and requirements.

**Outcomes to evaluate effectiveness of atrial fibrillation expert programmes**

Because ‘outcome assessment’ is crucial in evaluating effectiveness of clinical interventions, it is important to determine outcomes sensitive to implementation of AF programmes.10 Currently, no consensus exists on which outcomes should primarily be assessed.
Covering the whole spectrum of possible AF management-related outcomes, different classifications can be used to identify relevant outcomes. Currently, a study is in progress at the University Hospitals of Leuven, in which an international expert panel is established and consulted with respect to outcomes pertinent to mortality, morbidity, QOL, patient and caregiver experience, process evaluation, and economic consequences. Different outcomes will be ranked in the order of importance. Such lists can form the basis of ‘benchmarks’ to evaluate effectiveness of AF programmes or other interventions. We have mapped some tentative process and clinical outcomes that have already been measured, evaluated, or considered in literature, to the structural design of the AF expert programmes shown in Figure 3.

Effectiveness studies of AF nurse-led management interventions are scarce, especially with mortality as endpoint. Nevertheless, they suggest that such programmes provide facilitated access to medical care, deliver more efficient coordinated care, and improve guideline adherence and health outcomes.
Conclusions

As there is a growing need for putting guidelines into practice, many initiatives will be proposed over the coming years. We have argued here for nurse-coordinated AF expert programmes, but other approaches are imaginable. It is important that effects of such approaches are evaluated in a standardized way, by measuring universal outcomes. We call upon researchers and clinicians who are setting up AF expert programmes, to report on their efforts and to evaluate their effectiveness. Dialogue and communication will be vital to find solutions to tackle the AF epidemic most efficiently. The present article aims to start this process.

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Conflicts of interest: H.H. is holder of the AstraZeneca Chair in Cardiac Electrophysiology, University of Leuven. H.H. is Coordinating Clinical Investigator for the Biotronik-sponsored EuroEco study on health-economics of remote device monitoring. H.H. is a member of the scientific advisory board of Biosense Webster, Inc., St Jude Medical, Inc., Siemens Medical Solutions, Boehringer-Ingelheim, Bayer and Sanofi-Aventis.

References


Appendix III
Interdisciplinary, nurse-coordinated expert programmes as a panacea in atrial fibrillation management? Challenges we must face

Dana Berli, Clinical Nurse Specialist Arrhythmias Jeroen M.L. Hendriks, Axel Brandes, Christi Deaton, Harry J.G.M. Crijns, A. John Camm, Gerhard Hindricks, Philip Moons, Hein Heidbuchel

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We thank Jocasta Ball and colleagues for their interest in our article (1). We appreciate their support for the nurse-led disease management approach in atrial fibrillation (AF) management. As they are experts in home-based nurse-led interventions for patients with heart failure and chronic atrial fibrillation, they have indeed already delivered an excellent and valuable contribution to underpin the need for and the value of AF-specific management programs in order to improve AF management (2, 3).

In our article, we have argued for a nurse-coordinated AF expert programme (1). Although this can be run mainly as an outpatient service, in-clinic evaluation and delivery of care will definitely be needed in the more complex patients. We fully agree with the authors that although first experience has shown the benefit in less complex AF patients, the challenge is to confirm this in older AF patients, with more comorbidities and cognitive impairment. Therefore we are looking forward to the results of the SAFETY trial (4), but we are confident that more coordinated care will improve outcome, especially in this older patient cohort. Some of us have already had positive experience of schemas where nurses work both in the hospital clinic and the community within primary care settings. Moreover, we have to realise that there is a great variability between healthcare systems, and nurse-coordinated care might need adaptation to these different systems. Indeed, we have only started to explore this form of care, and certainly agree that ‘one-size-fits-all’ AF-clinics are not the panacea for all healthcare environments.

Reference List


Conflict of interest:

Hein Heidbuchel is holder of the AstraZeneca Chair in Cardiac Electrophysiology, University of Leuven. H.H. is Coordinating Clinical Investigator for the Biotronik-sponsored EuroEco study on health-economics of remote device monitoring. H.H. is a member of the scientific advisory board of Biosense Webster, Inc., St Jude Medical, Inc., Siemens Medical Solutions, Boehringer-Ingelheim, Bayer and Sanofi-Aventis.
Appendix IV
MONTREAL COGNITIVE ASSESSMENT (MOCA)

VISUOSpatial / EXECutive

Copy cube

Draw CLOCK (Ten past eleven) (3 points)

POINTS

NAMING

MEMORY
Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

FACE
VELVET
CHURCH
DAISY
RED

No points

ATTENTION
Read list of digits (1 digit/sec). Subject has to repeat them in the forward order.
Read list of letters. The subject must tap with his hand at each letter A. No points if 2 errors.

2 1 8 5 4
7 4 2

1/3

LANGUAGE
Repeat: I only know that John is the one to help today. The cat always hid under the couch when dogs were in the room.

2/2

Fluency / Name maximum number of words in one minute that begin with the letter F

N = 11 words

1/1

ABSTRACTION
Similarity between e.g. banana - orange = fruit [ ] train - bicycle [ ] watch - ruler

2/2

DELAYED RECALL
Has to recall words with no cue

FACE
VELVET
CHURCH
DAISY
RED

Points for uncued recall only

5/5

Optional

Category cue
Multiple choice cue

ORIENTATION
[ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

6/6

TOTAL

Add 1 point if ≤ 12 yr edu

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Appendix V
CORRESPONDENCE

Diagnosing vascular mild cognitive impairment with atrial fibrillation remains a challenge

To the Editor: we read with interest Ball et al’s4 article exploring the prevalence of mild cognitive impairment (MCI) in patients with chronic atrial fibrillation (AF). This study suggests that MCI is highly prevalent (50% to 65%) among older hospitalised patients with AF. This is valuable research, highlighting the much-overlooked association between cognitive impairment (CI) and AF. We feel, however, that the prevalence rates reported may overstate the true prevalence of MCI in older adults with AF. In this case, MCI was classified using a cut-off score of less than 26 (or 24) on the Montreal Cognitive Assessment (MoCA) in patients deemed not to have dementia following routine evaluation by hospital clinical teams. While the authors of the article acknowledge that the MoCA is a screening test and that further assessment is required to determine a diagnosis of MCI, using the MoCA as a single cognitive screen presents other challenges that need to be addressed. First, our experience of using the MoCA to identify CI in a memory clinic setting is that it overestimates CI in older adults with less time in formal education, irrespective of their subtype of CI. Among a sample of patients with memory loss attending our clinic, 50% (30/60) with normal cognition screened positive on the MoCA compared to 13% using a new rapid screen for MCI, the Quick MCI screen (Qmci),2 and only 3% on the Mini-Mental State Examination. Adjusting for age and education, the MoCA misclassified 38.5% (10/26) of those >75 years with >12 years of education. An acute hospital admission, given the increased likelihood of delirium, is likely to exaggerate this misclassification. Second, the diagnosis of MCI itself is under scrutiny given the lack of consensus in developing cut-offs for its defining characteristic, namely, the presence of CI without social and functional impairment. Presenting functional data, rather than stating that subjects were living independently, would provide context for the MoCA scores. Furthermore, the diagnostic criteria for MCI related to cerebrovascular disease are even less clearly defined,3 than MCI related to Alzheimer’s dementia. The MoCA has particularly poor specificity in these circumstances, resulting in high false-positive rates, which improve after application of age-adjusted and education-adjusted cut-offs.4 Presenting the prevalence of CI, both MCI and dementia, among similar age-matched and education-matched hospital patients, are necessary to give additional context to these results. Defining MCI as a score below a threshold on the MoCA in non-demented persons misses the complexity and can overestimate the condition. We agree with the authors that cognitive screening is important in persons with AF but reiterate that caution is needed in diagnosing vascular MCI in this fashion.

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