IMPROVING PATIENT OUTCOMES AND REDUCING HEALTH CARE BURDEN – THE NEED FOR A NEW PARADIGM OF CARE DELIVERY FOR ATRIAL FIBRILLATION

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Abstract

Atrial fibrillation (AF) is an emerging global epidemic. Incidence and prevalence of the condition continues to rise, and AF related health care utilisation has become costly and burdensome. Furthermore, quality of life in AF is akin to those with other chronic cardiovascular conditions such as heart failure. The literature review in Chapter 1 of this thesis explores current research in AF and explores the opportunities that exist for improving outcomes in this condition. Chapter 2 explores national trends in hospitalisations due to AF in Australia and compares this to two other common cardiovascular conditions, heart failure (HF) and myocardial infarction (MI). This demonstrates that hospitalisations due to AF have grown at a significantly greater rate than that of HF and MI and are now the most common cause for cardiovascular hospitalisation in Australia. The rising incidence of AF has led to a search for new risk factors for the condition in addition to exploring appropriate targets and thresholds for existing risk factors. In Chapter 3, the association between alcohol and AF is examined with a view towards determining a lower threshold at which risk of developing the condition is increased. Results of this study demonstrate that up to one standard drink per day does not confer an increase in risk, with gender differences apparent at moderate levels of intake.

Chapter 4 is concerned with exploring the current literature in relation to the use of the integrated care approach in AF and its impact on clinically relevant outcomes. This synthesis of the current literature shows that this approach is associated with improvements in several clinically relevant outcomes including reductions in all-cause mortality and cardiovascular hospitalisations. In Chapter 5, the contemporary

management of AF is reviewed in a cohort of symptomatic individuals who have presented to the emergency department due to AF with a view towards determining factors predictive of re-presentation. As hospitalisations remain the most expensive component of AF care, this is particularly relevant in the search for modifiable factors that may present an opportunity for intervention. Of interest, the use of a non-standardised personalised AF action plan for management of future episodes was associated with a significant increase in risk of both AF related emergency department presentations and hospitalisations. In Chapter 6, the impact of a brief nurse led educational intervention, which incorporates lifestyle and behavioural goal setting, in AF is evaluated. The brief approach used in this study did not impact on health-related quality of life or cardiovascular risk factor status in a contemporary cohort of individuals with AF at short term follow up. Finally, in Chapter 7, a new target for improving outcomes in this condition is examined, with a review of the current literature concerning polypharmacy and clinically relevant health outcomes in the AF population. This has demonstrated association with several important outcomes including increased all-cause mortality, major bleeding and clinically relevant non-major bleeding.

Statement of Original Authorship

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint award of this degree. I give permission for the digital version of my thesis to be made available on the web, vis the University's digital research repository, the Library Search and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

Signature:

Date: April 2019

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Publications and communications to learned societies

Chapter 1

Publications:

1. **Editorial:** Gallagher C, Sanders P and Wong CX. Anticoagulation for Atrial Fibrillation in Cirrhosis of the Liver: Are Low-Dose Non-Vitamin K Oral Anticoagulants a Reasonable Alternative to Warfarin? **Journal of the American Heart Association 2019*;*** 8(5): e012102.
2. **Editorial:** Gallagher C, Lau DH and Sanders P. Reducing the risk of dementia in AF: is oral anticoagulation the key? **Mayo Clinic Proceedings 2018;** Feb;93(2):127-129.
3. **Manuscript:** Rangnekar G, Gallagher C, Wong GR, Rocheleau S, Brooks AG, Hendriks JML, Middeldorp ME, Elliott AD, Mahajan R, Sanders P, Lau DH. Oral Anticoagulation Therapy in Atrial Fibrillation Patients Managed in the Emergency Department Compared to Cardiology Outpatient: Opportunities for Improved Outcomes. **Heart Lung & Circulation 2018;** Apr 4. 9506(18)30140-9.
4. **Manuscript:** Gallagher C, Hendriks JM, Mahajan R, Middeldorp ME, Elliott AD, Pathak RK, Sanders P, Lau DH. Lifestyle management to prevent and treat atrial fibrillation. **Expert Review of Cardiovascular Therapy 2016;** 14(7):799-809.

Presentation:

1. **Abstract:** Cardiac Society of Australia and New Zealand Annual Scientific Meeting (ASM), 2016, Adelaide, Australia.

   Gallagher C, Wong G, Rangnekar G, Rocheleau S, Brooks A, Hendriks J, Middeldorp M, Mahajan R, Sanders P, Lau D. Outpatient management of atrial fibrillation: Specialised care is associated with greater guideline adherence. **Heart, Lung and Circulation 2016**, Volume 25, Supplement 2, Page s129.

Chapter 2

Publication:

1. **Manuscript:** Gallagher C, Hendriks JML, Giles L, Karnon J, Pham C, Elliott AD, Middeldorp ME, Mahajan R, Lau DH, Sanders P, Wong CX. Increasing trends in hospitalisations due to Atrial Fibrillation in Australia from 1993-2013. **Heart 2019;** doi: 10.1136/heartjnl-2018-314471.

Presentations:

1. **Abstract:** Heart Rhythm Society ASM, 2018, Boston, United States of America (USA).

   Gallagher C, Hendriks JML, Giles L, Elliott AD, Middeldorp ME, Mahajan R, Lau DH, Sanders P, Wong CX. Hospitalizations due to Atrial Fibrillation in Australia over two decades: a relentless rise. **Heart Rhythm 2018**, 15:5, Supplement 1, S496-S497.

2. **Abstract:** European Heart Rhythm Association ASM, 2018, Barcelona, Spain.

Gallagher C, Hendriks JM, Giles L, Elliott AD, Middeldorp ME, Mahajan R, Lau DH, Sanders P, Wong CX**.** Trends in hospital admissions for atrial fibrillation in Australia: a relentless rise. **EP Europace 2018**, Volume 20, Issue suppl 1, Pages i19.

3. **Abstract:** Asia Pacific Heart Rhythm Society ASM, 2017, Yokohama, Japan.

   Gallagher C, Hendriks JM, Giles L, Elliott AD, Middeldorp ME, Mahajan R, Lau DH, Sanders P, Wong CX. AF related hospitalisation trends in Australia over a twenty year period: a relentless rise.

4. **Abstract:** Australian Cardiovascular Health and Rehabilitation Association ASM, 2017, Perth, Australia.

   Gallagher C, Hendriks JM, Giles L, Elliott AD, Middeldorp ME, Mahajan R, Lau DH, Sanders P, Wong CX. Trends in AF related hospitalisation in Australia over a 20 year period: a relentless rise.

5. **Abstract:** Cardiac Society of Australia and New Zealand ASM, 2017, Perth, Australia.

   Gallagher, C, Hendriks JML, Giles L, Eliott AD, Middeldorp ME, Mahajan R, Lau DH, Sanders P, Wong CX. Twenty year national trends in hospitalisations due to atrial fibrillation in Australia: a relentless rise. **Heart, Lung and Circulation 2017**, Volume 26, Supplement 2, Page s175.

6. **Abstract:** Florey Postgraduate Research Conference, University of Adelaide, 2017, Adelaide, Australia.

   Gallagher, C, Hendriks JML, Giles L, Eliott AD, Middeldorp ME, Mahajan R, Lau DH, Sanders P, Wong CX National trends in AF related hospital admissions in Australia: a relentless rise.

Prizes:

1. **First prize.** Original Research Prize Session. Australian Cardiovascular Health and Rehabilitation Association ASM, 2017.
2. **People's Choice Award.** Australian Cardiovascular Health and Rehabilitation Association ASM, 2017.
3. **Travel scholarship.** Australian Cardiovascular Health and Rehabilitation Association – SA/NT, 2017.

Chapter 3

Publications:

1. **Letter:** Gallagher C, Hendriks JML, Lau DH, Sanders P. Alcohol and atrial fibrillation. **International Journal of Cardiology 2018;** Jan 15; 251:56.
2. **Manuscript:** Gallagher C, Hendriks JML, Elliott AD, Wong CX, Rangnekar G, Middeldorp ME, Mahajan R, Lau DH, Sanders P. Alcohol and atrial fibrillation: a systematic review and meta-analysis. **International Journal of Cardiology 2017;** Nov 1; 246:46-52**.**

Presentations:

1. **Abstract:** Asia Pacific Heart Rhythm Society ASM, 2016, Seoul, South Korea**.**

   Gallagher C, Hendriks JLM, Elliott AD, Rangnekar G, Middeldorp ME, Mahajan R, Lau DH, Sanders P. Low alcohol intake and incident atrial fibrillation: is there a safe level? **Journal of Arrhythmia 2016**, Volume 32, Issue S, Pages EX1-EX26.

2. **Abstract:** Florey Postgraduate Research Conference, University of Adelaide, 2016, Adelaide, Australia.

   Gallagher C, Hendriks JLM, Elliott AD, Rangnekar G, Middeldorp ME, Mahajan R, Lau DH, Sanders P. Alcohol intake and incident AF: is there a safe threshold?

3. **Abstract:** Cardiac Society of Australia and New Zealand ASM, 2016, Adelaide, Australia.

   Gallagher C, Hendriks JLM, Elliott AD, Rangnekar G, Middeldorp ME, Mahajan R, Lau DH, Sanders P. Alcohol and atrial fibrillation – what should the recommendations be? Insights from a systematic review and meta-analysis. **Heart, Lung and Circulation** 2016, Volume 25, Supplement 2, Page s124-.

4. **Abstract:** Heart Rhythm Society ASM, 2016, San Francisco, USA.

   Gallagher C, Hendriks JLM, Elliott AD, Rangnekar G, Middeldorp ME, Mahajan R, Lau DH, Sanders P. Alcohol consumption and incident AF: is there a safe threshold? Insights from a systematic review and meta-analysis. **Heart Rhythm 2016,** 13:5 Suppl. 1, S353-S354.

Prizes:

1. **Northern Communities Health Foundation Award.** Florey Postgraduate Research Conference, University of Adelaide, 2016.

2. **Travel scholarship.** Heart Rhythm Society, 2016.

Chapter 4

Publications:

1. **Manuscript:** Gallagher C, Elliott AD, Wong CX, Rangnekar G, Middeldorp ME, Mahajan R, Lau DH, Sanders P, Hendriks JML. Integrated care in atrial fibrillation: a systematic review and meta-analysis. **Heart 2017;** Dec;103(24):1947-1953.

Presentations:

1. **Abstract:** Australian Cardiovascular Health and Rehabilitation Association ASM, 2016, Adelaide, Australia.

   Gallagher C, Elliott AD, Wong CX, Rangnekar G, Middeldorp ME, Mahajan R, Lau DH, Sanders P, Hendriks JML. Integrated care in atrial fibrillation: a systematic review and meta-analysis.

2. **Abstract:** Asia Pacific Heart Rhythm Society, 2015, Melbourne, Australia.

   Gallagher C, Elliott AD, Wong CX, Rangnekar G, Middeldorp ME, Mahajan R, Lau DH, Sanders P, Hendriks JML. The integrated care approach in atrial fibrillation: improving care delivery and patient outcomes.

Prize:

Travel fellowship. European Society of Cardiology, 2015.

Chapter 5

Presentation:

1. **Abstract:** Heart Rhythm Society ASM, 2019 (accepted), San Francisco, USA.

   Gallagher C**,** Wong CX, Hendriks JM, Bednarz JM, Elliott AD, Linz D, Middeldorp ME, Lau DH, Sanders P**.** Characterization of hospital re-presentations in Atrial Fibrillation: the REVIEW AF study.

Chapter 6

Presentations:

1. **Abstract:** EuroHeartCare, 2019 (accepted), Milan, Italy.

   Gallagher C, Orchard J, Sanders P, Neubeck L, Hendriks JM. NursE led ATrial Fibrillation Management - a randomised controlled feasibility study.

2. **Abstract:** Heart Rhythm Society ASM, 2019 (accepted), San Francisco, USA.

   Gallagher C, Orchard J, Sanders P, Neubeck L, Hendriks JM. NursE led ATrial Fibrillation Management: NEAT-AF – a randomized controlled trial.

Prizes:

Educational grant, EuroHeartCare, 2019.

Travelling Scholarship, 2019. Cardiac Society of Australia and New Zealand.

Chapter 7

Publications:

1. **Manuscript:** Gallagher C, Nyfort-Hansen K, Rowett D, Wong CX, Middeldorp ME, Mahajan R, Lau DH, Sanders P, Hendriks JM. Polypharmacy and health outcomes in atrial fibrillation: Is there a role for deprescribing? A systematic review and meta-analysis. (under review).

Presentations:

1. **Abstract:** European Heart Rhythm Association ASM, 2019, Lisbon, Portugal.

   Gallagher C, Nyfort-Hansen K, Rowett D, Wong CX, Middeldorp ME, Mahajan R, Lau DH, Sanders P, Hendriks JM. Polypharmacy and atrial fibrillation: a systematic review and meta-analysis.

2. **Abstract:** South Australian Health and Medical Research Institute Cardiovascular Research Showcase, 2018, Adelaide, Australia.

   Gallagher C, Nyfort-Hansen K, Rowett D, Wong CX, Middeldorp ME, Mahajan R, Lau DH, Sanders P, Hendriks JM. Polypharmacy and atrial fibrillation: Is there a role for deprescribing? A systematic review and meta-analysis.

3. **Abstract:** Asia Pacific Heart Rhythm Society ASM, 2018, Taipei, Taiwan.

   Gallagher C, Nyfort-Hansen K, Rowett D, Wong CX, Middeldorp ME, Mahajan R, Lau DH, Sanders P, Hendriks JM. Polypharmacy and AF: an opportunity for improved patient outcomes?

4. **Abstract:** Heart Rhythm Society ASM, Boston, USA.

   Gallagher C, Nyfort-Hansen K, Rowett D, Wong CX, Middeldorp ME, Mahajan R, Lau DH, Sanders P, Hendriks JM. Polypharmacy: A risk marker for Adverse Outcomes in Atrial Fibrillation. **Heart Rhythm 2018,** 15:5 Supplement 1, Page S496-.

Prize:

Best Poster Award. South Australian Cardiovascular Health Research Showcase, 2018.

Invited Faculty Invitations

1. **Invited presentation:** *EuroPrevent ASM*, European Society of Cardiology, 2018, Ljubljana, Slovenia. Overweight and atrial fibrillation.
2. **Chair:** *Heart Rhythm Society ASM*, Heart Rhythm Society, 2018, Boston, USA. The Evolving Roles of Advanced Practice Clinicians in the Care of EP Patients.
3. **Invited presentation:** *Asia Pacific Heart Rhythm Society ASM*, Asia Pacific Heart Rhythm Society, 2018, Taipei, Taiwan. The growing burden of hospitalisations due to AF – what is the role of the nurse?
4. **Chair:** *Asia Pacific Heart Rhythm Society ASM*, Asia Pacific Heart Rhythm Society, 2018, Taipei, Taiwan. Nursing Care in Heart Rhythm: Device and Ablation Therapy.
5. **Invited presentation:** *EuroHeartCare ASM*, European Society of Cardiology, 2019, Milan, Italy. Advances in Sleep and Cardiovascular Health.
6. **Invited presentation:** *Heart Rhythm Society ASM*, Heart Rhythm Society, 2019, San Francisco, USA. Incorporating Risk Factor Management & Education into Your AF Clinic: The Adelaide Experience.
7. **Invited presentation:** *Heart Rhythm Society ASM*, Heart Rhythm Society, 2019, San Francisco, USA. AF and Cardiovascular Risk Factors - A Growing Health Care Burden.
8. **Chair:** *Heart Rhythm Society ASM*, Heart Rhythm Society, 2019, San Francisco, USA. Allied Professionals and Clinical Research.

Chapter 1: Literature Review

1.1 EPIDEMIOLOGY OF ATRIAL FIBRILLATION

Atrial fibrillation (AF) is a growing global epidemic. The lifetime risk of developing this condition is one in four in adults over the age of 40.[1] Progressive increases in the incidence and prevalence of AF have been demonstrated over recent decades and show no sign of abating.[2] Over 50 years of follow up in the Framingham study cohort, an increased incidence of AF from 3.7 to 13.4 cases per 1000 person years in men and 2.8 to 8.6 cases per 1000 person years in women was demonstrated.[3] Over the same period of time, a quadrupling of AF prevalence was observed ranging from 20.4 to 96.2 cases and 13.7 to 49.4 cases per 1000 person years in males and females respectively.[3] In the Manitoba study, the incidence of AF rose sharply with age from 0.5 per 1000 person years in those younger than 50 to 9.7 per 1000 person years after the age of 70.[4] It is expected that by the year 2050, 15.9 million individuals in the United States of America (USA) will be living with this condition, underscoring the importance of strategies to prevent the onset of AF.[5] Furthermore, in part due to large populations and rising levels of modifiable cardiovascular risk factors, absolute numbers of individual living with AF in the Asia Pacific region is expected to far exceed that of North America in coming decades, with significant implications for this region.[6]

AF is associated with numerous complications, including increased risks of thromboembolic complications such as ischaemic stroke and heart failure (HF), and growing health care burden with hospitalisations due to the condition now outnumbering those for HF in Australia.[7] The last two decades alone have witnessed an almost doubling of all-cause mortality in the AF population.[2] In this context strategies to both prevent the

onset of the condition, and improve outcomes in the prevalent AF population have become an urgent global healthcare need.

1.2 HOSPITALISATION TRENDS FOR ATRIAL FIBRILLATION

Health care resource utilisation remains one of the greatest challenges borne out of the growing AF epidemic. Hospitalisations comprise the largest component of this with numerous countries demonstrating significant increases over recent decades. In the United States of America (US) between 2000-2010 an overall 23% increase in hospitalisations due to AF was observed with an associated 1787 United States Dollars (USD) per hospital admission increase over the same time period.[8] More recent data has supported a continuing upwards trend in the elderly population in the US with adjusted rates of hospitalisations for AF increasing at a rate of 1% per year from 1999-2013, but with an associated reduction in readmission rates and inpatient mortality over the same time period.[9] Contemporary data from the Nationwide Emergency Department Sample in the US demonstrated a 30.7% increase in Emergency Department presentations from 2007-2014.[10] Despite a reduction in rates of admission from the emergency department from 70% to 62% , there was still a significant 16% increase in hospitalisations over this time period driven by the large increase in emergency department presentations over this time.[10] In Europe, similar trends with rising hospitalisation rates have been demonstrated across numerous countries, although contemporary data is lacking.[11-13]

1.2.1 AF hospitalisations in the Asia Pacific region

Comparatively little is known about AF related hospitalisations in the Asia Pacific region. Recent data has suggested that in part due to larger populations and growing rates of modifiable cardiovascular risk factors, absolute numbers of individuals with AF in this region will be significantly greater than that of North America and Europe, with important implications for health care resource utilisation.[6] In the southwest of China, a 20 fold increase in AF has been observed in conjunction with a 13 fold increase in stroke in individuals with AF between 2001 and 2012.[14] Additionally, stroke rates in individuals with AF demonstrated significantly greater increases compared to those without the condition (6.4% vs 2.8% for AF vs no AF; Odds Ratio [OR] 2.28; 95% CI 1.81-3.08; $p<0.01$).[14] A contemporary nationwide Korean study demonstrated a 420% increase in hospitalisations associated with AF over the ten year period between 2006-2015 with the majority of admissions occurring in individuals over 70 years of age.[15] An increase in the complexity of individuals with AF was also demonstrated in this study with significant increases in CHA_2DS_2-VASc (Congestive Heart Failure, Hypertension, Age >75 years [doubled], Diabetes, Prior Stroke or Thromboembolism [doubled], Vascular disease, Age 65-74, sex category[female]) and HAS BLED (Hypertension, Abnormal renal or liver function, Prior stroke, Prior major bleeding, Labile international normalised ratio [INR], Elderly, Drugs or Alcohol) scores, in addition to a two fold increase in peripheral arterial disease and a 1.7 fold increase in chronic kidney disease.[15] There was, however, an associated reduction in inpatient mortality, which is consistent with recent US data.[9] The CHA_2DS_2-VASc score is used to predict risk of stroke in individuals with AF with higher numerical values denoting a higher stroke risk and resultant need for therapy with oral anticoagulation.[16] The HAS-BLED score is used to predict risk of bleeding with the use

of oral anticoagulant therapy and to identify individuals in which modifiable factors can be managed to reduce this risk.[17]

In Australia, in line with global data, the incidence and prevalence of AF is expected to continue rising with significant ongoing implications for health care resource utilisation. It is projected that by the year 2034, an approximate doubling of the number of Australians over the age of 55 living with AF will be observed.[18] Previous Australian data demonstrated that AF related hospitalisations significantly outnumbered those for HF over the 15-year period between 1993-2007, although there were larger absolute numbers of hospitalisations due to MI.[7] In Western Australia, age and sex standardised data demonstrated the largest rise in incident AF hospitalisations (as a principal diagnosis) in the 35-64 year old age group over the sixteen-year period between 1995 and 2010[19], with this representing significant health care resource implications as it is likely that these individuals will present to hospital on multiple occasions, thereby contributing to growing prevalent hospital admission rates. Indeed, this study also examined prevalent hospital admission rates and found similar, albeit greater, trends in increased hospitalisations for AF, and again demonstrated the greatest rise in the youngest age group of 35-64 years.[19]

1.2.2 Economic costs of AF

The cost of AF to healthcare systems worldwide is significant with hospitalisations the main driver of this. In Canada, hospital costs attributable to AF in 2010 were 815 million Canadian dollars, of which 710 million was due to the direct cost of hospitalisations.[20] In the United Kingdom (UK), 50% of AF related healthcare expenditure is due to hospitalisations.[21] Between 1995 and 2000 direct overall health care costs related to AF

rose by more than 53% from 244 million pounds sterling to 459 million pounds.[21] In the US, similar upwards trends have also been demonstrated with an absolute national increase in hospitalisation costs due to AF of 1.31 billion USD from 2001-2010.[8] The highest increase in cost was observed in the 50-64 year old age group, with a significantly greater rise observed in males.[8] Reasons for this are unclear but may be related to a greater prevalence of AF in males compared to females, and may also be due to a greater likelihood of receiving invasive therapy for AF such as electrical cardioversion and ablation.[22] The additional cost of AF as a comorbid diagnosis is also significant, with estimates that this added an incremental 1.95 billion USD annually to the cost of inpatient hospitalisations in 2001.[23] In this study, the overall cost of treatment for AF including hospitalisations, as a principal and secondary diagnosis, outpatient management and prescriptions was 6.65 billion USD.[23] It is likely that this number has exponentially grown over the last decade due to the rising incidence of AF, growing numbers of hospitalisations due to the condition and expanding indications for costly invasive procedures such as AF ablation.

In Australia, the total economic cost of AF was estimated at 1.25 billion Australian dollars (AUD) in 2010.[24] This takes in to account costs associated with AF related hospitalisations and its two major complications (stroke and heart failure), disability and residential aged care costs and costs due to lost productivity. Indeed, the combined cost of the two major complications of AF, stroke and heart failure, account for 35% of this expenditure and underscores the importance of efforts directed at risk mitigation. Hospitalisations due to AF itself accounted for 13% of all expenditure. It is likely that these costs have significantly grown in recent times, owing to the growing incidence and prevalence of the condition, and use of AF related procedures.

1.2.3 Quality of life in AF

Health related quality of life in paroxysmal AF has been demonstrated to be consistent with, or worse than, those with other forms of cardiovascular disease including ischaemic heart disease and heart failure.[25] Furthermore, it has been demonstrated that little correlation exists between traditional markers of disease severity, such as left ventricular ejection fraction, New York Heart Association (NYHA) class, left atrial dimension, AF frequency and duration, and health related quality of life.[25] In asthma and other chronic cardiovascular conditions, patient beliefs about their condition and treatment and strategies to manage symptoms are closely correlated with quality of life, depression and perceived disability.[26-28] Depression and/or anxiety is common in individuals with AF and is positively associated with greater AF symptom burden, impaired health related quality of life and AF recurrence. Furthermore, it has been demonstrated that individuals with persistent AF demonstrate a greater severity of depression than those with paroxysmal AF.[29]

Given the association between AF, poor quality of life and depression, factors associated with this are key to reducing the burden of this condition. From a qualitative study of interviews conducted with 30 individuals with AF undertaking three different treatment modalities (cardioversion, AF ablation and AV node ablation) several themes, which may contribute to poorer quality of life, emerged.[30] These themes were the unpredictable nature of AF episodes and symptoms; strategies for dealing with AF symptoms and treatment concerns and expectations. The 'vicious cycle' of AF was expressed by a number of participants with one reporting that they felt individuals who experienced a myocardial infarction were 'better off' as they attended cardiac rehabilitation classes and were able to return to normal life.[30] Concerns about side effects of medicines were common with some unable to attribute if symptoms were related to

the condition or therapy used to treat symptoms. The efficacy of invasive treatments such as AF ablation and AV node ablation was expressed by several participants, with many describing this as a 'last resort' as they were unable to tolerate living with the unpredictability and symptom burden of their condition.

A large registry of 10,087 individuals with AF demonstrated that higher symptom burden (European Heart Rhythm Association [EHRA] class ≥ 2 vs class 1) and poorer quality of life (highest quartile of the Atrial Fibrillation Effect on Quality of Life Questionnaire (AFEQT) were both significantly associated with a higher risk of all cause hospitalisation (Hazard ratio [HR] 1.23, 95% CI 1.15-1.31; p<0.001 and HR 1.49, 95% CI 1.2-1.84; p≤0.001 respectively).[31] It is possible that improved knowledge and enhanced chronic condition management, including control of symptoms, could lead to better patient outcomes, including improved quality of life, and reduced health care burden in this population.

1.3 MODIFIABLE RISK FACTORS FOR INCIDENT AF

1.3.1 Background

Temporal adverse trends in modifiable cardiovascular risk factors have been demonstrated in recent times. Indeed it has been speculated that the observed reduction in the rate of decline of mortality rates for cardiovascular disease (CVD) and stroke in the US observed since 2011 is partially driven by rising modifiable cardiovascular risk factors.[32] A cross sectional study of more than 5000 participants from four US communities with 25 years of follow up demonstrated unfavourable recent trends in modifiable cardiovascular risk factors.[33] Over this time period mean body mass index (BMI) increased from 24.5 to 30.2kg/m^2, a reduction in physical activity was also

observed although rates of smoking decreased from 30.4% to 17.1% over follow up. Whilst an initial reduction in total cholesterol and low density lipoprotein C (LDL-C) was observed over the first ten years of follow up, this was largely reversed in years 20-25 which demonstrated an upwards trend in levels with the exception of the cohort of black women enrolled in this study.[33] Obesity was significantly associated with elevation in LDL-C compared to individuals of normal weight. Similar patterns have also been demonstrated in other studies including the Mississippi Behavioural Risk Factor Surveillance System study which reported trends in self-reported cardiovascular risk factors in 11,978 participants.[34] Over 9 years of follow up, significant increases in rates of elevated cholesterol levels, diabetes and hypertension were observed across the entire cohort with racial differences noted between black and white participants.[34] Rates of diabetes were significantly increased across the black cohort with a decrease in the prevalence of smoking in whites that was not observed in the black population.[34] Gender differences are also apparent with the Global Burden of Disease Study from 2013 demonstrating that for women in high income countries, an elevated BMI contributed the largest attributable risk to death and disability adjusted life years (DALYs), whilst for men systolic blood pressure and use of tobacco contributed the largest risk.[35]

Indeed, similar trends have also been demonstrated in the Asia Pacific region with a decrease in smoking rates from 79% in 1980 to 45% of the population in 2007 at which point it has stagnated.[36] A BMI of $\geq$25kg/m^2 also increased from 29% to 34% in the over 30 year old population. Hypercholestrolaemia has also increased in prevalence in the Korean population between 1998 and 2011, although rates of hypertension have improved, largely driven by improved management of the condition in those with a prior diagnosis.[36] Rates of modifiable cardiovascular risk factors have also grown in China, and occur at greater rates in suburban Beijing compared to the rest of China.[37] In this

study of 16,371 suburban residents of China, 83.5%, 47.2% and 17.5% of participants had 1, 2 or ≥3 modifiable cardiovascular risk factors respectively, highlighting the importance of primary prevention strategies to manage risk.

1.3.2 Established risk factors for incident AF

Numerous established risk factors have been identified for incident AF. These are largely derived from large epidemiological studies which have consistently identified numerous factors associated with AF development. Several AF risk factors are non-modifiable and include ageing, gender and genetics.[38,39] Indeed, the incidence of AF has shown a steep increase associated with advancing age with European data demonstrating a rate of 1.1 per 1000 person years for the 50-59 year old age group rising to 20.7 per 1000 person years in the 80-84 year old age bracket.[40] North American data has demonstrated a quadrupling of the age adjusted incidence rate for AF from 3.7 to 13.37 per 1000 person years over the 50 year period up to 1998.[3] Additionally, both incidence and prevalence rates for AF are higher in males compared to females.[2] However, the observed increase in incidence of AF in recent decades cannot be accounted for by ageing populations alone.

Numerous potentially preventable or modifiable conditions are also associated with the development of AF and include coronary artery disease, heart failure and chronic kidney disease.[39] In recent years, the contribution of modifiable risk factors for AF has gained momentum as an appreciation of their role not only in the development of AF, but also progression of the condition, has been explored. Conditions such as hypertension, overweight and obesity, diabetes and smoking are established factors associated with AF development.[41] Recently, newer factors including obstructive sleep apnoea (OSA), epicardial fat, aortic stiffness and metabolic syndrome have emerged.[42-45] A case control

study from the Atherosclerosis Risk in Communities (ARIC) study, has demonstrated that numerous modifiable cardiovascular risk factors are evident in individuals more than 15 years prior to AF diagnosis and highlights potential opportunities to intervene to prevent onset of the condition.[46] The importance of modifiable risk factors in the development of AF has recently been highlighted with evidence from the Framingham cohort demonstrating a significantly lower lifetime risk of AF development in those with optimal control of five modifiable risk factors (not smoking, low alcohol intake, normal BMI, normal blood pressure and no prior history of MI or HF) with a one in five risk compared to a one in three risk in individuals with at least one elevated risk factor.[47] The cumulative risk of multiple cardiovascular risk factors has also been demonstrated in the ARIC study, with each component of the metabolic syndrome (elevated blood pressure, elevated waist circumference, low high density lipoprotein cholesterol, impaired fasting glucose and elevated triglycerides) independently conferring an increase in risk of AF development.[48] Collectively all five components was associated with a more than fourfold increase in risk of AF development compared to those without these risk factors (HR 4.40, 95% CI 3.25-5.94).[48] A particular focus on modifiable risk factors for AF is of significant importance due to potential for intervention at a primary prevention level to curtail this growing epidemic. Each of the major modifiable risk factors for incident AF will be discussed below.

1.3.3 Hypertension

Due to a high prevalence in the general population, hypertension is the largest population attributable risk factor for AF.[49] Hypertension is known to heighten the risk of AF development with increases in the order of 1.4 to 2-fold.[39,50-52] The likelihood of AF

development is also increased even at levels considered pre-hypertensive (systolic blood pressure of 130-139mmHg), with a 28% increase in risk observed (HR 1.28; 95% CI 1.00-1.63) in 34,221 females participating in the Women's Health Study.[53] This increased risk was also observed in the Multi-Ethnic Study of Atherosclerosis Study in which sustained pre hypertension, over a median follow up of 5.3 years, was associated with an increased risk of incident AF in 5,311 individuals (HR 1.8, 95% CI 1.004-3.2).[54] Over long term follow up of 35 years, pre-hypertension, as reflected by a systolic BP of 128-138mmHg, was also associated with an increased risk of incident AF in 2014 Norwegian males (HR 1.6, 95% CI 1.15-2.21).[55]

Furthermore, a longer duration of hypertension and treatment received for the condition were independently associated with development of incident AF in the Framingham Heart Study when time updated variables over a 15 year period were considered.[56] A baseline diagnosis of hypertension with an increase of systolic BP over time conferred an almost two fold increase in risk of incident AF (HR 1.95, 95% CI 1.08-3.49; p=0.03), whilst even an initial diagnosis with hypertension and a decrease in BP over time was associated with a more than two fold increase in risk (HR 2.05, 95% CI 1.24-3.37; p+0.005).[56] Mechanistically, the substrate for AF development due to hypertension is thought to involve both structural and electrical remodelling with numerous contributing factors such as atrial dilatation, interstitial fibrosis, inflammation and conduction disturbances.[57,58] Whilst numerous studies have described the association between hypertension and AF, the optimal target at a primary prevention level to reduce the risk of developing AF has not yet been established.

1.3.4 Obesity

A strong association between obesity and AF has consistently been demonstrated.[3,52,59,60] A 29% increase in risk of AF development has been demonstrated with each 5 unit increase in body mass index (BMI) in a recent meta-analysis of cohort studies.[61] Furthermore, heightened risk of AF occurrence has been demonstrated in post-operative and post-ablation populations with incremental increases in BMI, with each 5 unit increase conferring a 10% and 13% risk increase respectively.[61] A possible mechanism mediating the association between obesity and AF is increased left atrial pressures and volume and a shortening of the effective refractory period.[62] A sheep model has demonstrated structural and electrical remodelling in the setting of obesity including conduction slowing, conduction heterogeneity, increased left atrial size and interstitial fibrosis, resulting in an increased propensity for AF, in addition to more sustained episodes.[63]

1.3.5 Obstructive sleep apnoea

Obstructive sleep apnoea (OSA) confers a greater than two fold increase in the risk of incident AF.[64,65] The prevalence of OSA in individuals with AF ranges from 40-50%, although some have suggested it could be much higher.[42,66] In individuals with known AF, OSA is associated with worse outcomes including a greater risk of anti-arrhythmic drug therapy (AAD) failure, higher rates of AF recurrence post cardioversion and catheter ablation and a threefold increase in risk of ischaemic stroke.[67-69]

Mechanistically, the link between OSA and AF is complex and multifaceted. It encompasses both structural and electrical remodelling including atrial enlargement, conduction abnormalities, voltage reduction and electrogram fractionation.[70] Many other

acute and chronic mechanisms are postulated to contribute to the increased risk of AF observed in OSA including endothelial dysfunction, atrial fibrosis, acute respiratory obstructive episodes, sympatho-vagal imbalance and inflammation.[42,71] Treatment with continuous positive airway pressure (CPAP) has been shown to enhance the likelihood of freedom from AF post catheter ablation,[72] although it has not been shown to reduce the likelihood of cardiovascular events in those with known cardiovascular or cerebrovascular disease.[73]

1.3.6 Diabetes

Diabetes is associated with a significant increase in risk of incident AF.[39,52] A meta-analysis of studies that adjusted for other AF risk factors demonstrated a 24% increase in risk (RR 1.24, 95% CI 1.06-1.44).[74] Mechanistically the link between diabetes and AF has been postulated to be due to numerous factors including autonomic dysfunction, electrical and structural remodelling and inflammation.[75] Animal studies have demonstrated a greater propensity for AF in diabetic animals compared to controls, with higher levels of atrial fibrosis and conduction delay observed in the diabetic state.[76] Furthermore, the duration of diabetes is also an important factor with a case control study demonstrating a 3% increase in risk of incident AF for each additional year of treated diabetes.[77] Poor glycaemic control, as demonstrated by higher glycosylated haemoglobin (HbA1c) levels, was associated with incremental increases in risk of AF development.[77]

1.3.7 Physical activity

The association between physical activity and AF is somewhat complicated by a potential increased risk observed at very high levels of exercise.[78] However, in a large population

based sample each increase in metabolic equivalent achieved during exercise testing was associated with a 7% lower risk of incident AF, with a greater magnitude of effect observed in obese compared to non-obese individuals.[79] There may be an upper threshold of exercise at which risk of AF is increased with a reduction in risk observed at moderate intensity levels of exercise, but not high intensity levels in a population based study of 5446 individuals ≥65 years of age over 47,280 person years of follow up.[80] Exercise training has numerous benefits which may in part account for the observed reduction in AF risk. These include improved management of conditions such as hypertension and diabetes,[81] weight loss,[82] and improved cardiac structure and function.[83]

1.3.8 Dyslipidaemia

The association between dyslipidaemia and incident AF is yet to be firmly established. Unlike numerous other cardiovascular conditions at which elevated low density lipoprotein (LDL) levels are strongly correlated with outcomes, an inverse association between LDL and AF has been described.[51,84,85] HDL appears to confer a protective effect with higher levels associated with a reduction in risk of AF[86] and lower levels associated with an increased risk of AF.[87,88]

1.3.9 Smoking

Conflicting data exists as to the impact of smoking on the risk of incident AF. Whilst numerous epidemiological studies have not demonstrated any association with AF, [39,51,59] others have described an association with risk estimate increases ranging from 32% to 200%.[4,89,90] This may be due to variations across studies in numbers of cigarettes smoked or habit duration or may be due to baseline differences across populations. A recent meta-

analysis found a 23% increase in risk of AF attributable to current smoking.[91] The link between smoking and AF could be multifactorial and attributed to inflammation, atrial fibrosis and oxidative stress,[92] although an exact mechanism in the setting of AF is yet to be determined. In established AF, current cigarette smoking has been associated with numerous adverse events including increased all-cause mortality (Relative risk [RR] 1.82, 95% CI: 1.33–2.49; p=0.0002), cardiovascular death (RR 1.54, 95% CI 1.31–1.81; P<0.00001) and major bleeding (RR 1.93, 95% CI 1.08–3.47; P=0.03).[93] However, no impact on risk of stroke or thromboembolism was observed in this meta-analysis.[93] Cigarette smoking is also a known contributor to atherogenesis, endothelial dysfunction and promotion of a heightened prothrombotic state all of which are unfavourable in the setting of AF.[94]

1.3.10 Alcohol

Little uncertainty exists over the association between high levels of alcohol intake and incident AF. Numerous epidemiological studies have described this association, although the level at which risk is increased has not been well characterised. In the Framingham cohort study, alcohol intake of greater than 3 standard drinks (SD) per day was associated with a heightened risk,[95] whilst in other higher risk populations increases in risk were observed even at lower levels of intake.[96] Other studies have described gender differences with moderate to high levels of alcohol intake associated with risk of incident AF in males but not females.[97-99] Two meta analyses have demonstrated a small but significant increase of approximately 8% at alcohol intake of 1 SD per day, but due to methodology employed in these studies, it is possible that an overestimation of risk may have occurred.[100,101]

There are numerous plausible mechanisms linking chronic alcohol intake to AF development. Originally thought to be related to binge drinking only, due to the observation of increased atrial arrhythmias during holiday seasons ('holiday heart' syndrome),[102] more recent observations have come to appreciate the role of chronic consumption in risk of AF development. Numerous proarrhythmic electrical changes associated with alcohol intake including a shortening of the effective refractory period, increased sympathetic activation, a reduction in vagal tone modulation and alterations in atrial current densities, may all contribute to a heightened AF risk.[103-105] The dose of alcohol consumed may be an important factor with a study of 75 individuals undertaking ablation for AF demonstrating a significant increase in low voltage zones and conduction slowing in the atria of those consuming moderate levels of intake (mean 14.3±4.2 drinks per week), compared to mild drinkers (4.4±2.3 drinks per week).[106] It is also plausible that the observed increase in risk is partially mediated through other cardiovascular risk factors, such as hypertension and obesity, which chronic alcohol intake, particularly at higher levels of intake, is associated with.[107,108]

1.3.11 Emerging risk factors for AF

Several studies have described an association between epicardial and pericardial fat and incident AF. Epicardial fat has been defined as the layer of fat between the myocardium and visceral pericardium and has been linked to both prevalence and severity of AF. In a study of 273 individuals of which 76 were in sinus rhythm, with 126 and 71 with paroxysmal and persistent AF respectively, greater pericardial fat volumes were observed in those with AF compared to those in sinus rhythm, even after adjustment for traditional risk factors.[109] Furthermore, those with persistent AF demonstrated more voluminous

epicardial fat compared to those with paroxysmal AF.[109] In the Framingham study cohort, of 3,217 individuals who underwent computed tomography scanning, the 54 individuals with AF were found to have significantly greater pericardial fat volumes compared to those without, in a multivariate adjusted model.[110] The same association did not hold true for either intrathoracic or visceral abdominal fat and suggests that the fat layer surrounding the heart may have significant implications for AF risk. In another study of 110 individuals undertaking first time ablation for AF and 20 controls individuals, pericardial fat was associated with presence and severity of AF, in addition to being predictive of AF recurrence after ablation.[111]

Mechanistically, the link between pericardial fat and AF is potentially attributable to numerous factors. The autonomic system is likely to play a key role. Ganglionated plexi are located within the epicardial fat pad and can stimulate both the sympathetic and the parasympathetic nervous system, with this intrinsic cardiac nerve activity known to precede the onset of AF in animal models.[112] Unique gene expression found in human atrial pericardial fat tissue, but not in ventricular or coronary pericardial fat samples in another study, suggested that genes associated with oxidative phosphorylation, cardiac muscle contraction and calcium signalling pathways could also play a part in arrhythmia development.[113] Recently, a cardiac magnetic resonance imaging study demonstrated electro-anatomical remodelling including conduction slowing, low voltage areas and greater fractionation of electrograms in areas adjacent to pericardial fat depots.[114]

Aortic stiffness has also been identified as another potential risk factor for AF development. In a study of 68 individuals without other significant comorbidity, referred for catheter ablation for AF, measures of aortic stiffness were correlated with AF recurrence post procedure.[44] Mechanistically, the link between aortic stiffness and AF is

not well defined but may be a marker of pre hypertension, which has been independently associated with an increased risk of developing the condition.[53]

1.3.12 Treatment for AF

The four pillars of treatment for AF include the use of rate control, rhythm control, oral anticoagulation to reduce stroke risk and cardiovascular risk factor management. Each of these factors will be discussed below.

1.3.13 Rate and rhythm control

Preference for treatment of AF with a rate or rhythm control approach is dependent upon many factors. These include the presence or absence of left ventricular (LV) dysfunction, left atrial size, the presence of symptoms and their degree of severity, atrial size and ability to achieve adequate rate control with medication alone.[115] Patient preference is also an important factor to consider in choice of treatment approach. Contemporary trials of a rate control strategy compared to rhythm control are somewhat lacking, although earlier studies have suggested no mortality benefit with the use of a pharmacological rhythm control approach.[116,117] In the Atrial Fibrillation Follow Up Investigation of Rhythm Management (AFFIRM) study, 4060 'high risk' individuals with AF (over the age of 65 or with multiple concomitant risk factors) were randomised to a pharmacological rate or rhythm control strategy.[116] Pharmacological treatment in each arm was left to the discretion of the treating physician. After five years, there was no difference in mortality between these two treatment strategies (21.3% vs 23.8% for rate vs rhythm control respectively; HR 1.15, 95% CI 0.99-1.34, p=0.08). All cause hospitalisations occurred frequently in both groups, but with greater likelihood in the

rhythm control arm compared to a rate control strategy (73% vs 80.1% for rate vs rhythm control respectively, p<0.001).[116] Further evidence in support of this was demonstrated in the Rate Control vs Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) study.[117] In this study, 522 individuals were randomised to an aggressive rhythm control strategy, which included the use of serial cardioversions and pharmacological treatment, or a rate control strategy. Despite a greater likelihood of sinus rhythm in the rhythm control strategy (39% vs 10% for rhythm vs rate control respectively), the rate control strategy was non inferior to rhythm control in the primary composite outcome of cardiovascular death, heart failure, thromboembolism, bleeding, pacemaker implantation, and severe adverse effects of drugs (22.6% vs 17.2% for rhythm vs rate control respectively; absolute difference -5.4, 90% CI -11.0 to 0.4). No significant difference in any of the individual components of the composite end point was demonstrated.[117]

Whilst the use of AAD are associated with significantly lower risk of AF recurrence compared to placebo, there is no evidence of any other benefit including a reduction in stroke risk or mortality.[115] Their use in long term management in AF should take in to consideration patient preferences in addition to other factors such as age, symptoms severity, degree of physical activity and left ventricular (LV) dysfunction. Any use of long term AAD requires close monitoring due to potential for harm.

1.3.14 The evolving role of AF ablation

In recent years, the role of catheter ablation has played a growing role in the management of AF. In the US, ablation for AF increased 10-fold from 2,644 procedures in 2000 to 21,345 in 2013, with AF the fastest growing indication for ablation therapy of all cardiac arrhythmias.[118] In Australia similar trends have been demonstrated with AF ablations

growing at a rate of 30.9% per year (adjusted for population estimates) over the ten year period up to 2010.[119] This is in stark contrast to other commonly used cardiovascular procedures, such as percutaneous coronary intervention (PCI), which demonstrated a 5% annual growth, adjusted for population estimates, over the same time period.[119] However, whilst AF ablation is a widely used procedure that has demonstrated exponential growth over recent decades, the impact of this procedure on recurrent hospitalisations for AF is unknown. Indeed, whilst this procedure has demonstrated superiority in terms of freedom from AF compared to other treatments such as AAD therapy,[120,121] long term attrition rates are significant.[122,123] Furthermore, few studies have examined the impact of this procedure on clinical outcomes such as hospitalisations and mortality.

Trials of catheter ablation to date have not suggested any mortality benefit except in individuals with concomitant heart failure.[124] Recently, results of the Catheter Ablation versus Anti-Arrhythmic Drug therapy for Atrial Fibrillation (CABANA) study have provided further insights in to the role of this procedure for AF.[125] The intention to treat analyses did not demonstrate any difference in the primary composite endpoint of death, disabling stroke, major bleeding or cardiac arrest after a median 4 years of follow up in 2204 individuals between individuals who underwent ablation compared to those who were pharmacologically managed (HR 0.86, 95% CI 0.65-1.15; $p = 0.30$). However, there was a high rate of crossover (27.5% from pharmacological management to ablation) and 9.2% randomised to ablation did not receive this therapy. All-cause mortality did not differ between groups, although there was less death or cardiovascular hospitalisation (HR 0.83, 95% CI 0.74-0.93; $p = 0.001$) and fewer AF recurrences (HR 0.52 95% CI 0.45-0.60; $p < 0.001$) in the ablation group compared to those allocated to medical therapy.[125] In a secondary analysis of this study undertaken according to treatment received, ablation therapy proved superior to pharmacological management in respect to

the primary end point of this study at final follow up (HR 0.67, 95% CI 0.50-0.89; p=0.006). All-cause mortality (HR 0.60, 95% CI 0.42-0.86; p=0.005) and death or cardiovascular hospitalisations were all significantly reduced in the ablation arm compared to pharmacological therapy (HR 0.83, 95% CI 0.74-0.94; p=0.002).[125] Disease specific quality of life in this study, as assessed by the AFEQT, demonstrated greater improvement in the ablation arm compared to medical therapy at 12 month follow up (adjusted difference 5.3 points, 95% CI 3.7-6.9; $p < .001$) with a difference of ≥5 points deemed a 'clinically important difference'.[126] This difference persisted at five year follow up with a mean 3.4 point difference in favour of ablation (95% CI 2.1-4.8, p<0.001). Reduced symptom burden, as assessed by Mayo AF Specific Symptom Inventory (MAFSI), was also demonstrated in the ablation arm compared to medical therapy (adjusted difference, -1.5 points, 95% CI, -2.0 to -1.1; $p < 0.001$) with a pre-determined clinically important difference of ≤-1.5 at 12 months.[126] This effect was still evident at five year follow up with a mean adjusted difference of -1.1 (95% CI -1.5 to -0.8; p<0.001). AF frequency was also significantly reduced at both 12 month and five year follow up.[126]

In select populations ablation has demonstrated a more definitive benefit. The Catheter Ablation for Atrial Fibrillation in Heart Failure (CASTLE-AF) trial demonstrated a reduction in the primary composite endpoint of all-cause mortality and hospitalisation for worsening heart failure in a cohort of 336 individuals with either paroxysmal or persistent AF and heart failure, after a median follow up of 37.8 months (28.5% vs. 44.6%; HR 0.62, 95% CI 0.43 to 0.87; p=0.007).[124] A large retrospective analysis of 5238 individuals undertaking first time ablation for AF demonstrated a reduction in cardiovascular (arrhythmic and non arrhythmic) hospitalisations in the 12 months following the procedure.[127] Compared to the 12 months prior to undertaking the

procedure, a 56% reduction in arrhythmia related hospitalisations was observed, in addition to a 43% reduction in hospitalisations for heart failure. No impact on non cardiovascular hospitalisations was observed.[127] Current evidence would support the use of this procedure in symptomatic individuals (unless heart failure is present) who are intolerant or decline the use of AAD therapy, or who have poor quality of life as a result of their condition.

1.3.15 Anticoagulation

An essential component of AF management is the reduction of stroke risk with the use of oral anticoagulant therapy in those in which this is necessitated based on level of risk. In the majority of international guidelines, this risk is calculated based on the CHA_2DS_2-VASc score with scores of two or more in males and three or more in females the recommendation for treatment with oral anticoagulant therapy unless contraindicated.[128] Consideration should also be given to anticoagulation initiation in males with a CHA_2DS_2-VASc score of one and females with a CHA_2DS_2-VASc score of two. The recently published Australian AF guidelines have suggested a 'sexless' score due to the lack of significance of female gender in isolation on stroke risk in AF.[115] Therefore, a CHA_2DS_2-Va score of 2 or more is the threshold for recommendation of anticoagulant therapy in these guidelines. However, wide variation in stroke risk at the same CHA_2DS_2-VASc score across cohort studies has been demonstrated.[129] In a systematic review of 34 studies at a CHA_2DS_2-VASc score of two, stroke risk was reported as below 1% per year in 27% of studies, 1-2% in 40% of studies and greater than 2% in 33% of studies.[129] Furthermore, the dynamic nature of the CHA_2DS_2-VASc score has recently been highlighted in a large observational study from Taiwan and has demonstrated the need

for regular reassessment.[130] In this database of 31,039 low risk individuals with AF, 13% experienced an ischaemic stroke over a mean follow up of 5.5 years. In almost 90% of individuals who experienced a stroke, there was a change in their CHA_2DS_2-VASc score over follow up which may have necessitated institution of oral anticoagulation (OAC) to reduce stroke risk with potential to significantly reduce the likelihood of this devastating complication.

Numerous studies have demonstrated that OAC treatment to reduce stroke risk is often poorly managed with both over and underuse of appropriate therapy in AF populations. Data from large registries has confirmed that OAC is frequently inappropriately overused in those at low risk of stroke with 47% of individuals in the Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD) registry and 57% in the Outcomes Registry for the Better Informed Treatment of Atrial Fibrillation (ORBIT AF) treated with oral anticoagulant therapy despite a CHA_2DS_2-VASc score of 0.[131] Whilst the appropriate use of oral anticoagulant therapy in those in which it is recommended, i.e. with a CHA_2DS_2-VASc score ≥ 2, demonstrated improvement over time, it still remains suboptimal. In the GARFIELD registry, appropriate treatment occurred in 69% of participants and in the ORBIT AF registry this was 87% with evidence of significant regional variability. Across countries in GARFIELD this ranged from 31%-93% and across various states in the USA this ranged from 66%-100%.[131]

In Australia high rates of inappropriate use of oral anticoagulation therapy have also been demonstrated. In a study examining the use of OAC in Indigenous and non-Indigenous Australians with AF, 76.3% of the Indigenous cohort and 71.3% of the non-Indigenous cohort with a CHA_2DS_2-VASc≥ 2 were not prescribed this therapy. Overuse of OAC in those at low stroke risk was also evident with a greater likelihood of both

under and overuse in Indigenous compared to non-Indigenous Australians (p=0.045 and p<0.001 respectively).[132] The provision of appropriate anticoagulation has also demonstrated to be of greater likelihood for those attending specialist care provided by an electrophysiologist, compared to that delivered in the emergency department.[133]

1.3.16 Cardiovascular risk factors in established AF

Cardiovascular risk factor management, in addition to rate control, rhythm control and anticoagulation, has emerged as the *'fourth pillar'* of AF management and is considered an essential component of holistic management of the condition. Numerous cardiovascular risk factors have demonstrated an association with both AF burden and progression of the disease. In Olmsted County, Minnesota a longitudinal cohort study of 3,248 individuals with paroxysmal AF were followed for a median of 5.1 years.[134] Both obesity (BMI 30-34.9kg/m^2) and severe obesity (BMI >35kg/m^2) were associated with progression to permanent AF (HR 1.54, 95% CI 1.2-2.0, p=0.0004 and HR 1.87, 95% CI 1.4-2.5, p<0.0001 respectively).[134] The Euro Heart Survey examined predictors of progression to permanent AF in 1,219 individuals with paroxysmal AF.[135] In this study independent predictors included heart failure, age, chronic obstructive pulmonary disease, previous transient ischaemic attack or stroke and hypertension.[135] Those who progressed to more permanent forms of the arrhythmia also had a greater likelihood of admissions for any cardiovascular reason (71% vs 50%; p<0.001), were more likely to undertake electrical cardioversion (26% vs 13%; p<0.001) and more likely to experience an ischaemic stroke (5% vs 1%; p=0.005).[135] In another study of 1385 individuals presenting with paroxysmal AF with relatively short term follow up (approximately 6 months), risk of progression to permanent AF was incrementally increased with

escalating BMI levels [HR 1.26 (95% CI: 0.92-1.72); 1.35 (95% CI 0.96-1.91); 1.50 (95% CI 0.97-2.33); and 1.79 (1.13-2.84) for overweight, obese 1, obese 2 and obese 3 respectively].[136] Other modifiable cardiovascular risk factors such as diabetes and hypertension were not independently associated with progression in this short term follow up study.[136] However, a Korean study from a large national database demonstrated that a blood pressure of greater than 130/80mmHg was associated with a greater risk of major cardiovascular events with an incremental increase in risk observed in those with poorly controlled BP, defined as ≥140/90mmHg.[137] An increased risk was also observed in those with intensively controlled BP of ≤120/80mmHg.[137] Furthermore, in a community based cohort of individuals with AF, the progression to more permanent forms of the arrhythmia has been associated with a greater risk of adverse effects including a combination of mortality and all cause hospital admissions (HR 2.89, 95% CI 1.28-6.55; p=0.011).[138]

1.3.17 Risk factor management in AF

Over recent years, the role of cardiovascular risk factor modification in AF has asserted itself as a key component of gold standard management of this condition. This has become evident through its inclusion in numerous recent international guidelines.[115,128,139] Several studies have demonstrated the efficacy of this approach, although multi-centre randomised controlled evidence in this area is lacking.

The first study to address the concept of targeting cardiovascular risk factor management (RFM) in AF was a randomised controlled trial (RCT) which enrolled 150 overweight or obese individuals with AF.[140] The intervention group attended a physician led cardiovascular RFM clinic at three monthly intervals for a total of 15 months follow up. The primary outcome measure in this study was AF symptom severity and burden,

both of which were significantly less in the intervention group compared to control. This was corroborated by 7-day Holter monitoring which demonstrated a reduction in number of AF episodes and total duration of AF in the intervention group. In the Aggressive Risk Factor Reduction study for Atrial Fibrillation cohort study (ARREST AF cohort study), a comprehensive risk factor management (RFM) program in overweight individuals (BMI≥27kg/m^2 with paroxysmal or persistent AF who had been referred for AF ablation, resulted in significantly greater arrhythmia free survival in those who participated in the program compared to those who declined (HR, for likelihood of sinus rhythm at final follow up for RFM vs control, 4.8; 95% CI 2.04-11.4; p<0.001).[141] This RFM program had several unique factors which may attribute to its success. Firstly, the program targeted numerous risk factors simultaneously. Weight loss was targeted with a resultant BMI aim of ≤27kg/m^2, or a reduction of at least 10% of initial body weight, in all participants. Physical activity was recommended, beginning at 150 minutes per week, with increases of up to 250 minutes per week. Other risk factors were concomitantly managed including lipid profile and blood pressure, with the addition of pharmacotherapy to lifestyle measures as necessary to achieve pre-defined targets. Obstructive sleep apnoea and diabetes was screened for and treated in all eligible individuals. Smoking cessation and reduction of alcohol intake were also aggressively targeted. This clinic was delivered by a single provider, which ensured care standardisation, and had regular follow up at 3-6 monthly intervals with more frequent visits scheduled as required. All participants were encouraged to maintain a lifestyle journal, which was a record of all food and drink intake, exercise undertaken and thrice daily home blood pressure measurements, and was reviewed at each visit to assist in meeting risk factor targets.

The results of this intervention were further affirmed in longer term follow up as was demonstrated in the 'Long term effects of goal directed weight management in an

atrial fibrillation cohort' (LEGACY) study.[142] In this study, 355 individuals with paroxysmal or persistent AF participated in a multifactorial risk factor management program with a mean follow up of approximately 4 years. In this observational cohort study, participants were divided in to three groups according to the degree of weight loss achieved at final follow up (≥10% weight loss, 3-9% weight loss or <3% weight loss or weight gain). Freedom from any atrial arrhythmia at final follow up was significantly greater in those who achieved >10% weight loss compared to those who achieved the smallest amount of weight loss or gained weight (HR 5.9; 95% CI 3.4-10.3, p<0.001).[142] Structural remodelling including a significantly greater reduction in left atrial size and interventricular septal thickness was also demonstrated in the group achieving the greatest degree of weight loss compared to those who attained smaller degrees of weight loss or gained weight. Furthermore, post hoc analysis of this study has demonstrated that weight loss, as part of an overall cardiovascular risk factor management program, is effective in reducing the likelihood of progression to more permanent forms of AF.[143] The cost effectiveness of this approach has also been demonstrated with this risk factor management program demonstrating an incremental cost effectiveness ratio of $62,653 per quality adjusted life year gained.[144] These studies underscore the importance of targeting cardiovascular risk factors as a rhythm control strategy in the overweight and obese AF population.

However, in those with more advanced forms of the arrhythmia, weight loss has not demonstrated the same degree of effectiveness as a rhythm control strategy. In a study of 90 individuals with longstanding persistent AF, despite substantial weight loss in those participating in a dietician led weight loss program (median reduction of -24.9kg, Interquartile Range [IQR] -19.1 to -56.7kgs; p<0.001) with no significant difference observed for those who declined the weight loss program, no objective or subjective

difference in AF burden was demonstrated as evidenced by 7 day Holter monitoring or AFSS questionnaire post catheter ablation for AF.[145] It is possible that a more advanced substrate for AF is evident in these individuals, accounting for the lack of observed effect. Despite the lack of observed impact on AF burden, the weight loss group did demonstrate improved physical and mental component summary scores of the SF-36 (8.4±3; p=0.013 and 12.8±8.2; p<0.02 for physical and mental component summary scores respectively), with no significant difference observed in those who declined this program (2.4 ± 14.3; p=0.43 and 3.1 ± 9.6; p=0.53 for physical and mental component summary scores respectively).[145]

Other studies have also demonstrated enhanced outcomes with the use of cardiovascular risk factor management. In the post ablation field, the role of cardiac rehabilitation in paroxysmal and persistent AF has demonstrated enhanced outcomes with a statistically significant increase in peak $V0_2$ in the intervention group compared to controls.[146] In this study of 210 individuals, who were enrolled prior to undertaking catheter ablation, the intervention included 12 weeks of thrice weekly exercise sessions and four educational sessions delivered by a nurse which commenced one month following catheter ablation for AF. The education sessions focussed on both information and education about AF, in addition to dealing with physical and psychological symptoms associated with the condition and the ablation procedure. After four months of follow up, the primary endpoint of peak $V0_2$ was significantly greater in the intervention group, with no significant impact on quality of life as assessed by the Short form 36 (SF-36) questionnaire. This is in keeping with other studies in AF management which also demonstrated no significant impact on quality of life.[147] In the post ablation study, there was no significant difference in serious adverse events between groups, although an increase in non-serious adverse events was observed in the cardiac rehabilitation group.

The concept of targeting cardiovascular risk factors as a rhythm control strategy was further endorsed with the recently published 'Routine vs Aggressive risk factor driven upstream rhythm Control for prevention of Early atrial fibrillation in heart failure (RACE 3)' trial.[148] This study enrolled 245 individuals, with early persistent AF (>7 days but <6 months with ≤1 prior cardioversion) and early HF (preserved or reduced ejection fraction, duration < 1 year), who were randomised to control or an intervention which consisted of four pharmacological and lifestyle components: 1. Mineralocorticoid receptor antagonists (MRAs); 2. Statins; 3. Angiotensin converting enzyme (ACE-I) or Angiotensin Receptor Blockers (ARBs); 4. Cardiac Rehabilitation. Six weekly visits occurred for the duration of the study to the HF/arrhythmia nurse to specifically address any AF or HF related symptoms or issues in the intervention group. Results of this study demonstrate greater utilisation of MRAs and statins in the intervention group compared to control. At 1 year, maintenance of sinus rhythm, delineated by 7 day Holter monitoring, was significantly greater in the intervention group compared to controls (75% vs 63% for intervention vs control respectively; OR 1.765; 95% CI 1.021–3.051; p=0.042).[148] This intervention had no impact on AF symptom burden, as determined by the EHRA class. At one year follow up, significant differences were observed between the intervention and control groups with respect to several cardiovascular risk factors including systolic blood pressure, diastolic blood pressure, BMI, weight, total cholesterol and LDL cholesterol. However, a number of these results, particularly blood pressure and lipid profile, could be attributed to pharmacologic measures which were utilised more frequently in the intervention group (as per protocol). However, other risk factors such as BMI and weight, whilst achieving statistically significant results are unlikely to represent significant clinical difference (e.g. there was a mean increase of 0.12 kg/m^2 in BMI in the intervention group with an overall -0.13% reduction in weight over one year

follow up). This is likely reflective of the counselling in which participants in the intervention group received. Dietary counselling by dieticians was only provided in those with a BMI $\geq$ 30kg/m^2. All participants were allowed up to 2 standard alcoholic drinks per day and there were no predefined targets for BP, lipids, BMI or waist circumference.

Treatment of isolated risk factors in AF has not resulted in enhanced outcomes compared to usual care populations. Aggressive management of blood pressure, via pre-defined protocols, in a symptomatic AF population undertaking catheter ablation did not result in significantly different likelihood of atrial arrhythmia recurrence after a six month follow up period, despite significantly improved blood pressure control.[149] This is likely due to management of one isolated risk factor without consideration of other factors, such as the metabolic syndrome[150] and obstructive sleep apnoea,[151] which are known contributors to AF recurrence post ablation. However, in those with resistant hypertension and paroxysmal or persistent AF treated by catheter ablation, renal denervation in addition to pulmonary vein isolation enhanced the likelihood of freedom from AF, as determined by implantable cardiac monitoring (HR 0.40, 95% CI: 0.21-0.80) and significantly reduced blood pressure (mean between group systolic blood pressure difference of -8mmHg, 95% CI -12 to -3mmHg) in a combined analysis of two studies enrolling 37 and 39 individuals in the intervention and control group respectively.[152] Importantly, the AF substrate in those with resistant hypertension is likely to be of a more advanced nature and require a different treatment approach to that of the wider AF population. This underscores the importance of services directed at comprehensive and holistic AF care, considering each individual's differing profile, as most likely to result in enhanced patient outcomes.

1.4 HOSPITALISATIONS IN AF – OPPORTUNITIES TO REDUCE HEALTH CARE BURDEN

1.4.1 Hospital readmissions in the AF population

Given the growing burden of hospitalisations due to AF, insights in to potentially modifiable factors associated with these is of great interest due to their ability to stem the growing epidemic of health care resource utilisation due to AF. Whilst the growing incidence of AF is a significant contributor to the increasing burden of hospitalisations,[2,5] other factors have also been identified. Rates of hospital readmission in individuals with AF are significant. A US sample of 6439 individuals demonstrated an 18% readmission rate within 30 days in those hospitalised primarily for AF.[153] In this cohort more than 10% of readmissions were due to AF, with other complications of the condition such as heart failure and cerebrovascular disease accounting for 7.1% and 6% of readmissions respectively.[153] Another study of 3498 individuals found similarly high readmission rates which approached 40% for all causes at 12 months following an initial presentation with AF or atrial flutter.[154] For cardiovascular re-hospitalisation, AF or atrial flutter was the most dominant cause accounting for 47.5% of all readmissions, with congestive heart failure the primary diagnosis for readmission in 9.9% of all cases, coronary artery disease in 7.4% and stroke/TIA in 6.2%.[154] Follow up admissions for AF or atrial flutter as a primary diagnosis were significantly longer, and associated with higher cost.[154]

1.4.2 Factors associated with repeat hospitalisations

A large dataset from the Nationwide Inpatient Sample in the US which examined almost 193,000 hospital admissions due to AF between January 1, 2009 and 31 December, 2010 demonstrated that 67% of all hospitalisations occurred in individuals over the age of

65.[155] The highest rate of hospitalisations occurred in individuals over 85 years of age in this dataset, which is in keeping with Australian data demonstrating higher rates of hospitalisations for AF in older age groups.[156] Interestingly, this US study demonstrated different rates of associated comorbidities in younger vs older patients hospitalised for AF (<65 years of age vs ≥65 years of age). Whilst hypertension and diabetes were the two most common comorbidities in each age demographic, there were higher rates of associated obesity and alcohol abuse in the younger age group, with more chronic kidney disease evident in the older population.[155] This raises the question of potentially modifiable factors amenable to intervention, particularly in younger age groups due to the modifiable nature of these risk factors including obesity and alcohol intake, to reduce the burden of hospitalisations. Significant geographical variations have been demonstrated too, although reasons for this are unclear.[10,155] This is potentially related to co-morbid conditions, patient acuity or variations in practice across hospitals, some of which may be amenable to intervention.

A Canadian based study of 2068 community dwelling, anticoagulated individuals with AF examined factors associated with all cause hospitalisations in the cohort of 879 individuals who were admitted to hospital during a median follow up time of 2.7 years. In this study, 66% of all hospitalisations were due to non-cardiac causes. A multivariate adjusted model demonstrated that advanced age, heart failure and the presence of vascular disease were all predictive of hospitalisation in this cohort.[157] However, in a similar cohort of 9484 community dwelling individuals with AF in the USA, cardiovascular causes were found to be the dominant cause of hospitalisations, accounting for 49% of all hospitalisations during the one year follow up period.[158] In this study, 31% of all participants experienced at least one hospitalisations during follow up, with more than 10% experiencing two or more admissions over this time. Individuals experiencing a

hospitalisation tended to be older, were more likely to be female and were more likely to have co-existent cardiovascular conditions including coronary artery disease, hypertension, cerebrovascular disease and peripheral vascular disease.[158] A higher $CHADS_2$ (Congestive Heart Failure, Hypertension, Age ≥ 75 years, Diabetes and Prior Stroke or TIA [doubled]) score and worse AF symptom severity, as determined by the EHRA class category, were also associated with hospitalisations. The $CHADS_2$ and CHA_2DS_2-VASC scores were also found to be predictive of first cardiovascular hospitalisation in another large retrospective cohort study of 377,808 individuals with AF. A threefold increase in risk of cardiovascular hospitalisation was observed in those with a CHA_2DS_2-VASc score of 9 compared to those with a score of 0 with a 2.3-2.7-fold increase in those with a $CHADS_2$ score of 6.[159]

In Olmsted County, Minnesota, a case control observational study of 1430 individuals with AF, demonstrated significantly higher rates of hospitalisations in the AF group compared to controls (58.8 vs 26.4 per 100 person years for AF vs control group) over a mean follow up of 6.3 years.[160] Numerous factors were associated with hospitalisations during follow up with the highest risk associated with heart failure and chronic kidney disease. Other factors related to admission included coronary artery disease, stroke, cancer, ever smokers, heart failure, chronic obstructive pulmonary disease and depression.[160] Hospitalisation and death due to cardiovascular causes occurred more frequently in the AF cohort compared to controls. Similar predictive factors for admission to hospital were also demonstrated in another US based study of ED presentations with advanced age (≥75 years), heart failure, diabetes, hypertension, chronic kidney disease, chronic obstructive pulmonary disease and income.[10] In this study, significantly greater rates of admission were observed in metropolitan hospitals compared to those in non-metropolitan areas.[10]

1.4.3 Strategies to reduce AF related hospitalisations

Significant geographical variation in management of AF in the emergency department has been demonstrated. In a survey of Canadian, American and Australasian emergency department physicians the use of rate control as an initial strategy varied from 43.1% in the United Kingdom (UK) to 94% in the USA.[161] The use of cardioversion in the emergency department also varied significantly ranging from 25.9% in the USA to 65.9% in Canada.[161] Even within countries significant variation in practices have been demonstrated. A review of eight academic centres in Ottawa, Canada demonstrated large variations in the use of strategies for the acute management of AF.[162] Potentially modifiable predictors of the use of electrical cardioversion included the prior use of electrical cardioversion and hospital site with odds ratios varying between 0.38 to 3.05.[162] Significant variation in rates of admission after successful cardioversion were also demonstrated with this occurring in only 27.2% of cases in the United Kingdom compared to 84.6% in Canada. This is clearly supportive of the concept that factors beyond that of clinical need play a part in contemporary AF care and is reflective of the lack of evidence based clinical guidance and lack of agreement in this area as demonstrated in current AF guidelines.[163] Importantly, this represents a potential avenue to curtail the growing health care burden due to AF.

In hospital strategies, such as the use of emergency department protocols, have been tested in numerous studies to standardise care and reduce unnecessary hospital admissions for AF. In a pilot 'before and after' study in the USA, an emergency department protocol which included early referral (generally next day appointment) to an AF clinic resulted in a dramatic reduction in rates of admission to hospital. In the pre-intervention period, rates of admission to hospital were 43% compared to 19% in the post intervention period ($p<0.001$)[164] The AF clinic was run by clinical pharmacists and

included a review of appropriate use of rate control and stroke preventative therapies, risk factor assessment and modification, patient education and facilitating communication between the emergency department and primary care practitioners. The number of AF clinic visits in this study is not reported on. Length of hospital admission did not significantly differ between the pre and post intervention period in this study and, surprisingly, a comparison of rates of re-presentation to hospital for AF in the pre and post study period was not reported on. Similarly, another US based study of an emergency department management protocol for AF also resulted in significantly fewer admissions (80% vs 16%, $p<0.01$); a significantly lower length of stay for inpatient hospital admission (mean length of stay 32 vs 85 hours; $p=0.002$) and a longer length of stay for emergency department presentations in the intervention group compared to control (mean 8 vs 16 hours; $p<0.001$)[165]. There was also a greater likelihood of restoration of sinus rhythm in the intervention group compared to control. The AF pathway in this study differed significantly from the prior study with greater collaboration between emergency department physicians and specialist EP cardiologists and was also without onwards referral to a specialist AF clinic or indeed any structured follow up care.[165] This may in part account for the lack of observed difference in rates of re-presentation to hospital for AF in the pre and post intervention study periods. Another US based study of an AF emergency department protocol followed by one clinic visit in a specialised AF clinic run by Nurse Practitioner's or Physician's Assistants under the oversight of electrophysiologists, resulted in a significant improvement in AF related quality of life, as assessed by the AFEQT questionnaire, at 90 days of follow up.[166] Over the 90 day follow up period, there were 15 repeat emergency department visits in 100 individuals and four hospitalisations. There was no control group or assessment of the pre-intervention period to determine the true impact of this intervention.

1.4.4 Management of AF in the Emergency Department

The early use of cardioversion has been evaluated in several studies to assess the impact of this strategy on early discharge from the emergency department. An emergency department protocol for AF management in Ottawa, Canada which involved the initial use of intravenous procainamide followed by early electrical cardioversion if restoration of sinus rhythm did not occur, resulted in 93.3% of the 660 enrolled patients reverting to sinus rhythm prior to discharge.[167] AF recurrence rate within 7 days was 8.6% with no control group for comparison purposes. There was no structured onwards referral pathway in this study. A medical record review of 289 visits in 168 low risk patients who had presented to emergency department with a primary diagnosis of AF in Ottawa, Canada demonstrated that 97% of patients were discharged directly from the emergency department with an average length of stay of five hours.[168] Electrical cardioversion was utilised in 28% (this was following failure of chemical cardioversion in 89% of individuals in this group) with success in 89%, with chemical cardioversion attempted in 62% with a 50% success rate. Short term follow up, which was limited to events at the treating hospital only, demonstrated a low risk of major adverse events with one patient requiring admission following administration of diltiazem which resulted in bradycardia and atrioventricular (AV) block.[168] In another US based study of 388 electrical cardioversion procedures undertaken at 4 emergency departments, restoration of sinus rhythm occurred in 86% of cases.[169] In the 7 day follow up of this study 39 patients returned to the emergency department, of which 25 were for repeat episodes of AF. Again, this study was undertaken by medical record review. Similarly, another study undertaken by medical record review of 30 participants treated with electrical cardioversion compared to a control group who were treated with a rate control strategy (based upon physician discretion) demonstrated that electrical cardioversion was

successful in 97% of cases. Six individuals who underwent electrical cardioversion were admitted to hospital however, the mean length of stay was significantly lower in those undertaking electrical cardioversion compared to a rate control strategy (22.8 hours vs 55.6 hours; p<0.001).[170] Hospital charges associated with each of these strategies was also examined in this study with electrical cardioversion significantly cheaper than that of a rate control approach (1598 USD vs 4271 USD; p=0.001). Recently, a strategy of delayed cardioversion in individuals presenting to emergency with an AF duration of <36 hours was demonstrated to be non inferior to a strategy of early pharmacological and/or electrical cardioversion in a randomised controlled trial.[171] In this study of 433 individuals, there was no difference in observed rates of sinus rhythm as recorded on ECG at four weeks post emergency department presentation. Furthermore, adverse events did not significantly differ between groups including transient ischaemic attack, ischaemic stroke, acute coronary syndrome and unstable angina.[171] There was no evidence of between group differences in recurrent ED visits due to AF, nor in time to first recurrent episode or any documented ECG evidence of AF recurrence during study follow up. However, a recently published study demonstrated that in 150 individuals with persistent AF, a strategy of presenting to the emergency department within 36 hours of symptom onset for electrical cardioversion was superior to usual care (cardiologist appointment followed by elective outpatient cardioversion) in reduced symptom burden at 12 months (EHRA score ≥2 in 44% vs 72%; p<0.005 for emergency department cardioversion vs usual care respectively) and in longer time to next AF recurrence (295 ± 15 vs 245 ± 15 days; $p = 0.001$ for emergency department cardioversion vs usual care respectively).[172] Whilst observational studies have demonstrated low risk of complications with the use of electrical cardioversion in low risk individuals,[173] the superiority of this approach over other strategies has not been demonstrated. The studies

undertaken to date have been limited due to generally small numbers and short term follow up. There is a lack of both prospective and randomised data to guide clinicians in this area. Additionally, the lack of structured follow up in each of these studies is perhaps accountable for the high rate of return visits to the emergency department for repeat AF episodes.

1.5 OPPORTUNITIES TO IMPROVE OUTCOMES IN THE AF POPULATION

1.5.1 Exercise based interventions in AF

Other studies have focussed on the impact of physical activity, as an isolated intervention, on outcomes in the AF population. A RCT of 51 individuals with paroxysmal or persistent AF evaluated the impact of thrice weekly aerobic interval training on AF burden, symptoms, quality of life, cardiac function and lipid profile. After short term follow up (four weeks) mean AF burden, as assessed by an implantable loop recorder, increased in the control group (from 10.4% to 14.6%) and decreased in the intervention group (from 8.1% to 4.8%; p=0.001 for difference between groups).[174] Peak VO_2 was also significantly increased in the intervention group compared to control, left ventricular ejection fraction significantly improved, there was a significant decrease in total cholesterol, LDL cholesterol and triglycerides in the intervention group compared to control. At short term follow up, weight and BMI were also significantly decreased in the intervention group compared to control subjects. There was no statistically significant difference in cardioversions or hospital admissions between groups, although the study was not adequately powered to address this issue. Aside from the 'vitality' domain of the

SF-36, which was improved in the intervention group, there was no impact on overall quality of life with this intervention.

In those with permanent AF, a small scale study of 49 individuals randomised to a 12 week aerobic exercise intervention or control, demonstrated a significant improvement in exercise capacity (as determined by cycle ergometer testing) and six minute walk test distances in the intervention group compared to the control group (both p=0.001).[175] Furthermore, at final follow up (immediately post cessation of the 12 week intervention), greater improvements in the Minnesota Living with Heart Failure (MLWHF) Questionnaire was observed in the intervention group, in addition to an improvement in the physical functioning, general health and vitality domains of the SF-36. However, between group differences for either questionnaire were not significant at follow up.[175] Whilst resting heart rate was reduced in the intervention group, surprisingly this intervention did not impact on blood pressure. Similarly, another small study with short term follow up in individuals with chronic AF demonstrated improvements in four of the subscale domains of the SF-36 questionnaire (physical functioning, bodily pain, vitality and role emotional) as well as the physical component summary score (49±6 pre-program compared to 52±6 post program; $p<0.05$).[176] Symptom burden, as assessed by the generic arrhythmia Symptoms and Severity Checklist, also demonstrated improvements in symptoms of tiredness/lethargy and a reduction in severity of shortness of breath, following the exercise training sessions. Interestingly, this study, despite its randomised nature, did not report on between group differences. The control group also undertook the intervention on completion of the initial follow up period and aggregate results of both groups are presented.

Overall, whilst numerous studies have described benefits attached to exercise training across varying AF types, the studies to date are limited by small numbers, a lack

of clinically relevant outcomes and short term follow up periods. As part of a comprehensive risk factor management program, exercise demonstrated incremental benefit to that of weight loss in 308 individuals with non-permanent AF.[177] In this study, individuals who lost ≥10% of their body weight over follow up and gained ≥2 metabolic equivalents (METs) on standard exercise testing, had a 75.6% likelihood of freedom from AF, as delineated by 7 day Holter monitoring, compared to a 44.8% likelihood in those who lost ≥10% of body weight but gained <2 METs in fitness over follow up ($p<0.001$). Further reduction in likelihood of AF freedom were evident in those who lost <10% of their body weight over follow up regardless of gain in METs.[177] Whilst there are clear benefits to regular exercise in relation to overall cardiovascular health, further larger scale studies are required to elucidate the optimal mode and intensity of exercise programs to enhance patient outcomes.

1.5.2 Polypharmacy and adverse outcomes

Polypharmacy represents a potential novel risk factor which may offer opportunity to improve outcomes in the AF population. Numerous adverse outcomes have been demonstrated with polypharmacy in a broad range of other conditions. An observational study of older men (65-83 years) in Western Australia demonstrated an increased statistically significant risk of numerous adverse outcomes including all cause death (OR 1.04, 95% CI 1.00-1.07, $p=0.046$), all cause hospitalisation (OR 1.04, 95% CI 1.03-1.06, $p<0.001$) and cardiovascular events (OR 1.09, 95% CI 1.06-1.12, $p<0.001$) with increasing numbers of prescribed medicines.[178] In a large prospective observational registry (n=46,946) of adults with type 2 diabetes, the prescription of four or more medications at baseline was associated with a linear increase in the risk of falls (HR 1.22;

95% CI 1.04-1.43 for 4-5 medications, HR 1.33; 95% CI 1.12-1.58 for 6-7 medications and HR 1.59; 95% CI 1.34-1.89 medications; p values not reported).[179] In another study of older men (>70 years of age), each one numerical increase in prescription of medication conferred an increased risk of disability (OR 1.08; 95% CI 1.00-1.15; p-0.04), falls (OR 1.07; 95% CI 1.03-1.12; p=0.002) and mortality (OR 1.09; 95% CI 1.04-1.15; p=0.0009).[180]

1.5.3 Polypharmacy and AF

Few studies have examined the impact of polypharmacy on outcomes in the AF population. Two of the direct oral anticoagulants (DOAC) studies have examined the impact of polypharmacy in AF as post hoc analyses and found this to be independently associated with numerous adverse outcomes.[181,182] Other studies have described on impact on quality of life, however a systematic search and synthesis of this literature to date has not been undertaken.

1.5.4 Mobile health technology in AF

Few interventions have examined the use of mobile health technology in AF. In China a cluster RCT, involving two hospitals, of a mobile health application demonstrated enhanced patient reported outcomes in the intervention group compared to usual care.[183] The application was designed to integrate clinical risk scores, such as the CHA_2DS_2-VASc and HAS-BLED scores, with patient test results, which would allow the application to make a recommendation concerning appropriate anti-thrombotic therapy. There was a patient education component to the software which covered areas such as basic AF pathophysiology, risks associated with the condition, AF ablation, use of

medications, use of left atrial appendage occlusion devices, and treatment of AF with concomitant conditions such as ischaemic heart disease, pulmonary embolism and deep vein thrombosis. The application also had capability for individuals to maintain a record of parameters such as their heart rate and blood pressure. After a mean follow up of 95 days, the intervention arm demonstrated an improvement in AF related knowledge, as assessed by a validated AF Knowledge Questionnaire, compared to baseline measures. There was also a demonstrable improvement in several quality of life parameters (EuroQol questionnaire) although no effect on anxiety and/or depression was observed. Self-reported medication adherence, as assessed by a 3 item Adherence Estimator tool, was also improved in the mobile health application group compared to usual care. Although it is reported that there was a health care provider component to this application, this was not further explored and the interplay between the patient application and the health care provider is unclear. No objective outcomes were reported in this study.

Recently, in conjunction with release of disease specific guidelines, the European Society of Cardiology has released two mobile health applications specifically related to AF.[184] The applications were developed to both ensure patient involvement in their care, and support health professionals in decisions concerning care delivery. The first is an application specifically for patients and includes educational material in addition to acting as an electronic health record and forum for individuals to keep electronic records of AF episodes with an in-built symptom diary. The second application is for health care professionals and acts as a facilitator to ensure that AF care is guideline adherent. Treatment algorithms, based on current guidelines, are integrated in to the application and it is also capable of maintaining a list of all consenting individuals using the patient application. Communication between the health care professional and patient is

facilitated through the applications. At this stage, there has not been a prospective study evaluating these applications.

1.6 INTEGRATED CARE FOR ATRIAL FIBRILLATION

The growing burden of AF demands a new paradigm in care delivery for this condition. As prevalence continues to increase, hospitalisations related to the condition outnumber those of other common cardiovascular conditions such as HF and MI, and poor quality of life is evident in this population, urgent action is needed to comprehensively develop strategies to improve outcomes in the AF population. Alternative models of care delivery have demonstrated improved outcomes in the setting of numerous chronic cardiovascular conditions including HF and across the spectrum of ischaemic heart disease.[185,186] However, significant heterogeneity in models utilised has evolved for chronic cardiovascular condition management, with group programs such as cardiac rehabilitation used more frequently for ischaemic heart disease, and more intense and individualised models used in the HF population. This is perhaps due to the perceived 'severity' of the condition and may account for some of the observed differences in outcomes. This has led to uncertainty concerning optimal methods and components of care delivery in these populations. This situation is compounded by the frequent co-existence of these conditions in any given individual. In AF, there is a pressing need to develop and evaluate alternative models of care delivery to address the growing health care burden associated with this condition.

1.6.1 Heart failure management: the role of ambulatory care

A commonly applied model in the outpatient heart failure setting is nurse led with support from a range of health care professionals. In the heart failure population, a recently updated Cochrane meta-analysis reviewed three different models of care in the outpatient setting.[187] A case management approach, typically involving close monitoring of the patient following admission to hospital, was undertaken in 28 of the 47 studies identified. This was generally undertaken by a nurse and usually involves home visits and/or telephone calls with reporting and referral to other members of the healthcare team. There were seven clinic based models identified, which involved care delivery in a specialist outpatient clinic run either by a cardiologist or specialist nurse. A multidisciplinary model was evaluated in nine studies with this defined as holistic care delivered by numerous professions with a view towards ensuring a smooth transition from health care facility to home.[185,187] Three studies were unable to be categorised as any particular type of intervention.

All-cause mortality was significantly reduced in both the case management (RR 0.78, 95% CI 0.68 to 0.90) and multidisciplinary approaches (RR 0.67, 95% CI 0.54 to 0.83) based on 26 and eight studies respectively. There was no evidence that a clinic-based approach impacted on this outcome. Case management and multidisciplinary interventions reduced all cause readmissions (RR 0.92, 95% CI 0.83 to 1.01 and RR 0.85, 95% CI 0.71 to 1.01 respectively), with no impact of clinic based RCTs on this outcome. The case management approach was associated with reduced heart failure readmissions (RR 0.64, 95% CI 0.53 to 0.78), as was multidisciplinary interventions (RR 0.68, 95% CI 0.50 to 0.92). Many outcomes in this meta-analysis were hampered by low to moderate quality evidence, giving rise to concern about the validity of results obtained. Furthermore, assessment of outcomes including cost and quality of life could not be

adequately undertaken. Based on the evidence to date either case management or multidisciplinary models of care appear to be most effective in relation to improved patient outcomes and reduced health care burden. In 30 of the 47 studies included in this meta-analysis, nurses were responsible for delivery of the intervention, often within the construct of a multidisciplinary team. Subgroup analysis of the case management approach by provider of the intervention (specialist nurse, nurse/community nurse, pharmacist or multidisciplinary care provision) did not demonstrate any significant impact of any one provider on *all-cause mortality*. However, the use of a specialist nurse in this model was associated with a significant reduction in both *all cause* (RR 0.85, 95% CI 0.73 to 0.99) and *heart failure specific hospital readmissions* (RR 0.58, 95% CI 0.47 to 0.70) with no evidence of statistically significant impact from other providers.[187] Whilst nurse led models, often within the construct of a multidisciplinary team, have been the most widely studied models to date, it is possible that significant benefit may also be demonstrated by other health care providers or team constructs, however further research in this area is required.

Despite the relatively large number of studies exploring alternative models of care delivery for heart failure, only one study utilising a case management model has been undertaken in the Australian health care setting. This single centre study enrolled 200 participants admitted to hospital for heart failure, with usual care comprising standard cardiologist and primary care provider visits, contact with cardiac rehabilitation programs, dieticians and social workers as per standard treatment pathways.[188] The intervention of this study comprised one home visit delivered by a specialist nurse 7 to 14 days post discharge from hospital. An extensive home and physical assessment were undertaken at this visit, with the nurse providing information and education to empower individuals to self-manage their condition. A written report was sent to the treating

cardiologist and general practitioner and, when it was deemed appropriate, a flexible diuretic regime was devised for patients and their families to self-manage. Repeat home visits only occurred if two or more unplanned hospital admissions for heart failure occurred over follow up. After six months of follow up, this intervention resulted in a significant 40% reduction in the composite endpoint of out of hospital death and unplanned hospital readmissions in favour of the intervention group. Further exploration of components of this composite endpoint demonstrates no significant difference between groups for all-cause mortality (18 vs 28 deaths in intervention vs usual care respectively; p=0.098) but significantly less hospital readmissions in favour of the intervention group (68 vs 118 events for intervention vs usual care respectively; p=0.031). Beyond six months, this effect was no longer evident with similar readmissions across both groups.[188]

1.6.2 Ischaemic heart disease: the role of secondary prevention clinics and cardiac rehabilitation

In the ischaemic heart disease population, greater heterogeneity in outcomes has been demonstrated. Whilst the use of individualised approaches to care management in these populations has demonstrated significant benefit, with nurse led outpatient clinics participating in a cluster randomised controlled study of 19 general practices in Scotland demonstrating superior outcomes with reductions in all cause and cardiovascular mortality at four-year follow up,[189] at longer term follow up of 10 years this benefit was no longer evident.[190] A cluster randomised controlled trial of 1316 participants from 20 primary care practices in England evaluated the impact of nurse delivered intervention which included patient assessment, medication up titration and management and liaison with secondary care, including referral to a secondary prevention clinic if this was

deemed necessary.[191] This study demonstrated an improvement in those meeting target blood pressure and lipid levels in the nurse intervention group compared to usual care (OR 1.61, 95% CI 1.22-2.13, p=0.0113 and OR 1.58, 95% CI 1.05-2.37, p=0.0314 for blood pressure and total cholesterol respectively). Greater prescription of lipid lowering and beta blocker therapy in the intervention group was also demonstrated with no impact on Aspirin prescription or ACE inhibitors. Significant improvement in systolic BP, diastolic BP and total cholesterol values were also demonstrated with no impact on BMI. Conversely, another primary care cluster randomised controlled study of 597 individuals post admission to hospital for myocardial infarction or angina, demonstrated no impact on objectively measured cardiovascular risk factors at 12 months (blood pressure, cholesterol, BMI) with the use of a cardiac liaison nurse which aimed to ensure structured follow in general practices.[192]

Few studies have examined outcomes at long term follow up, so it is possible that attrition in benefit is observed over time. Two studies examining follow up beyond 12 months failed to demonstrate any sustained benefit from nurse delivered interventions focussing on modification of risk factors.[190,193] This is likely to be multifactorial and encompass both provider and patient factors including a reduction in intensity of follow up and consequent lack of accountability in addition to patient factors such as motivation and commitment to ongoing self-monitoring and lifestyle change. A systematic review of seven randomised controlled trials demonstrated significant heterogeneity in methodology, care delivery structure and outcomes measured, resulting in difficulty assessing the impact of nurse led care in this ischaemic heart disease population.[194] Whilst it was concluded that the use of such clinics was not associated with any harm, evidence of benefit was difficult to ascertain.[194]

The use of group based cardiac rehabilitation (CR) programs is an established paradigm in the management of a broad range of chronic cardiovascular conditions including stable angina, acute coronary syndromes, post percutaneous coronary intervention (PCI) and following cardiac surgery. This is evidenced by the highest level of recommendation in numerous national and international guidelines[195,196], with a class II recommendation in the most recent European acute coronary syndrome guidelines.[197] Furthermore, a dose dependent increase in benefit has been demonstrated with a US based study demonstrating significantly improved outcomes in 30,161 Medicare beneficiaries attending 36 sessions of cardiac rehabilitation compared to those attending one, 12 or 24 sessions.[198] Compared to those attending one session, attendance at 36 sessions was associated with a 47% reduction in all cause death (HR 0.53, 95% CI 0.48 to 0.59) and a 31% reduction in risk of MI (HR 0.69, 95% CI 0.58 to 0.81) with dose dependent decreases observed in those attending less sessions.[198]

Despite heterogeneity in the structure of group based programs, the most recently published systematic review and meta-analysis of 14,486 participants from 63 RCTs demonstrated that the use of CR was associated with significant reductions in cardiovascular mortality, all-cause hospital admissions and improved quality of life.[199] However, no impact on all-cause mortality, MI or the use of revascularisation was demonstrated.[199] Important differences in outcomes were observed by subgroup analysis. Higher exercise dose was associated with a significant reduction in cardiovascular mortality (RR 0.75, 95% CI 0.65-0.86), which was not evident at lower exercise doses (RR 0.47, 95% CI 0.19-1.15). Similar to the ischaemic heart disease clinic models of care, interventions recording outcomes at longer than 12 months duration did not demonstrate any significant impact on any outcome with reductions in myocardial infarction (RR 0.60, 95% CI 0.39 to 0.91), cardiovascular mortality (RR 0.72, 95% CI

0.62 to 0.84) and all cause hospitalisation (RR 0.63, 95% CI 0.46 to 0.88) which was observed in those recording outcomes at ≤ 12 months.[199] Importantly, no impact on any outcome was observed in studies undertaken in Australasia, although this is somewhat hampered by the small number of studies involved (five out of 63 included studies). Unanswered questions remain about the optimal method of delivery for cardiac rehabilitation programs including exercise dose, the added benefit of comprehensive programs including education, the optimal duration of program delivery and follow up regime. Additionally, the optimal mix of health care providers involved in service delivery is yet to be fully delineated.

A contemporary analysis of cardiac rehabilitation trials published between 2010 and 2015 confirmed a statistically significant overall reduction in cardiovascular mortality, in addition to reductions in MI and cerebrovascular events.[200] Interestingly, sub group analyses of these contemporary studies revealed a significant reduction in all-cause mortality in programs managing six or more cardiovascular risk factors, compared to those who managed less, as well as in programs who had the ability to prescribe and up-titrate cardioprotective medications, which was not evident in those who did not have this capacity.[200] It is plausible that the intensity of the intervention delivered is a key component in delivering enhanced patient outcomes in this population.

However, brief interventions have also demonstrated enhanced patient outcomes in the ischaemic heart disease population. In a single centre study of 710 individuals with documented coronary heart disease (prior MI or angiographically proven disease), semi personalised text messages delivered four times per week over 24 weeks resulted in an improved cardiovascular risk factor status. The text messages were targeted according to each individual's baseline risk factor profile and were designed to encourage participants modify their lifestyle. There was no capacity for interactive communication between

health care professionals and participants. This resulted in a small but significant improvement in the primary outcome of LDL cholesterol (mean difference -5mg/dL, 95% CI -9 to 0; p=0.04) at 6 months, in addition to more marked improvements in other cardiovascular risk factors including systolic blood pressure, physical activity levels, numbers of current smokers and BMI.[201]

1.6.3 Integrated care

Integrated care is an approach to health care delivery which was borne out of the Chronic Care Model developed by Wagner and colleagues[202], with recognition that standard medical care is often inadequate in meeting the needs of those with chronic conditions. This approach takes in to account the needs, values and preferences of patients in addition to care delivery based on the best available evidence. The original Chronic Care Model identified five effective interventions to improve outcomes in those with chronic illness. These included:

1. The use of evidence-based care;
2. Reorganisation of systems of practice and providers;
3. Assistance in patient self-management strategies;
4. Increased availability of expert care;
5. Increased access to clinical information.[202]

Translation of this model into clinical practice further identified six areas deemed critical to the successful application of the Chronic Care Model.[203] These key areas include: *Health Care Organisation* which involves leadership and organisational support for the use of a chronic condition management program, as this can often involve extensive

change to current practice management. *Community resources* was also identified as a key area with accessibility to care not readily available at the primary organisation. *Self-management support* involves a shift from more paternalistic health consultations to encounters that empower individuals to self-monitor and manage their condition. Communication with patients is a critical component of this and ensures that individuals play an active role in their care decisions. *Redesigned health systems* allow for support for promotion of behaviour change and self-management support, assessment of response to therapy and protocol driven care delivery. *Decision support systems* allow for delivery of evidence based guidelines and should be integrated into standardised care pathways and, finally, *clinical information systems* support the delivery of this model of care, usually through the support of software systems.[203]

The integrated care model is based on this concept although a consistent definition and care delivery structure has yet to be fully delineated. A study reviewing the evidence for integrated health systems yielded 175 definitions of the concept and little consistency in methods of evaluation.[204] Indeed, at a relatively early stage of this concept, the inconsistency in definition and application of this approach was widely recognised.[205] Therefore implementation and evaluation of integrated care delivery is fraught with numerous challenges. To address these challenges, a definition of integrated patient care has been proposed by a Harvard based research group, as opposed to health service delivery organisational integration, to allow for greater standardisation and ability to evaluate this concept. This has been proposed as: "patient care that is coordinated across professionals, facilities, and support systems; continuous over time and between visits; tailored to the patients' needs and preferences; and based on shared responsibility between patient and caregivers for optimizing health."[206] A framework of seven different

constructs has been proposed for implementation and evaluation of this concept. These include:

1. Co-ordination within the care team;
2. Co-ordination across care teams;
3. Co-ordination between care teams and community resources;
4. Familiarity with the patient over time;
5. Continuous proactive and responsive action between visits;
6. Patient-centred; and
7. Shared responsibility for care.[206]

Application of this framework would support greater consistency and evaluation of integrated care delivery from both a research and clinical perspective. As this has not been successfully undertaken to date, this has led to inherent difficulties in implementation and evaluation of the integrated care concept.

1.6.4 Integrated care for chronic condition management

Despite these challenges, numerous studies have demonstrated enhanced patient outcomes with the use of an integrated care approach. A meta review of twenty seven systematic reviews examined the impact of integrated health care delivery on outcomes in a number of chronic diseases including heart failure, diabetes, chronic obstructive pulmonary disease and asthma.[207] Whilst there was inconsistency in definitions and outcomes in the use of this approach, most studies demonstrated benefit with evidence of reduced hospital admissions and readmissions, improved adherence to guideline recommended care and improved quality of life, although a meta-analysis of results was

not possible.[207] One of the largest evaluations of an integrated care concept to date is that of the Intermountain Health Service in Utah, USA. This study evaluated the use of integrated team-based care at 27 primary care practices, and compared outcomes to individuals attending 75 primary care practices using a traditional practice management approach.[208] Key elements of the team based care approach included care co-ordination for chronic diseases through the use of standardised protocols, patient involvement and engagement in care planning, involvement of family and community and clearly defined roles and expectations for all team members, supported by an accessible electronic patient record for each individual. Over a four year period, the use of team based integrated care was associated with reduction in hospital admissions (IRR 0.89, 95% CI 0.85-0.94, $p<0.001$), reduced emergency department visits (IRR 0.77, 95% CI 0.74-0.80, $p<0.001$) and reduced primary care physician visits (IRR 0.93, IRR 0.92-0.94, $p<0.001$).[208] Payments received by health care professionals and organisations for those in team based care were also significantly lower than that of traditional practice management, and highlights the lack of a structured funding model for the use of this approach.

1.6.5 Integrated care in AF

Comparatively little evidence exists concerning alternative models of care delivery in the AF population. In recent times, recognition of AF as a chronic cardiovascular condition has led to the development of several studies examining the impact of care co-ordination on outcomes in the AF population. A widely used approach in studies thus far is the use of an integrated care model. The first of these studies utilised an integrated care approach in a single centre RCT in the Netherlands. This study enrolled 712 individuals with newly diagnosed AF who had been referred to an outpatient clinic primarily for AF

management.[209] Those in the intervention group attended a nurse led, physician supported outpatient clinic which included a number of key elements. These were: 1. Delivery of protocol driven care; 2. Guideline adherent care according to the most recent European guidelines for AF 3. The use of a software support system to ensure standardisation of care, and 4. Patient involvement in all decisions concerning care. Patients in usual care received care by a cardiologist in the outpatient setting. Over a mean follow up of 22 months, this intervention resulted in a significant reduction in the primary endpoint, a composite of cardiovascular hospitalisations and mortality, in those attending the integrated care clinic (OR 0.65, 95% CI 0.45-0.93, p=0.017).[209] This intervention was also cost effective with a gain of 0.009 quality adjusted life years and a saving of 1109 euros (approximately $1,753 Australian dollars) per patient,[210] but did not significantly impact on quality of life as assessed by the SF-36.[210]

Another study examined the impact of home-based care co-ordination in AF in a multi-centre RCT at three centres in Australia. For this study, individuals who had been hospitalised primarily due to AF were eligible, with the intervention including a home based educational visit 7-14 days after enrolment, written patient education, protocol driven diagnostic testing and recommendation concerning guideline adherent treatment to the treating general practitioner (GP) and cardiologist.[211] This intervention did not result in a reduction of the primary endpoint of all-cause mortality and hospitalisations in the intervention group compared to control (HR 0.97, 95% CI 0.76-1.23; p=0.851). It did, however, result in proportionately more days alive and out of hospital in the intervention group compared to control.

Finally, the use of an integrated care approach was used in a Canadian multi-centre study, which applied this model to a population of individuals presenting to three emergency departments (ED) primarily due to AF. The intervention in this before and

after study comprised an educational telephone call 2-3 days post discharge, a group-based education session, individual review of each case by a physician and nurse with diagnostic testing, and a detailed letter to the treating physician concerning treatment recommendations. Following this, care was returned to the treating physician. In a propensity matched analysis, this intervention resulted in a reduction in the composite primary endpoint of death, cardiovascular hospitalisation and AF related ED visits (OR 0.71, 95% CI 0.59-1.00, p=0.049).[212] This reduction was largely driven by reduced AF related ED visits.

Whilst variability in methodology and outcomes for each of these studies is evident, they have made significant advances in our understanding of improving outcomes in AF through alternative models of care delivery. However, significant uncertainty exists as to optimal methods and models of care delivery.

1.6.6 Shared decision making in AF

An essential component of the integrated care approach for chronic condition management is the use of a shared decision-making process. This process moves away from paternalistic models of care, where the patient is instructed by the health care professional on treatment recommendations, and instead moves toward a shared process in which treatment options are discussed in the context of patient values and preferences. This process involves discussion between the patient and clinician with the clinician discussing treatment options, benefits and risks and the patient expressing their values and preferences in relation to these options.[213] Ideally this process should also include family members or significant others, and may require discussion within a multidisciplinary team.[213]

In AF, the choice of stroke prevention therapy presents an important opportunity to utilise a shared decision-making process with the aim to improve adherence to the treatment regimen. In this context, the use of a shared decision making process would involve discussion concerning risk of stroke based on risk assessment scores such as the CHA_2DS_2-VASc score, risk of bleeding according to scores such as the HAS-BLED score, discussion of patient preferences for treatment, agreement on a treatment regime and regular follow up to assess the impact of this decision.[214] The use of shared decision making by a multidisciplinary team as part of an integrated care approach has been highlighted in numerous recent international AF guidelines.[115,215]

Several studies have evaluated the use of decision support aids to facilitate this process in AF with mixed results. Most of these studies relate to use of OAC for stroke prevention. The largest study in which this was evaluated involved examining the outcomes of five decision support tools recommended by current AF guidelines at that time, in 15,129 newly diagnosed AF patients.[216] Concordance with recommendations from three of these tools resulted in a significant reduction in the risk of any adverse AF events, which included a composite of any thromboembolic or major bleeding event, with the use of three of these tools, but after adjustment for potential confounders this benefit was no longer evident. Similarly, a Canadian cluster randomised controlled study of 434 non-valvular AF patients from 102 community-based practices examined the impact of an educational booklet and audiotape, which was tailored to each individual's stroke risk, on appropriate use of OAC. Despite a small improvement in the absolute use of OAC at 3 months follow up (12% increase), this benefit was not evident at 12 months.[217] Another RCT of participants in the Stroke Prevention in AF (SPAF III) study cohort examined the impact of a decision aid which encompassed an educational booklet, a worksheet and an audiotape.[218] Whilst the intervention group demonstrated greater knowledge about OAC,

were more able to quantify their stroke and bleeding risks and were more likely to reach a decision concerning their treatment, there was no significant impact on adherence to treatment at 6 months.[218] Clinical outcomes were not reported in this study. Another RCT which examined the impact of an educational intervention, which encompassed a small group session facilitated by a DVD, an educational booklet and a self-monitoring diary, resulted in a greater amount of time spent in the therapeutic range (TTR) for the intervention group in 97 patients with AF taking warfarin.[219] There were no significant differences between groups in quality of life, anxiety and depression, knowledge scores or illness perceptions as determined by questionnaires.[219] Although not a prespecified endpoint of this study, adverse events occurred less frequently in the intervention group compared to control (one event compared to seven events in intervention and usual care respectively).

In Australia, a cluster randomised controlled study examined the impact of a computerised decision assist tool on the prescription of antithrombotic therapy by 48 General Practitioner's in New South Wales on moderate to high risk individuals with AF (CHA_2DS_2-VASc score ≥ 1).[220] Use of this tool resulted in a small but statistically significant improvement in the prescription of OAC from 89.3% to 92.2% (p=0.02). When the tool recommended a change in therapy, this occurred in 64% of cases with reasons for disagreement including GPs considering the treatment inappropriate, patient declined therapy or cardiologist had recommended alternative therapy.[220]

1.6.7 The role of education in AF

Education forms an important component of providing holistic chronic condition management. Several studies have evaluated the impact of education alone on outcomes

in AF populations. A RCT of a brief nurse delivered educational intervention for individuals with AF presenting to the ED, demonstrated a reduced rate of adverse events in the intervention group compared to control. In this study of 240 individuals, the intervention consisted of standardised advice regarding AF including: a basic explanation of the arrhythmia, condition and treatment related complications, medication adherence, attending appointments for treatment follow up, signs and symptoms of future episodes including how to monitor the pulse to assist with arrhythmia recognition.[221] Outcomes evaluated include AF related complications such as stroke, heart failure and any bradycardia requiring treatment, in addition to other non-specific outcomes including ventricular tachycardia, any arrhythmia causing haemodynamic instability and any haemorrhage in anticoagulated individuals. At 12 months, there were significantly less cumulative adverse events in the intervention group (31.9% vs 48.4%; p=0.005). However, there was no statistically significant difference between ED presentations or hospitalisations between the groups. Heart failure was the most commonly observed complication and occurred less frequently in the intervention group (16.6% vs 26.6%; OR 0.55, 95% CI 0.28-0.99; p=0.04 for intervention vs control respectively). The significant result observed in the primary cumulative endpoint was largely driven by a reduction in heart failure in the intervention group, with no other significant differences evident between groups for any other outcome.

In a post ablation cohort, a nurse led educational intervention, delivered at five different timepoints, resulted in a significant improvement in quality of life and AF symptom burden in a RCT.[222] The education was delivered in hospital, both pre and post procedure, and followed pre-defined topics which spanned basic information concerning their condition, causes and risk factors, typical AF symptoms and when help should be sought, procedural information, goals of treatment and lifestyle modification. Following

this, three telephone calls were received by participants in the intervention arm lasting 5-10 minutes with a focus on symptoms, queries concerning medications and lifestyle management. No further contact was permissible with the nurse after three months post AF ablation. At six months, statistically significant improvements in numerous symptoms including palpitations, tiredness, difficulty sleeping, headache, trouble concentrating, and light-headedness/dizziness were evident in the nurse led educational group. Furthermore, the physical functioning and vitality domains of the SF-36 were also significantly improved in the intervention arm.[222] At six months, there was no difference in either all cause or AF related hospitalisations. There was no reporting of between group differences for objective AF burden or cardiovascular risk factor outcomes.

1.7 CONCLUSIONS

The burgeoning AF population and poor outcomes observed in this population deserves urgent attention. As incidence and prevalence levels of this condition continue to rise, opportunities abound to improve patient outcomes and reduce associated health care burden. This ranges from enhanced management of risk factors to prevent onset of the condition to improved management of those with established AF. Optimal components of service delivery to achieve this are yet to be fully delineated, with further research in this area an urgent healthcare priority.

Chapter 2: National Trends in Hospitalisations due to Atrial Fibrillation in Australia

2.1 INTRODUCTION

2.1.1 Background

Atrial fibrillation (AF) poses a major global healthcare burden. In contrast to many other chronic cardiovascular conditions, the incidence and prevalence of AF has dramatically risen over the last two decades and is expected to continue rising at an exponential rate.[2,5,223] AF confers a significant increase in risk of all-cause mortality, with this risk evident even in low risk individuals with few comorbidities.[224,225] A significant component of the healthcare system burden associated with AF is due to hospitalisations, related not only to the condition itself but also due to complications such as syncope, stroke and heart failure (HF).[153]

2.1.2 AF hospitalisation trends in the USA and Europe

Although AF hospitalisations are a significant global issue, most published data has emerged from North America and Europe. Previous US data demonstrated a 2-3 fold increase in AF hospitalisations over the 14 year period to 1999[226] with more recent data demonstrating that AF admissions increased by 23% over the decade from 2000-2010, with greatest absolute increases observed in the age groups of 35-49 year olds and over 80 years olds.[8] In this same cohort, gender differences were apparent with greater absolute increases in AF hospitalisations for males at 16.9% compared to females at 12.1%. More

recently, a study of over 65 year old Medicaid eligible individuals in the US over the fourteen year period until 2013 demonstrated that AF related hospitalisations increased by 0.85% per annum, with greatest increases observed in those of more advanced age (2.22% per annum in those aged over 85).[9] Once again, gender differences were notable with greater rates of increase observed in females at 1.2%, compared to males at 0.35% per annum. Similar hospitalisation trends have also been demonstrated in Europe across numerous countries. In France, over a three year follow up period between 2005 and 2008 a 26% increase in hospitalised individuals with a diagnosis of AF was demonstrated.[13] In Scotland, a threefold increase in hospitalisations with AF as a principal diagnosis was demonstrated in the ten year period leading up to 1996.[11] The Danish Hospital Discharge Registry also demonstrated a 60% increase in hospitalisations due to AF over the thirteen year period leading up to 1994.[12]

2.1.3 AF hospitalisations in the Asia Pacific region

Comparatively little data exists on AF epidemiology and hospitalisations from the Asia Pacific region. Recent data has projected rates of AF in this region to be far greater than that of the USA and Europe, in part due to larger populations and the growing rates of associated cardiometabolic risk factors.[6] Other studies have confirmed trends for AF hospitalisations in western countries are also occurring in Asian countries. A 420% relative increase in AF hospitalisations from 2006-2015 in Korea has been demonstrated (with AF listed as any diagnosis).[15] Previous Australian data on AF hospitalisations over the fifteen-year period between 1993 and 2007 demonstrated a greater relative increase of 203% for AF hospitalisations compared to 79% for MI and 17% for HF,[7] but it is unclear if this trend has continued unabated or tempered in recent years.

2.1.4 Economic cost of atrial fibrillation

In addition to the individual and societal burden, the economic cost associated with AF is significant, the largest component of which is related to hospitalisations. In the United Kingdom, hospitalisations accounted for approximately 50% of AF-related healthcare expenditure.[21] The cost of AF-related admissions has also demonstrated an upwards trend in the US, rising by an average total of USD 1,787 per admission over a 14-year period.[9] Recently, the management of AF has continued to evolve considerably to include advances such as the routine use of catheter ablation techniques, non-vitamin K antagonist anticoagulants, and aggressive cardiovascular risk factor management.[128,227] The potential impact of these advances on hospitalisation rates, length of stay and cost remains uncertain.

In the present study, we sought to characterise contemporary national trends in hospitalisations due to AF in Australia. We determined the number, rate and length of stay for AF hospitalisations compared to two other common cardiovascular conditions, MI and HF. We also quantified associated healthcare costs and examined changes in AF-related procedures over a two-decade period in Australia.

2.2 METHODS

2.2.1 Hospitalisation Data

Data on AF, MI and HF hospitalisations were extracted from the National Hospital Morbidity Database, which is maintained by the Australian Institute of Health and Welfare (AIHW). For the years 1993-1997, data were coded according to the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) classification system with the code 427.3 for AF and atrial flutter, 428.0 for HF, and

410 for MI. From 1998-2013, data were coded according to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM) with AF and atrial flutter coded as I48, HF as I50, and MI as I21. Coding by principal diagnosis only was utilised for each condition. Data were acquired on the overall number and average length of stay of hospitalisations for each condition according to year, and further subdivided according to age and gender categories.

2.2.2 Procedural Data

Procedural data were obtained from two sources: the National Hospital Morbidity Database from the AIHW, and Medicare Item Reports maintained by the Department of Human Services. AIHW data are reflective of procedures undertaken in all public and private hospitals, whereas Medicare data are based upon procedures billed for by physicians and other health care providers utilising the Medicare Benefits Schedule at private hospitals across Australia. AIHW procedural data for AF ablation were available from 2000-2013. Data were also acquired for analyses comparing the rate of increase of AF ablation and other ablation procedures.

Medicare data for AF ablation were available from 1995-2013. As with data from AIHW, Medicare data were also collected for analyses comparing the rate of increase of AF ablation and other ablation procedures. Medicare data for electrical cardioversion were available from 1993-2013.

Ethics approval for use of the AIHW database is not required as this data is deidentified and publicly available.

2.2.3 Statistical Analysis

Time trends in the aggregate annual number of hospitalisations due to AF, MI and HF were assessed using negative binomial regression models. All models were age and gender adjusted and included an offset term for the logarithm of the estimated midyear Australian population, which was obtained from the Australian Bureau of Statistics. The same approach was used in the analysis of procedural data with changes in rates for each procedure over the period examined as raw data, and then as a proportion of total cardiovascular procedures, and finally adjusted for population estimates. Likelihood ratio (LR) tests were used to compare between nested negative binomial models in which interactions between predictor variables (age, gender, and year) were included and then excluded. A linear regression model was used to examine changes in length of stay for each condition over the study period, with an F-test used to assess the interaction between condition and year. Cost weights for relevant Australian Refined-Diagnostic Related Groups (AR-DRGs) were derived from the National Hospital Cost Data Collection Database (NHCDC) from 1997-2009, and from the Independent Hospital Pricing Authority (IHPA) for the years 2011-2013. Cost weights for the year 2010 are not available and were unable to be acquired. Annual average cost weights per AF, MI, and HF inpatient episode were estimated as the sum of the product of the cost weights for the relevant AR-DRGs for each condition and their proportion of the total inpatient episodes for each condition. The NHCDC and IHPA reported inpatient data from an incomplete sample of Australian hospitals and so the estimated annual average cost weights were multiplied by the total number of inpatient episodes for each condition, which were reported by the AIHW to obtain a total yearly cost for each condition (the AIHW did not report episodes by AR-DRG). All analyses were undertaken using Stata version 14.1, and a two-tailed p value of 0.05 considered significant.

2.3 RESULTS

2.3.1 AF, MI and HF Hospitalisations

National AF hospitalisations increased by 295% over the 21-year period from 1993 to 2013, reaching an annual total of 61 424 admissions at the end of the study period. In comparison, MI and HF hospitalisations only increased by 73% and 39%, reaching an annual total of 54 116 and 53 643 hospitalisations, respectively ($p<0.001$; Figure 1 and Table 1). These effects persisted after adjustment for population estimates. The annual increase in AF hospitalisations was 5.2% (incidence rate ratio [IRR] 1.052; 95% CI 1.046-1.059; $p<0.001$), compared to a 2.2% increase per annum for MI (IRR 1.022; 95% CI 1.017-1.027; $p<0.001$) and negligible annual change for HF hospitalisations (IRR 1.000; 95% CI 0.997-1.002; $p=0.78$). As a percentage of all hospitalisations across Australia, there was a relative increase in AF hospitalisations of 87%, from 0.34% in 1993 to 0.63% in 2013 (Figure 2). The incidence rate per 10,000 of the population increased by 199% for AF from 8.8 to 26.3 admissions, compared to a 5% increase for HF from 21.9 to 23.0 admissions, and 31% for MI from 17.7 to 23.2 admissions, per 10,000 population (Table 1).

2.3.2 Age and gender subgroup analyses

All age categories demonstrated a significant rise in AF hospitalisations relative to the youngest age group (Figure 3). The associated rise was relatively homogenous for all age groups at 3.8-4% annually, until the over 80 age category which demonstrated a steeper rise at 4.8% per annum ($p=0.008$). Males and females showed similar relative increases over time ($p=0.35$).

2.3.3 Length of stay and total bed days used

Whilst length of stay significantly decreased over the time studied across all three conditions, the observed decline in length of stay for AF hospitalisations was significantly less (decrease of 0.05 days per year; 95% CI 0.03-0.08; $p<0.001$) than that for HF (decrease of 0.12 days; 95% CI 0.10-0.15; $p<0.001$) and MI (decrease of 0.14 days; 95% CI 0.12-0.17; $p<0.001$; both $p<0.001$ compared to AF; Table 1). However, due to the increasing number of hospitalisations, there was still a significant annual increase in total bed days attributable to AF (estimated annual increase of 5,440 days; 95% CI 4,986-5,894; Table 1).

2.3.4 Hospitalisation costs

The total cost of AF hospitalisations demonstrated a 479% relative increase from $50,927,140 Australian dollars (AUD) in 1997 to $295,003,937 AUD in 2013. Comparatively, the cost of hospitalisations for MI and HF increased by only 210% for both conditions over the study period (Figure 4). The cost per admission increased by 137% for AF hospitalisations from $2,029 to $4,803 AUD, compared to an increase of 90% in cost per admission for MI, and a 141% increase for HF.

2.3.5 Procedural trends

The use of AF ablation rose steeply over the two decades studied with data from both the AIHW and MBS broadly consistent and demonstrating a 26% annual increase (IRR 1.26, 95% CI 1.22-1.30 for AIHW, $p<0.001$). Procedural numbers rose from 59 in 2000 to 1 743 AF ablations in 2013. All age and gender groups demonstrated a significant rise in rates of AF ablation. Analyses excluding codes for AF ablation also showed increases,

although to a lesser degree than in the main analyses (IRR 1.09, 95% CI 1.07-1.13, p<0.001). AF ablation represented a small percentage of all cardiovascular procedures undertaken in Australia at 0.01% in 2000, increasing to 0.32% in 2013. As a proportion of all AF hospitalisations, AF ablation represented 0.01% in 2000, increasing to 2.80% in 2013. The rate of increase of AF ablation was greater in males than females (IRR 1.69, 95% CI 1.28-2.24: p<0.001). Gender subgroup analysis showed that the use of AF ablation has increased annually by 28% in males (IRR 1.28, 95% CI 1.22-1.34, p<0.001) and 23% in females (IRR 1.23, 95% CI 1.18-1.28, p<0.001).

Electrical cardioversion increased significantly over the study period with a 10% annual increase (IRR 1.10; 95% CI 1.09-1.10, p<0.001). This rose from a total of 1,340 procedures in 1993 to 9,724 in 2013. As a proportion of all cardiovascular procedures, this is represented by a 7% annual increase (IRR 1.07; 95% CI 1.05-1.09, p<0.001).

2.4 DISCUSSION

Hospitalisation data and the associated costs have important implications for the rationalisation and optimisation of service delivery. In this study, using a National prospective dataset the following new information is demonstrated:

- Hospitalisations due to AF continue to progressively grow over this 21-year period and have almost doubled since the beginning of this century;
- AF surpassed HF in 2008, MI in 2011 and is now the most common cause for hospitalisation amongst these three conditions;
- All age and gender categories have demonstrated a significant increase with the most notable increases in those of a more advanced age;

- A significant increase in the use of AF ablation that is unlikely to account for the increase in AF hospitalisation rates;
- A modest increase in the use of cardioversion;
- A significant rise in the cost of AF hospitalisations, with little difference in length of stay over the time period studied.

AF hospitalisations have demonstrated a progressive increase such that AF is currently the most common cause of cardiovascular hospitalisation in Australia. Furthermore, the associated cost of AF hospitalisations has more than quadrupled over the 21-year study period from 1993 to 2013. Whilst AF-related procedures have significantly increased, they are unlikely to account alone for the observed rise in hospitalisations.

2.4.1 Reasons underpinning the growth in AF hospitalisations

The growing trend in hospitalisations due to AF is likely to be multifactorial and encompass both modifiable and non-modifiable components. The ageing population is in-part responsible for the growth in total number of AF hospitalisations. However, an 11.3% increase in the age-standardised hospitalisation rate for AF from 2003 to 2011 demonstrates the growing burden of this condition independent of the impact of the ageing population. These trends are in stark contrast to other cardiovascular conditions, such as coronary heart disease, which has demonstrated a 32% reduction over the same time period.[228] In line with this rising prevalence rate is recent data suggesting a growing rate for incident AF hospitalisations, particularly in younger age groups (35-64 year olds).[19] It is likely that these individuals will make frequent hospital presentations, thereby contributing to continuing growth in prevalent hospital admission rates. Numerous modifiable risk factors for AF are likely to be fuelling these trends, including

hypertension, coronary artery disease, obesity and diabetes.[39,50,52,61] In line with data from the USA demonstrating suboptimal cardiovascular risk factor profiles in the majority of the population,[229] the prevalence of cardiovascular risk factors remains high in Australia; 1 in 3 are hypertensive, 2 in 3 are overweight or obese, and over half are physically inactive.[230] In the USA, a slowing of the rate of decline in cardiovascular mortality has been speculated to be in-part attributable to the epidemic rates of obesity and its associated complications such as diabetes.[231] It is likely that rising AF incidence and associated hospitalisations may be partially driven by the rise in these modifiable cardiovascular risk factors. Efforts directed at these are likely to slow or even reverse the ongoing growth in health care burden both related to AF and other cardiometabolic conditions.

2.4.2 Opportunities to reduce AF hospitalisations

Previous data have demonstrated that the greatest burden of AF hospitalisations lies in prevalent (recurrent) admissions.[19] Directed management strategies aimed at addressing individuals known to have AF could therefore have the greatest potential benefit in preventing re-hospitalisation in these individuals. Although our data are unable to discriminate between incident and prevalent AF admissions, a substantial proportion is likely to be attributable to prevalent admissions. The present study thus suggests that efforts to reduce these recurrent hospitalisations are thus an urgent priority. Although there are minimal data pertaining to alternative models of care delivery in the AF population, early results have been promising, with some studies demonstrating a reduction in emergency department visits, hospitalisations, and cardiovascular mortality.[209,212]

2.4.3 AF hospitalisations in Australia compared to other populations

Notably, the continued rise in AF hospitalisations in Australia appears to be exceeding that of other comparable countries. For example, a recent USA study examining trends in AF related hospitalisations demonstrated an absolute 23% increase in hospitalisations from 2000-2010.[8] In our study, there was an absolute increase of 68% over the same time. Although other countries such as Scotland and Denmark have also reported significant increases in AF hospitalisations, published data are from earlier time periods.[11,12] Whilst the global burden of hospitalisations due to AF is clearly increasing, the rate of increase in Australia appears to be comparatively higher, presenting a major public health issue that demands further investigation. Furthermore, our data suggests that the increase in AF hospitalisations spans all age and gender strata, in contrast to comparable recent data emerging from the USA, which demonstrates significant heterogeneity across various age and gender groups.[8,9] Reasons for these differences are unclear, but support the concept that factors underpinning this growing trend in hospitalisations extend beyond an ageing population.

2.4.4 Procedural trends and their impact on AF hospitalisations

Whilst the use of AF ablation has grown considerably over this two-decade period, it does not appear to be the major driver of the increase in AF hospitalisations. Our results show a 21% annual increase in the number of AF ablation procedures, which far exceeds that of ablation used for other purposes. Whilst AF ablation has evolved as an effective therapy for rhythm control in those with drug-refractory AF, with favourable outcomes over pharmacological rate control, recurrence rates over longer term follow up are significant.[121,232] The role of risk factor management, which has now been described as

the ‘fourth pillar’ of AF care in addition to rate and rhythm control and appropriate oral anticoagulation,[227] has proved highly effective in this regard.[140,141] Furthermore, the ongoing role of weight and risk factor management has proven pivotal in the reduction of AF symptoms in longer term follow up,[142] although the impact of this intervention on other outcomes such as healthcare resource utilisation, is not yet known. Our findings concerning a greater use of AF ablation in males compared to females is consistent with other published data.[22,233] This trend is in line with gender differences in treatment in other cardiovascular conditions[234-236], and is worthy of further investigation. As AF ablation is currently a treatment recommended for symptomatic management of AF, it is possible that differences in symptom presentation account for this difference. It is also possible that females are less likely to be offered this procedure, although reasons for this are unclear and require further investigation.

2.4.5 Costs of AF hospitalisations

Finally, direct costs of hospitalisations due to AF have grown significantly and at a greater rate than that of MI and HF. Whilst costs of hospitalisations across all three conditions have similarly increased over time, the increase in the number of AF hospitalisations appears to be mostly responsible for the significantly greater increase in total costs for this condition compared to MI and HF. Whilst total direct costs associated with AF hospitalisations remain the lowest of all three conditions studied, this is likely to change in coming decades unless the current trajectory of AF related health care burden is curtailed.

2.5 LIMITATIONS

Our data have several limitations. Firstly, whilst our data suggest a progressive increase in AF hospitalisation over a 21-year period, it is likely to be an underestimation of the true burden of the condition. Complications due to AF, such as stroke and HF, are likely to account for a significant component of AF-related hospitalisations and are not accounted for in our data. Therefore, the true burden of AF is likely to be significantly greater than that represented by the present analyses. Our data are also unable to discriminate between repeat hospitalisations and procedures as discussed above. Therefore, whilst total rates of AF hospitalisations have increased significantly, we cannot determine from our data what proportion of this is due to greater rates of incident hospitalisations or recurrent admissions for highly symptomatic individuals. Finally, national trends in cardioversion data were only available through the Medicare database maintained by the Department of Health, although it is unlikely that the use of cardioversion has contributed significantly to overall increases in AF hospitalisations given the relatively small increase observed in the Medicare Benefits Schedule database.

2.6 CONCLUSIONS

The burden of AF continues to rise at a rapid rate, with hospitalisations for AF now outnumbering other common chronic cardiovascular conditions. Moreover, the increase in number and economic cost of AF hospitalisations in Australia appears to be exceeding that of other comparable countries. Further strategies to mitigate these trends, such as new models of care delivery and cardiovascular risk factor management, should be widely implemented to address this growing epidemic.

Table 1: Number of hospitalisations, average length of stay and total bed days from 1993-2013 in Australia
(AF – atrial fibrillation, MI – myocardial infarction, HF – heart failure)

Year	No. of hospitalisations (AF)	No. of hospitalisations (MI)	No. of hospitalisations (HF)	Incidence of AF hospitalisations per 10,000 of the population	Incidence of MI hospitalisations per 10,000 of the population	Incidence of HF hospitalisations per 10,000 of the population	Average length of stay (AF)	Average length of stay (MI)	Average length of stay (HF)	Total bed days used (AF)	Total bed days used (MI)	Total bed days used (HF)
1993	15,555	31,194	38,700	8.8	17.7	21.9	4.0	8.0	10.0	62,220	249,552	387,000
1994	17,996	31,624	39,617	10.1	17.7	22.2	4.0	7.0	10.0	71,984	221,368	396,170
1995	19,601	32,997	40,543	10.8	18.3	22.4	4.0	7.0	9.0	78,404	230,979	364,887
1996	22,056	32,807	40,851	12.0	17.9	22.3	4.0	7.0	9.0	88,224	229,649	367,659
1997	25,096	33,258	41,660	13.6	18.0	22.5	3.0	7.0	8.0	75,288	232,806	333,280
1998	27,245	33,548	41,825	14.6	17.9	22.4	3.0	7.0	8.0	81,735	234,836	334,600
1999	31,110	35,417	41,624	16.4	18.7	22.0	3.0	6.0	8.0	93,330	212,502	332,992
2000	33,249	37,670	41,049	17.4	19.7	21.4	3.0	6.0	8.0	99,747	226,020	328,392
2001	36,157	40,331	41,824	18.6	20.8	21.5	3.0	6.0	8.0	108,471	241,986	334,592
2002	36,656	43,764	41,007	18.7	22.3	20.9	3.0	6.0	8.0	109,968	262,584	328,056
2003	36,191	46,883	41,355	18.2	23.6	20.8	3.0	6.0	8.0	108,573	281,298	330,840
2004	38,296	47,629	41,263	19.0	23.7	20.5	3.0	6.0	8.0	114,888	285,774	330,104
2005	41,510	49,533	42,005	20.4	24.3	20.6	3.0	6.0	8.0	124,530	297,198	336,040
2006	45,619	51,664	43,631	22.0	25.0	21.1	3.0	6.0	8.0	136,857	309,984	349,048

Year	No. of hospitalisations (AF)	No. of hospitalisations (MI)	No. of hospitalisations (HF)	Incidence of AF hospitalisations per 10,000 of the population	Incidence of MI hospitalisations per 10,000 of the population	Incidence of HF hospitalisations per 10,000 of the population	Average length of stay (AF)	Average length of stay (MI)	Average length of stay (HF)	Total bed days used (AF)	Total bed days used (MI)	Total bed days used (HF)
2007	47,164	55,676	45,128	22.4	26.5	21.5	3.0	5.0	8.0	141,492	278,380	361,024
2008	48,869	55,233	45,197	22.6	25.7	21.0	3.0	5.0	7.0	146,607	276,165	316,379
2009	51,381	55,003	45,004	23.2	25.2	20.6	3.0	5.0	7.0	154,143	275,015	315,028
2010	55,984	56,545	50,089	25.2	25.5	22.6	2.9	4.9	7.2	162,354	277,071	360,641
2011	59,148	56,172	50,983	26.3	24.9	22.6	2.8	4.8	7.2	165,614	269,626	367,078
2012	59,781	54,068	52,041	26.1	23.6	22.7	2.8	4.8	7	167,387	259,526	364,287
2013	61,424	54,116	53,643	26.3	23.2	23.0	2.6	4.7	6.9	159,702	254,345	370,137
Change (%)	**295**	**73**	**39**	**199**	**31**	**5**	**-35**	**-41**	**-31**	**157**	**2**	**-4**

Figure 1: Hospitalisations for AF, MI and HF for the time period 1993-2013
(AF – atrial fibrillation, MI – myocardial infarction, HF – heart failure)

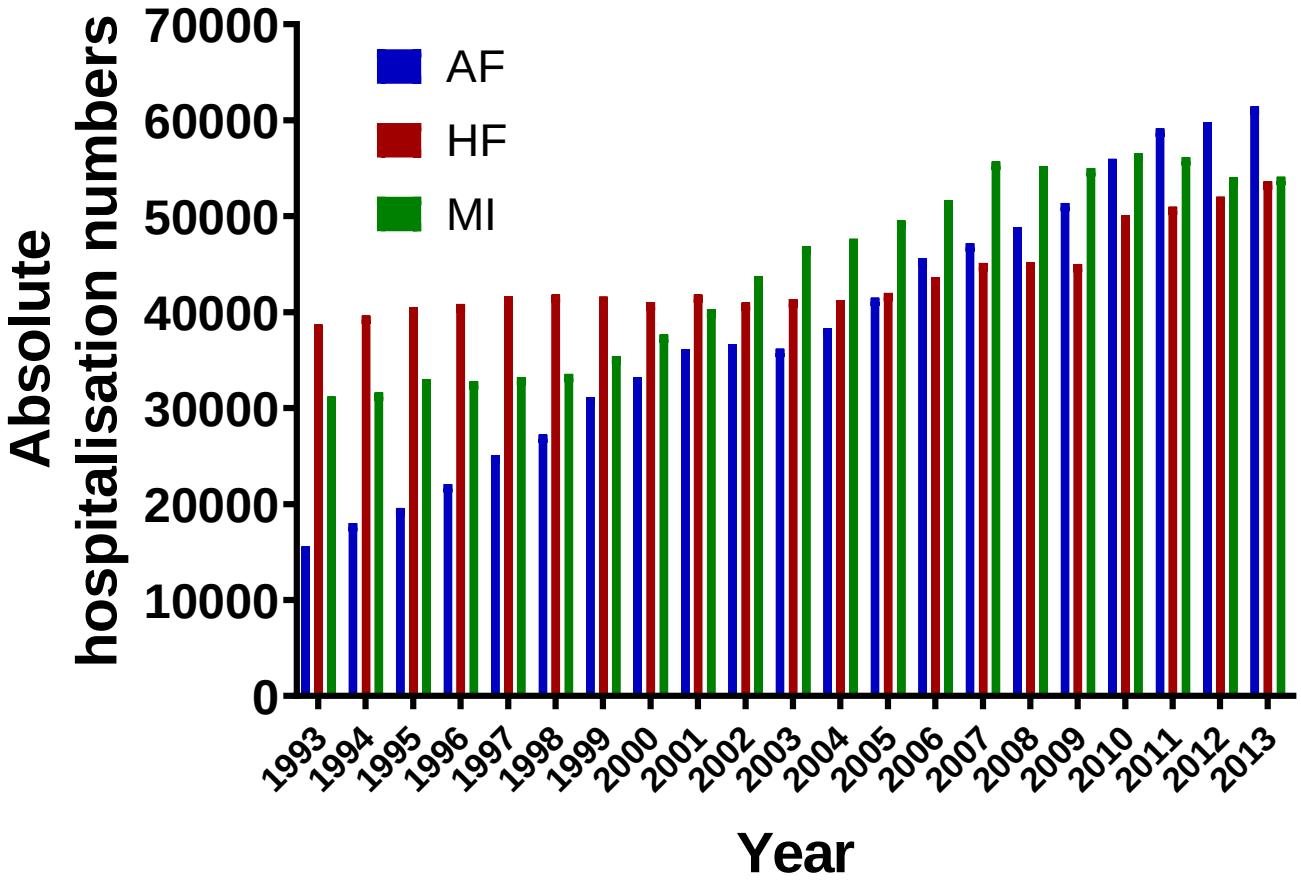


Figure 2: AF hospitalisations as a percentage of total hospitalisations from 1993-2013
(AF – atrial fibrillation)

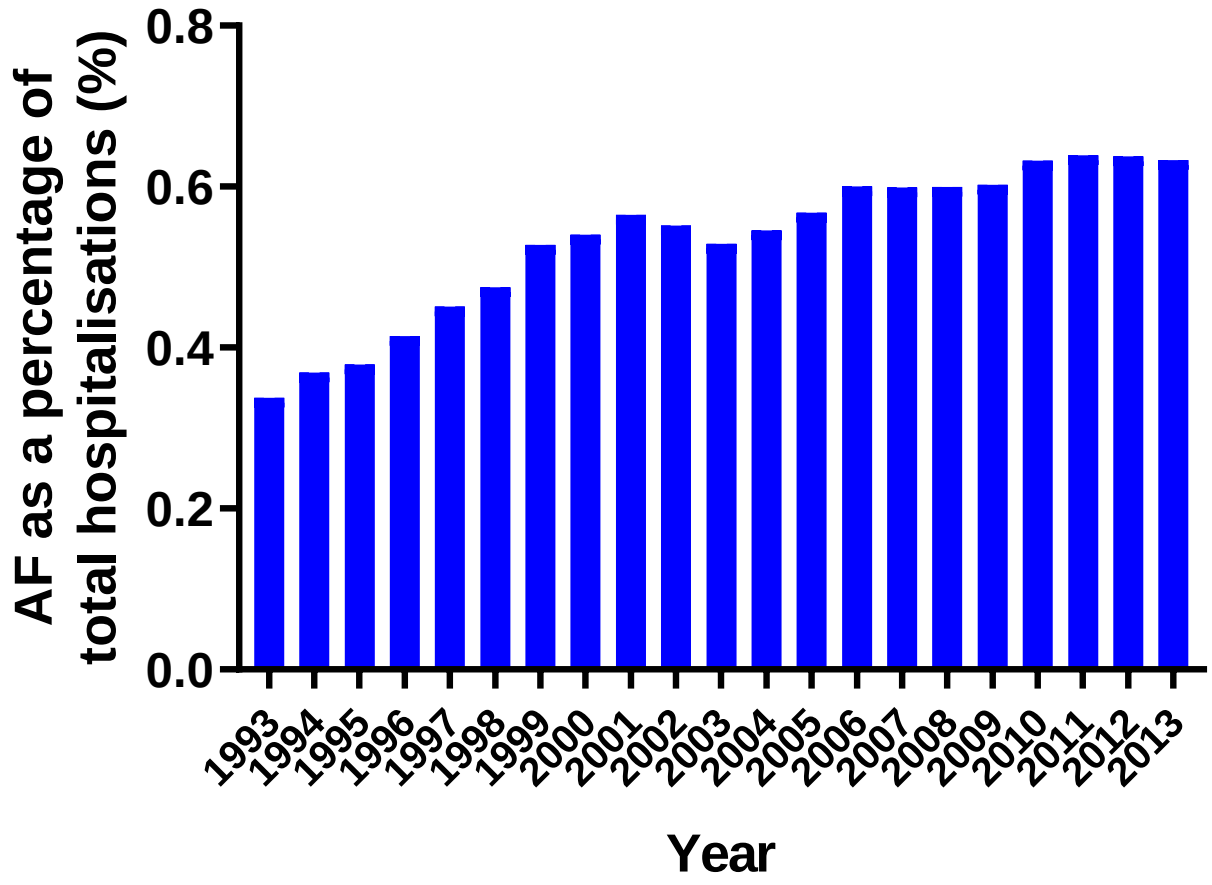


Figure 3: Absolute numbers of AF hospitalisations by age group from 1993-2013
(AF – atrial fibrillation)

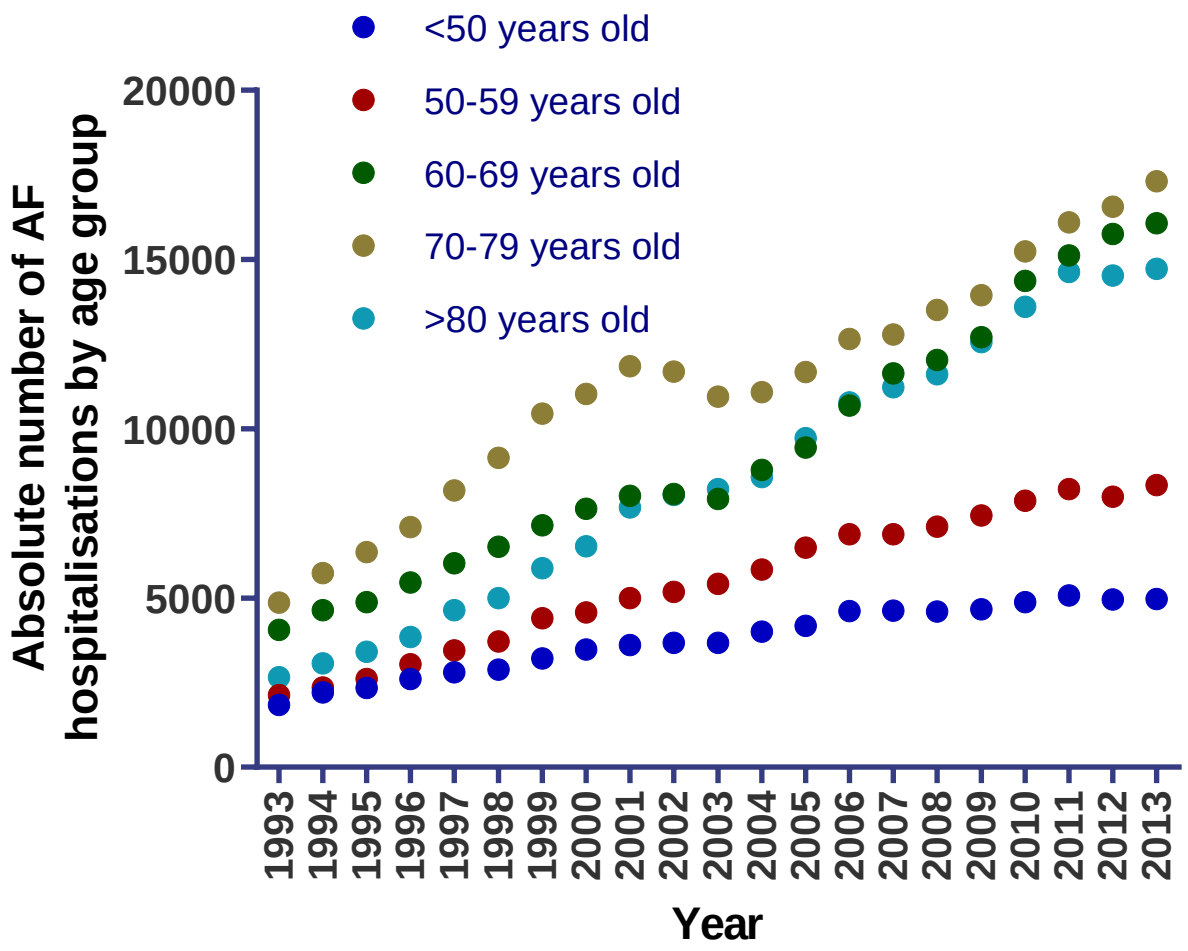
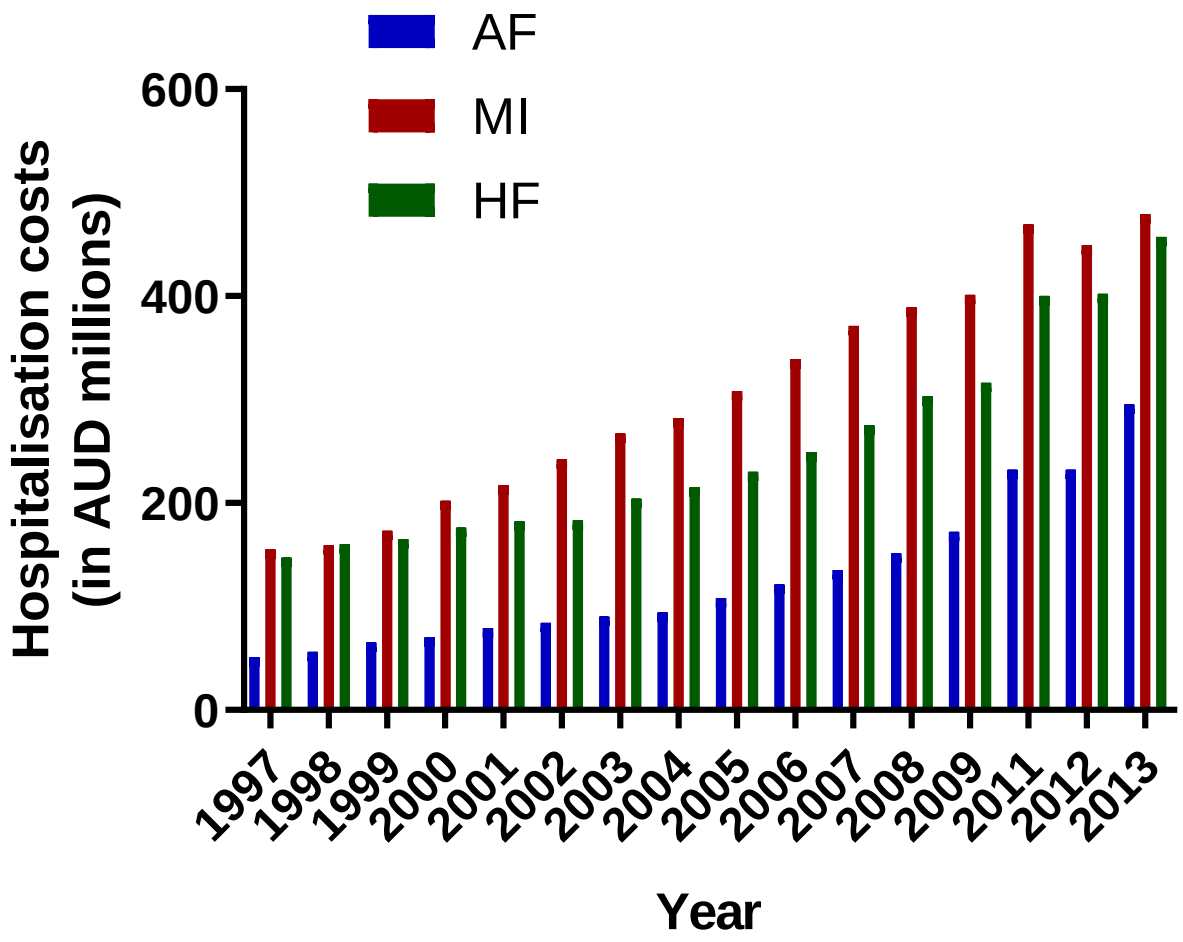


Figure 4: Costs associated with AF, MI and HF hospitalisations from 1993-2013 in AUD (AF – atrial fibrillation, MI – myocardial infarction, HF – heart failure, AUD – Australian Dollars)



Chapter 3: Alcohol and Incident Atrial Fibrillation

3.1 INTRODUCTION

3.1.1 Background

Atrial fibrillation (AF) poses a significant personal and healthcare burden and is poised to become one of the greatest healthcare challenges of this century. It is associated with significant morbidity and mortality,[224] and has demonstrated globally increasing incidence and prevalence rates.[2] Much of the burden related to this condition is due to healthcare resource utilisation with AF related hospitalisations and associated complications demonstrating a rapid global rise.[7,237] New ways of both preventing and treating this condition have become urgent healthcare needs.

3.1.2 Alcohol and health outcomes

The association between alcohol and health outcomes is complex with reports of both benefit and harm. Recent data has suggested that whilst alcohol may be associated with some cardiovascular benefits, this may be offset by an increase in mortality, alcohol-related cancers and injury, raising questions about the overall net benefit of alcohol consumption.[238] In this study of 114 970 individuals in 12 countries, high levels of alcohol intake were associated with an increase in all-cause mortality with no impact of high levels of alcohol intake on any other outcomes including cancer, stroke, cardiovascular disease and myocardial infarction.[238] At the moderate intake level, a reduction in risk of MI was observed, although no impact on incident cardiovascular

disease was evident.[238] This was also evident in a case control study of 27,778 individuals across 52 countries, low to moderate alcohol consumption was associated with a reduction in risk of incident MI.[239] A meta-analysis of 84 studies examining the risk of varying levels of alcohol intake on incident coronary heart disease events, incident stroke, cardiovascular mortality, coronary heart disease mortality and stroke mortality demonstrated that low alcohol intake of ≤1 SD per day was associated with a reduction in all of the outcomes of interest.[240] Specifically, any alcohol consumption was associated with a 29% reduction in incident coronary heart disease events (OR 0.71, 95% CI 0.66-0.77; p<0.001) and a 25% reduction in coronary heart disease mortality (OR 0.75, 95% CI 0.68-0.81; p<0.001).[240]

3.1.3 Alcohol and AF

The association between alcohol and AF has been extensively described with the term 'holiday heart' first coined nearly 40 years ago with the observation that atrial arrhythmia-related hospitalisations occurred more frequently following holiday periods and weekends.[241] Since then, alcohol has been identified as a modifiable risk factor for the development of AF with numerous cohort studies describing various degrees of association. Furthermore, two recent meta-analyses have described a graded dose response with increasing consumption of alcohol demonstrating a greater risk of incident AF.[100,101] However, it is unclear if there is a 'safe' level of alcohol intake that can be recommended to prevent the onset of AF. Furthermore, considerable uncertainty exists concerning appropriate recommendations for alcohol consumption in those with established AF. The aim of this study is to update the evidence for the strength of the association between various levels of alcohol consumption and incident AF to determine

if a ‘safe’ threshold exists, and to summarise the evidence concerning alcohol and prognosis in those with established AF.

3.2 METHODS

3.2.1 Literature search

This systematic review was performed in accordance with the Meta-Analysis of Observational Studies in Epidemiology guidelines.[242] Electronic literature searches were undertaken using PubMed and Embase databases with no date restriction up to 1 February, 2016 to identify studies examining the impact of alcohol on the risk of incident AF and prognosis in those with established AF. Keywords used include atrial fibrillation, alcohol drinking OR alcohol OR binge drink OR ethanol OR risk OR incidence OR prevalence, dose-response relationship, drug OR dose OR drinking behavior. Reference lists of selected articles were manually searched to ensure all relevant papers had been identified. The full search strategy is outlined in Table 1.

3.3 STUDY SELECTION

3.3.1 Inclusion and exclusion criteria

The primary outcome for this study was the development of incident AF or a combination of AF and atrial flutter. Inclusion criteria for this study were: 1) prospective design; 2) reported at least three categories of alcohol intake; 3) published in English; 4) included only participants who were free of AF of AF/flutter at baseline; 5) reported AF or a combination of AF/atrial flutter as an outcome measure. Exclusion criteria were: 1)

retrospective or case control design; 2) described less than three levels of alcohol intake which would not allow ascertainment of a dose response and 3) reported alcohol intake in a dichotomous fashion, i.e. yes or no response or alcohol abusers compared to non-abusers.

3.3.2 Study selection and data extraction

Two investigators independently reviewed all relevant articles to identify studies meeting criteria for inclusion. Any discrepancies were discussed, and a consensus decision reached. Data extracted from relevant publications included: first author, years of data collection, year of publication, number of participants, gender balance, mean age, follow up period, reported alcohol categories including reference group used, number and gender in each reported alcohol category, ascertainment of AF diagnosis and covariates adjusted for. Risk of bias in each study was assessed utilising the Quality in Prognosis Studies tool (QUIPS) tool and classified as low, moderate or high.[243] See Table 2 for an assessment of risk of bias for included studies.

3.3.3 Statistical analysis

The hazard ratio (HR) for the development of the outcome was extracted from each study according to each category of alcohol intake. The most adjusted model in each study was utilised. Risk estimates reported separately by sex were pooled separately. Heterogeneity across studies was assessed using the I^2 statistic. The presence of publication bias was visually assessed using funnel plots of effect size against standard error. A 2-tailed value of $p<0.05$ was considered statistically significant and all analyses were performed using

a random effects model in Review Manager (RevMan) Version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

3.4 RESULTS

3.4.1 Characteristics of included studies

A total of 1,877 articles were identified from the electronic literature search examining the impact of alcohol consumption on incident AF. 1,771 were excluded based on title and abstract review leaving 106 articles retrieved for full text review. 97 articles were excluded for reasons outlined in Figure 1 with a total of 9 studies, incorporating 249,496 participants, meeting criteria for inclusion in the meta-analysis.

Reported mean age was 60.4±10.4 years and 56.6% of the overall study population were female. Seven studies reported incident AF as their primary outcomes measure with two studies including both incident AF and atrial flutter as a primary outcome.[101,244] Most studies were undertaken in either the USA or Europe with one study undertaken in Japan[99] and another study incorporating Asian countries in their population.[245] Mean study follow up ranged from 4 to 17.6 years. Eight of the nine included studies had a low risk of bias. One study, published in abstract form only, had a moderate risk of bias.[246] Attempts to contact the authors of this study to obtain further details were unsuccessful. Each analysis was conducted with both the inclusion and exclusion of this study to ensure it did not significantly impact on results obtained. There was no evidence of publication bias.

3.4.2 Estimation of alcohol consumption

Alcohol intake was assessed by questionnaire in six studies, interview in two studies and was not reported in another study. Confirmation of AF diagnosis was mixed with studies utilising ECG criteria, hospital codes or international classification of disease (ICD) codes. Reference groups varied with five studies reporting no alcohol intake and the remaining four using low alcohol intake which was generally classified as less than one standard drink (SD) per week. Remaining categories of alcohol intake varied with two studies reporting gender differences in alcohol classification at the moderate and high levels of intake.[98,247] Three studies reported on a total of 32,684 males separately[97-99] and four studies reported on alcohol intake in 73,587 females.[97-99,248] Characteristics of the included studies are outlined in Table 3.

3.4.3 High alcohol intake

The highest alcohol category in each study compared to the reference group (Table 3) was associated with a significant increase in risk of AF development (HR 1.34; 95% CI 1.20-1.49; p<0.001) without evidence of statistically significant heterogeneity between studies (I^2 statistic = 22%, p=0.23; Figure 2). Sensitivity analysis excluding studies whose highest alcohol intake was less than three standard drinks (SD) per day did not materially alter this result (HR 1.40; 95% CI 1.19-1.64; p<0.001). Exclusion of one study, which has only been published in abstract form,[246] and another study who reported a large variation in their highest alcohol intake group (13-161 grams of ethanol per day)[249] also did not significantly alter this result. High alcohol intake was significantly associated with incident AF in males and females (HR 1.68; 95% CI 1.18-2.41; p=0.004 and HR 1.29; 95% CI 1.01-1.65; p=0.04 respectively). There was no evidence of significant

heterogeneity between studies reporting gender differences (I^2= 53%; p=0.12 and I^2 = 0%; p=0.45 respectively).

3.4.4 Moderate alcohol intake

Moderate alcohol intake, reported by most studies as 1-2 SD per day, was associated with a small but significantly increased risk of incident AF (HR 1.11; 95% CI 1.05-1.18; p=0.0002) without evidence of statistical heterogeneity between studies (I^2 = 0%; p=0.66; Figure 3). Exclusion of one study published in abstract form only did not impact on this result.[246] Exclusion of two studies, which classified moderate alcohol intake as up to 3 to 4 SD per day for men, did not impact on this result.[96,249] Whilst moderate alcohol intake in males was also significantly associated with AF development, this was not the case for females (HR 1.26; 95% CI 1.04-1.54; p=0.02 and HR 1.03; 95% CI 0.86-1.25; p=0.74; respectively) with no evidence of statistical heterogeneity (I^2=0% for both analyses, p=0.61 and p=0.86, respectively; Figures 4 and 5).

3.4.5 Low alcohol intake

Consumption of low alcohol compared to the reference group in each study was not associated with risk of AF (HR 1.03; 95% CI 0.97-1.09; p=0.30) with no evidence of significant heterogeneity (I^2=0%; p=0.88). There was no evidence of gender variation with non-significant results reported for low alcohol intake in both males and females (HR 1.01; 95% CI 0.82-1.24; p=0.93 and HR 0.93; 95% CI 0.82-1.05; p=0.25; respectively). Sensitivity analyses excluding studies who did not utilise 'no alcohol intake' as their reference group did not materially alter this result. Four studies reporting

on the impact of up to 6-7 SD per week, compared to no alcohol as a reference group, did not demonstrate a significant association with AF (HR 0.95; 95% CI 0.85-1.06; p=0.37; Figure 6).

3.4.6 Alcohol consumption and established AF

Eight studies were identified from the systematic review which included all relevant articles using the search criteria outlined above until 1 February 2016. The study population comprised 19,547 individuals (39% female, mean age 69.6±10.1 years) and examined outcomes including mortality, thromboembolism, maintenance of sinus rhythm post catheter ablation and progression from paroxysmal to permanent AF.

3.4.7 Mortality

Two studies have examined the impact of mortality in relation to alcohol consumption in those with established AF.[250,251] Results are inconsistent with one finding an association with former alcohol consumption (HR 1.27; 95% CI 1.06-1.52) but not any other level of alcohol intake,[250] and the other study reporting an association between men consuming > 27 SD per week (HR 1.40; 95% CI 1.06-1.86) but not at any level of alcohol intake in females.[251]

3.4.8 Thromboembolism

Five studies have examined the impact of alcohol consumption on risk of thromboembolism (TE).[251-255] Two studies reported overall TE risk with one describing an association in women consuming > 20 SD per week (HR 2.78; 95% CI 1.02-7.60) but

no association in men[251] and another reporting a reduction in TE risk with any level of alcohol intake, reported in a dichotomous manner (OR 0.70; 95% CI 0.52-0.95; p=0.02).[252] Two studies have examined the impact of alcohol consumption on risk of ischemic stroke (IS) with one finding no association[253] and another describing a reduction in risk for those consuming > 14 SD per week (RR 0.4, p=0.04).[254] In the final study examining this outcome, alcohol was not associated with the composite endpoint of cardiovascular death and IS or either of these components separately.[255]

3.4.9 Progression from paroxysmal to chronic AF

One study described an increase in the risk of progression from paroxysmal to chronic AF in those consuming moderate to high levels of alcohol (greater than 21 SD per week; OR 3.0; 95% CI 1.1-8.0).[256]

3.4.10 Catheter ablation

The role of alcohol consumption on the outcome of catheter ablation has been examined in one study of 122 patients with paroxysmal AF.[257] Multivariate analysis in this study showed that any level of alcohol intake was associated with an increased risk of AF recurrence after 21 months of follow up (HR 1.58; 95% CI 1.09-2.30; p=0.017).[257] Furthermore, increasing levels of alcohol intake were associated with a reduced likelihood of success post catheter ablation with alcohol abstainers demonstrating a higher success rate compared to both moderate and heavy alcohol consumers.[257]

Whilst not specifically examining the impact of alcohol on outcomes in the AF population, studies have demonstrated that reduction in alcohol intake to 30 grams

(approximately 2.5-3 SD) or less per week as part of a physician led cardiovascular risk factor management program, was associated with a reduction in AF burden and severity and favorable structural remodeling in those with established AF.[140-142] In this program there was an almost fivefold increase in arrhythmia free survival in overweight individuals who had been referred for ablation of symptomatic AF participating in the aggressive risk factor management program compared to the control group.[141]

3.5 DISCUSSION

Alcohol use has been linked to the development of AF. However, the nature of this association and the resultant prognosis remains poorly characterised. As such, the development of treatment guidelines has been limited. The current systematic review and meta-analysis demonstrates the following new information:

- Low levels of alcohol intake are not associated with incident AF with up to 6-7 SD per week not conferring an increase in risk;
- Moderate levels of alcohol consumption are associated with an increase in AF risk in males but not females;
- High alcohol intake is associated with an increased risk of incident AF across both genders;
- Recommendations in those with established AF are yet to be definitively established, but observational data would suggest that reducing alcohol to 30 grams per week or less is associated with favorable patient outcomes.

3.5.1 Gender differences in risk of incident AF with alcohol intake

Our findings concerning high and moderate levels of alcohol consumption are consistent with previously published research examining the impact of alcohol on AF development but provide new insight in to the association between low alcohol intake and AF with up to one SD daily not demonstrating an impact on incident AF. Gender differences were apparent in our study and this has previously been described in the literature. The Malmo Diet and Cancer Study failed to find an association between any level of alcohol intake in women and incident AF, but did report an association in men at high levels of alcohol intake.[258] A case control study of the Framingham cohort demonstrated that increasing levels of alcohol intake was significantly associated with incident AF in men but not women,[95] and two studies included in this current study, describing gender subgroup analyses, found an association in males, but not females, at the highest level of alcohol intake.[98,244] In each of these studies, no association between any level of alcohol intake and incident AF was demonstrated for women whilst for men the highest level of alcohol intake significantly increased risk. However, it should be noted that levels of alcohol intake in two of the four studies reporting gender subgroup analyses reported a lower level of alcohol intake in the highest category group in females compared to males which could possibly account for some of the reported differences. Each study is also somewhat limited by smaller numbers of women in the highest alcohol category, perhaps reflecting generally different trends in drinking patterns between males and females. As the majority of studies have not provided gender subgroup analyses, it is possible that moderate alcohol intake is an AF risk factor for men but not women, but further prospective studies would be required to address this.

3.5.2 Low alcohol intake and incident AF

Our findings concerning low alcohol intake are somewhat in contrast with two previously published meta-analyses which describe a small but significant increase in AF risk with each 1 SD per day consumed of approximately 8%.[101,259] In our study we restricted the inclusion criteria to that of prospective studies only, whilst the two previously published meta analyses also used studies of a retrospective and/or case control design, perhaps accounting for some of this difference. Furthermore, our meta-analysis included two recent studies from Japan and Italy which have not been included in previous reviews and provide an increasingly global perspective on the role of alcohol in incident AF. One of the previously published meta-analyses describes significant heterogeneity between studies utilised which we did not find in our analysis.[259] It also reported larger risk estimates for incident AF when incorporating studies of a case control design, which we excluded in our study, and may have possibly accounted for an overestimation of risk.

3.5.3 Mechanisms linking alcohol intake to AF

Mechanisms by which alcohol may impact on AF development are yet to be clearly elucidated. Proposed mechanisms include conduction slowing, with the original 'holiday heart' study demonstrating a prolongation of PR, QRS and QTc intervals thereby raising speculation that this may facilitate re-entry and enhance the likelihood of AF.[260] Other proposed mechanisms include a shortening of the effective refractory period,[261] increased sympathetic activity as a result of catecholamine release and a rise in plasma free fatty acids which are thought to be arrhythmogenic in nature. [260] More recently, the role of vagal activation has also featured with one study suggesting that individuals reporting vagal triggers for episodes of paroxysmal AF were also likely to report alcohol as a trigger

thereby giving rise to the theory that alcohol may stimulate a vagal response and greater propensity for AF episodes.[262] It is unclear if the association between alcohol and incident AF is mediated only through its cardio-metabolic effects including weight gain and hypertension which are independent risk factors for AF. A graded association has been demonstrated linking alcohol consumption and hypertension.[263]

3.5.4 Alcohol intake in established AF

There is little data concerning prognosis in individuals with AF in relation to alcohol consumption. The few studies that have published in this area have demonstrated conflicting results, making recommendations in this area difficult. However recent observational data, whilst not specifically examining the impact of alcohol consumption on outcomes in the AF population, has demonstrated that reduction in alcohol intake to 30 grams per week or less is associated with enhanced patient outcomes. [141,142] Further research in this field is warranted to address the gap in the literature concerning appropriate recommendations for alcohol consumption in the AF population.

3.6 LIMITATIONS

Whilst the data is limited by the alcohol categories stipulated in each study, the impact of up to one SD per day does not appear to demonstrate an association. However, at exactly what threshold this may become significant remains unknown. This is due to the limitation of not knowing, within each category of alcohol intake, exactly what each individual is consuming. In the low alcohol category for many studies, this could range from 1-7 SD per week and the risk associated with each level of intake and the optimal

threshold at which this increases incident AF risk would be difficult to elicit without very detailed data collection from study participants. Furthermore, little is known about patterns of drinking habits and its impact on AF – whilst the data may suggest that up to 6-7 SD per week is not associated with AF, it is unclear if this risk is the same in an individual who consumes 7 SD in one day or 1 SD over seven days, and the majority of studies to date have not addressed this issue. The risk associated with former drinking is also not clearly elucidated, although this is clearly less amenable to intervention. The impact on type of alcohol consumed and risk of AF is also not clear and further research in this area is warranted. One study reported no association between type of alcohol consumed and AF risk,[250] whilst another study describes an increase with consumption of spirits or wine of more than 14 SD per week (but not beer),[101] and another reporting beer and spirits at more than 21 SD per week in males increased AF risk, with no association demonstrated for females.[98] Further research in this area is warranted to make appropriate recommendations.

3.7 CONCLUSIONS

Low alcohol intake, of up to one SD per day, does not appear to confer an increase in risk of incident AF. Whilst both moderate and high levels of alcohol intake are associated with incrementally increasing levels of AF risk, gender differences are apparent. High alcohol consumption heightened AF risk across both genders, whereas moderate levels of alcohol intake conferred an increase in AF risk in males but not females. Recommendations in those with established AF remain elusive due to conflicting findings in studies but should be put in the context of overall cardiovascular and general health and each individual's

situation. Recent data would suggest that limiting alcohol intake to 30 grams per week in this population is associated with enhanced patient outcomes.

Table 1 – Search strategy for PubMed and Embase

PubMed

(Atrial fibrillation [all]) AND (alcohol drinking [MH] OR alcohol*[all] OR binge drink*[all] OR ethanol[all]) AND (risk[all] OR incidence [all] OR prevalence [all]) AND (dose-response relationship, drug [MH] OR dose [all])

Embase

('Atrial fibrillation') AND ('Drinking behavior'/syn OR alcohol* OR binge next/1 drink* OR ethanol) AND (Risk* OR incidence OR prevalence) AND (dose)

Table 2 – Assessment of risk of bias in studies included in meta-analysis

Study	Study participation	Study attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Statistical Analysis and Reporting	Overall risk of bias
Liang et al	Moderate	Low	Low	Low	Low	Low	Low
Sano et al	Low	Low	Low	Low	Low	Low	Low
Frost and Vestergaard	Low	Low	Low	Low	Moderate	Low	Low
Mukamal et al (CHS)	Low	Low	Moderate	Low	Low	Low	Low
Conen et al	Low	Low	Low	Moderate	Low	Low	Low
Shen et al	Low	Low	Low	Low	Moderate	Low	Low
Mukamal et al (Copenhagen)	Low	Low	Low	Low	Moderate	Low	Low
Di Castelnuovo et al	Low	Low	Moderate	Moderate	Low	Moderate	Moderate
Larsson et al	Low	Low	Low	Low	Low	Low	Low

(CHS – Cardiovascular Health Study)

Table 3: Characteristics of studies included in meta-analysis

Authors (reference number)	Year of publication	% female	Mean age (years)	Geographical region	Study population	Number of participants	Alcohol data collection
Liang et al[96]	2012	29.8	66.4	Multiple regions – 40 countries from Europe, US, Australia, Asia	>55 years of age plus history of CVD (CAD, PAD or CVD) or diabetes mellitus with end organ damage	30433	Questionnaire
Sano et al[99]	2014	63	57.1	Japan	Population based study	8602	Interview
Frost and Vestergaard[97]	2004	53	56	Denmark	Population based study – the Danish Diet, Cancer and Health Study	47949	Questionnaire
Mukamal et al[98]	2005	54	51	Denmark	Population based study – the Copenhagen City Heart Study	16415	Interviews
Conen et al[264]	2008	100	53.5	US	Population based study – the Women's Health Study	34715	Questionnaire

Authors (reference number)	Year of publication	% female	Mean age (years)	Geographical region	Study population	Number of participants	Alcohol data collection
Shen et al[249]	2011	56	62	US	Population based study - Framingham	4526	Questionnaire
Mukamal et al[250]	2007	56	73.1	US	Population based study – the Cardiovascular Health Study	5609	Questionnaire
Di Castelnuovo et al[246]	2015	53	NR >35 years	Italy	Population cohort study: the MOLI-SANI study	22228	Unclear
Larsson et al[101]	2014	45	64	Sweden	Population based cohort study	79019	Questionnaire

(CVD – cardiovascular disease; CAD – coronary artery disease; PAD – peripheral arterial disease; NR – not recorded; BMI – body mass index; g – grams; BP – blood pressure; FEV_1 – forced expiratory volume; CHF – congestive heart failure; ICD – international classification of disease)

Authors (reference number)	Reported alcohol categories	Reference group	Duration of follow up	Outcome measure	Confirmation of AF diagnosis	Covariates adjusted for
Liang et al[96]	Low <1 drink per week Moderate 1-14 drinks for women and 1-21 drinks for men High < 2 drinks per day for women and > 3 drinks per day for men Binge drinkers more than 5 drinks per day	Low alcohol intake <1 drink per week	56 months (median)	Incident AF	ECG	Age, sex, BMI, region, past medical history of CAD, stroke or TIA, hypertension, diabetes, chronic renal disease, sleep apnea, smoking status, education, physical activity, stress, use of statin, trial allocation (Ramipril, telmisartan, both vs placebo)
Sano et al[99]	Never Past Light (<23g/day ethanol) Light to moderate (23-45 g/day ethanol) Moderate (46-69 g/day ethanol) Heavy (>69 g/day ethanol)	Never	6.4 years (median)	Incident AF	ECG verified by physician with minority (2%) from hospital reporting of embolic stroke due to AF	Age, sex, smoking status, BMI, hypertension, hyperglycaemia, hyperlipidaemia, major ST-T abnormalities, previous MI
Frost and Vestergaard[97]	Quintile 1 4.1±2.6g/day Quintile 2 12.1±2.1g/day Quintile 3 20.0±3.0g/day Quintile 4 36.1±4.9g/day Quintile 5 68.7±22.8g/day	Quintile 1 4.1±2.6g/day	5.7 years (mean)	Incident AF or atrial flutter	ICD codes	Age, height, BMI, smoking, systolic BP, treatment for hypertension, total serum cholesterol and level of education

Authors (reference number)	Reported alcohol categories	Reference group	Duration of follow up	Outcome measure	Confirmation of AF diagnosis	Covariates adjusted for
Mukamal et al[98]	Weekly number of drinks: Females: <1, 1-6, 7-13, 14-20, ≥21 Males: <1, 1-6, 7-13, 14-20, 21-27, 28-34 and ≥35	<1 drink per week	17.63 years (mean)	Incident AF	Predominantly hospital records. Small number by study ECG.	Age, smoking, education, cohabitation, family history of CVD, diabetes, income, physical activity, BMI, FEV_1, height, use of BP medication, systolic BP, incident diagnoses of CHD or CHF
Conen et al[264]	None, <1 drink per day, 1-2 drinks per day, ≥2 drinks per day	None	12.4 years median	Incident AF	ECG or medical report noting AF in past medical history verified by a physician	Age, systolic blood pressure, history of hypertension, BMI, race/ethnicity, smoking, history of diabetes, history of hypercholesterolaemia, exercise, education and randomised treatment assignment
Shen et al[249]	None, 1-3 g/day, 3-13 g/day, 13-161 g/day	None	4 years	Incident AF	ECG	Age, sex, BMI, systolic BP, hypertension treatment, ECG, PR interval, significant heart murmur and heart failure

Authors (reference number)	Reported alcohol categories	Reference group	Duration of follow up	Outcome measure	Confirmation of AF diagnosis	Covariates adjusted for
Mukamal et al[250]	None, former drinkers, <1 drink per week, 1-6 drinks per week, 7-13 drinks per week and greater than 14 drinks per week	None	9.1 years	Incident AF	ECG and ICD codes for hospital admissions	Age, sex, race, income, height, waist circumference, physical activity, psychoactive medication, diabetes, hypertension, CHD, congestive heart failure and total cholesterol
Di Castelnuouvo et al[246]	Never, former drinkers, occasional drinkers, 1-12 g/day, 13-24 g/day, 24-48 g/day, >48 g/day	None	4.2 years median	Incident AF	Hospital discharge codes	Age, sex, smoking, education, income, physical activity, BMI, total calorie intake, history of CVD, hypertension or diabetes
Larsson et al[101]	Never, past, <1 drink per week, 1-6 drinks per week, 7-14 drinks per week, 15-21 drinks per week, >21 drinks per week	<1 drink per week	12 years	Incident AF or atrial flutter	ICD codes	Age, sex, education, smoking status, BMI, family history of MI before the age of 60, history of CHD or heart failure, history of diabetes and history of hypertension

(BMI – body mass index, CAD – coronary artery disease, TIA – transient ischaemic attack, FEV – forced expiratory volume, CHD – coronary heart disease, CHF – congestive heart failure)

Figure 1: Study flow chart

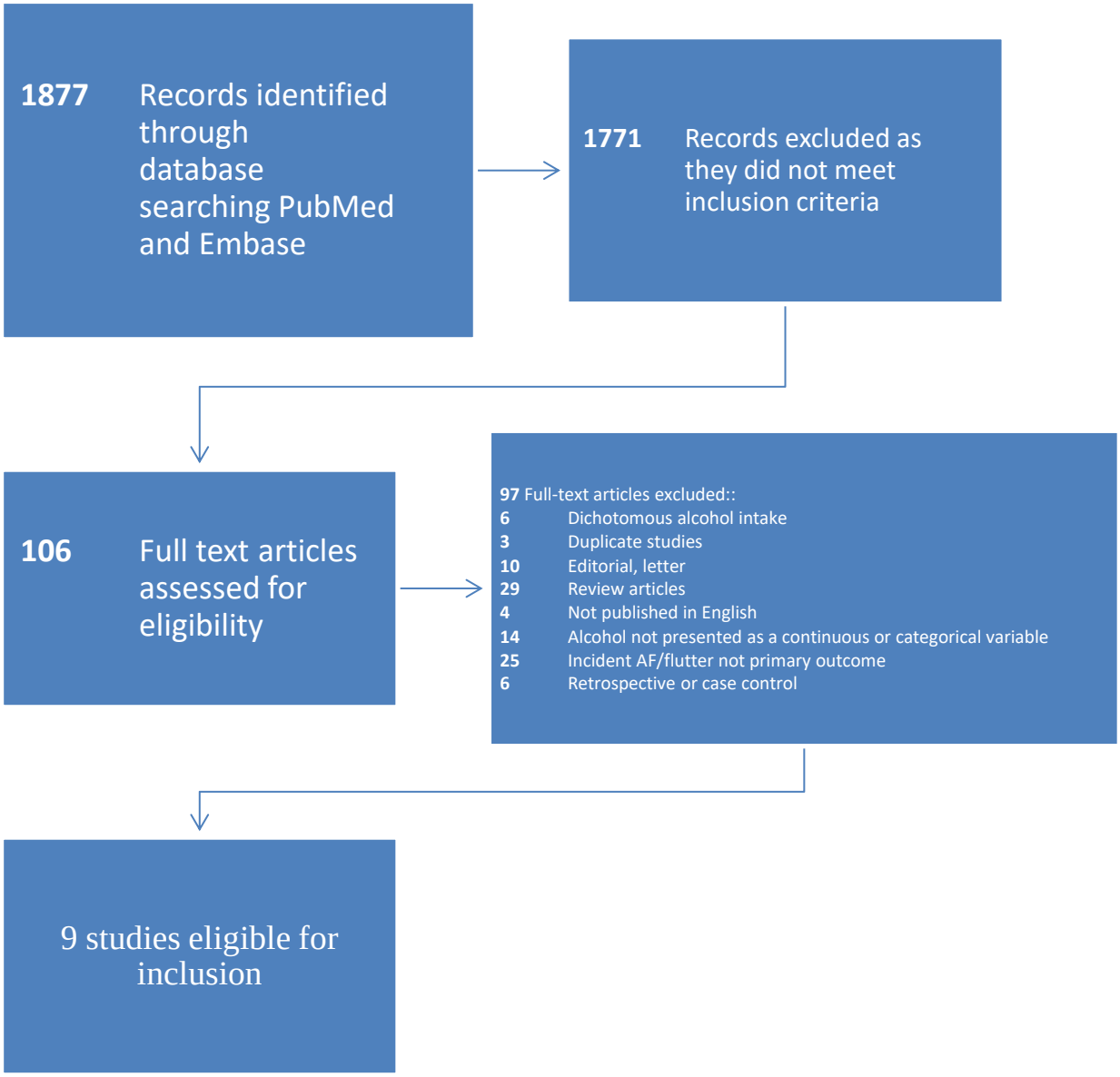


Figure 2: Risk of incident AF with high alcohol intake compared to low or no alcohol intake

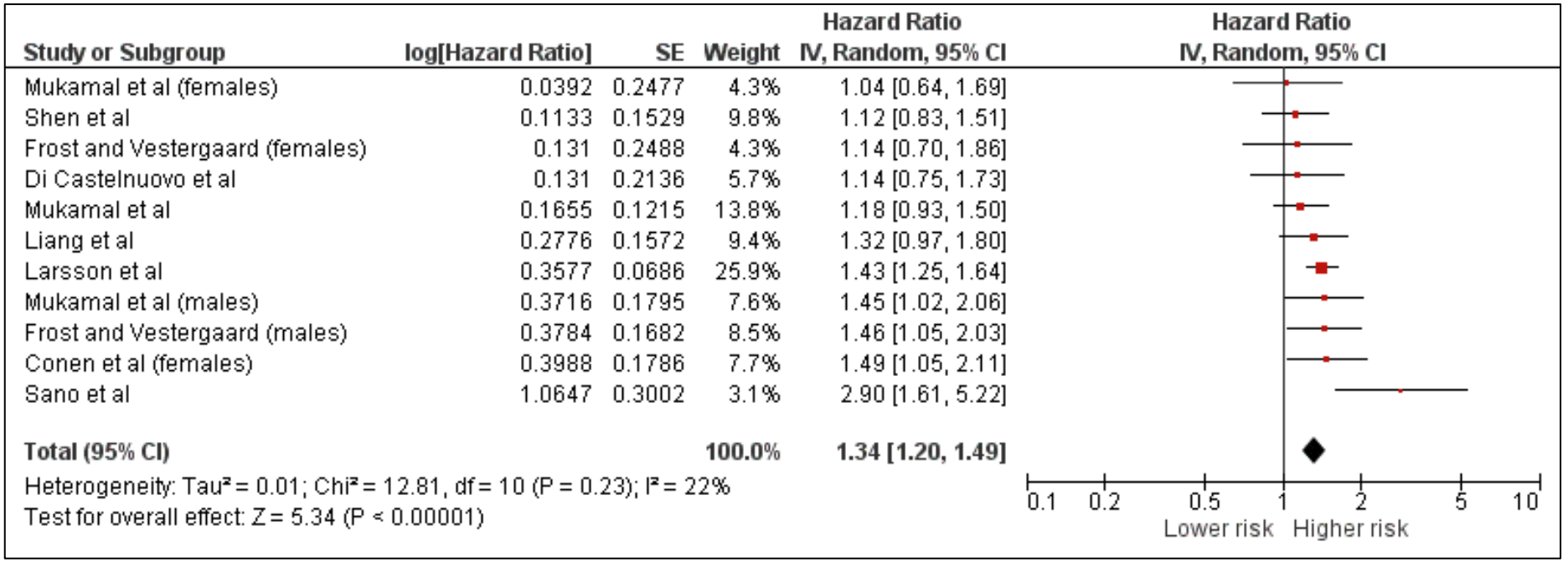


Figure 3: Risk of incident AF with moderate alcohol intake

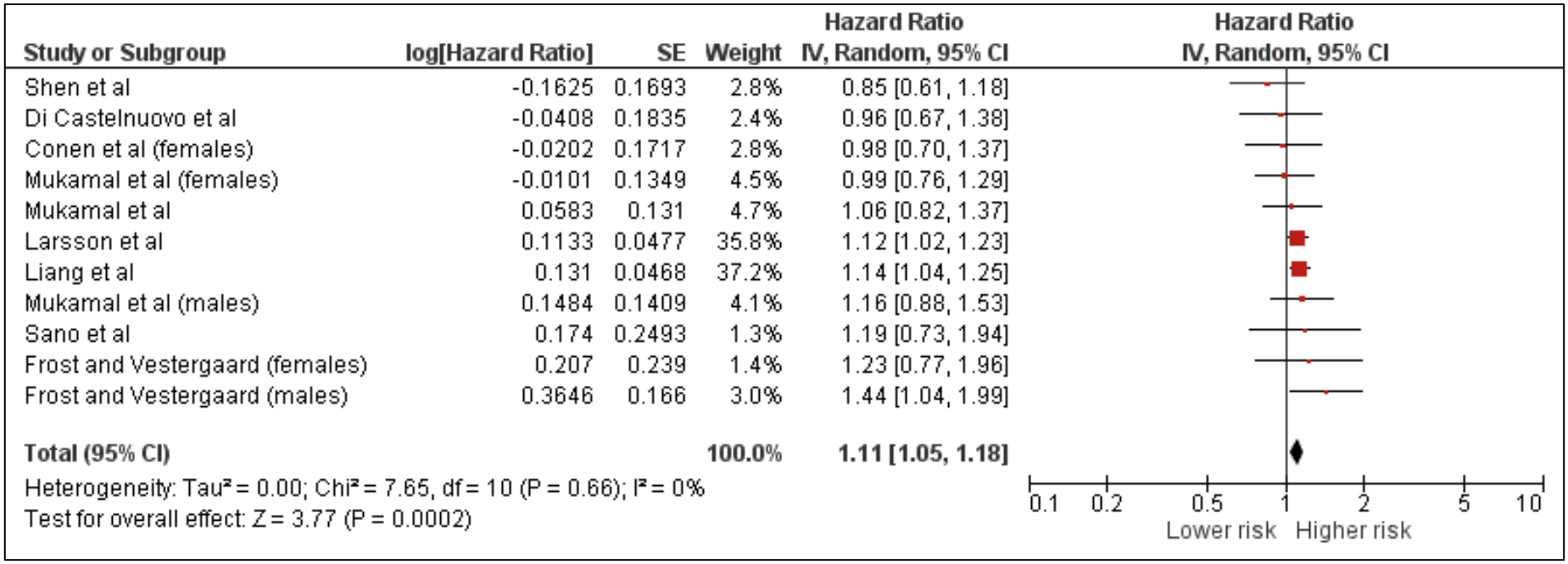


Figure 4: Risk of incident AF with moderate alcohol intake in males

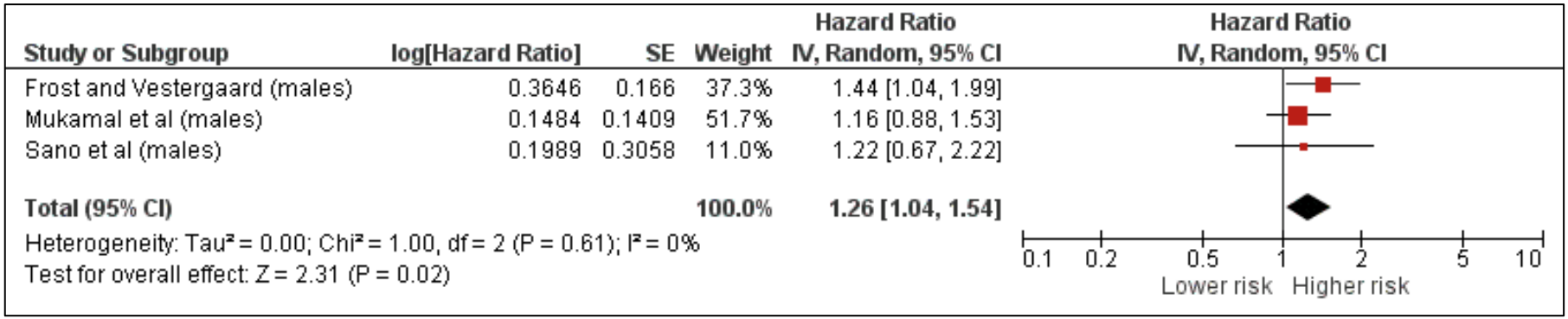


Figure 5: Risk of AF with moderate alcohol intake in females

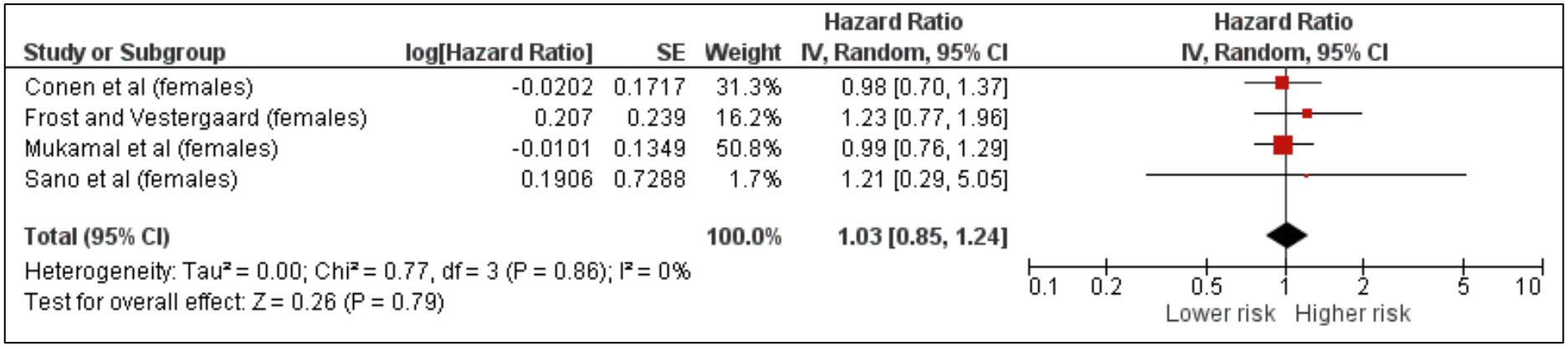
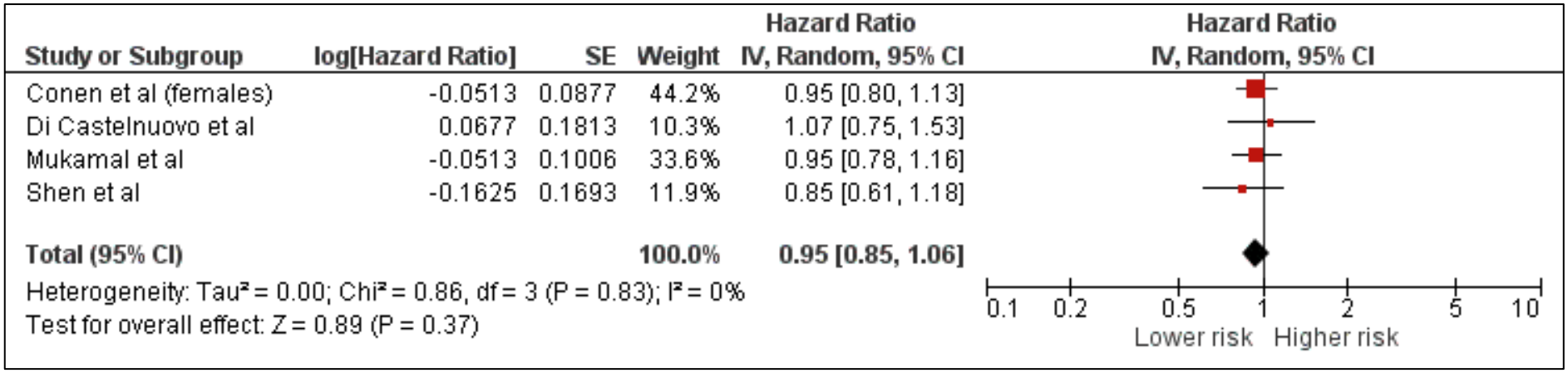


Figure 6: Risk of incident AF with up to one standard drink per day



Chapter 4: Integrated Care for Atrial Fibrillation

4.1 INTRODUCTION

Atrial fibrillation (AF) is an emerging global epidemic. In 2010, it was estimated that 33.5 million individuals were living with AF globally, with this figure expected to rise significantly over the coming decades.[2] In stark contrast to other chronic cardiovascular conditions which have seen associated declines in mortality, recent data has demonstrated an almost doubling of age adjusted mortality rates related to AF over the last two decades.[2] Furthermore, significant resultant costs are associated with AF, with hospitalisations as the main driver, due to both the condition itself, and related complications including stroke and heart failure.[8] Indeed, this rapid increase in hospitalisations has been described as a 'rising tide' showing no sign of abating with data suggesting that hospitalisations for AF have now surpassed those related to heart failure.[7,265] Both hospitalisation and complications related to AF may be preventable with appropriate guideline adherent care delivery to enhance outcomes in this population. Indeed, current registry data suggests that AF is often sub-optimally managed with poor guideline adherence to appropriate anticoagulation for stroke prevention.[266] It is clear that a new approach to care delivery is urgently needed to address the burgeoning AF population.

4.1.1 The Chronic Care Model

The integrated care approach has its origins in the chronic care model developed by Wagner and colleagues,[267] with the recognition that chronic condition management calls for a different approach to more traditional models of care delivery. Central to this model is the patient as the primary focus, with other essential elements including a multidisciplinary team and community support structures. This model is in stark contrast to more traditional paternalistic models of care in which the patient played a passive role in decisions concerning their care. Enhancing patient outcomes with the use of chronic condition management is achieved through redesigning daily practice to ensure care is delivered tailored to the patient's needs and values and based on best available evidence. This is often supported with the use of electronic clinical support systems.

Numerous studies have demonstrated the efficacy of this approach in chronic condition management. In a small cluster randomised controlled trial in diabetes care, implementation of a chronic condition management (CCM) program which demonstrated strong fidelity to the original chronic care model, resulted in a significant reduction in HbA1c in those attending these practices compared to an education only arm or usual care.[268] There was also significant reductions in non HDL cholesterol although no impact on blood pressure was observed in this intervention. The frequency of self-monitoring of blood glucose also improved in the CCM group compared to others although no statistically significant between group differences was observed in relation to diabetes knowledge.[268]

In another observational study of CCM practice sites compared to traditional models of care in the UK, the use of CCM was associated with a statistically significant reduction in cardiovascular risk as delineated by the United Kingdom Prospective Study

(UKPDS) risk score after one year follow up of 1170 participants across 13 health care organisations.[269] This model also demonstrated strong fidelity to the original chronic care model and implemented all of the critical components of this model. A greater magnitude in risk reduction was observed in those at higher risk of cardiovascular events as per the UKPDS score.[269]

One of the largest studies to date based on the chronic care model was an observational study of 102 primary care practices in Utah, USA. In this study, practices that participated in team based approach care based on the chronic care model were compared to those who undertook traditional practice management.[208] Over long term follow up of approximately four years, team based approach care was associated with improvements in quality related outcomes including screening for depression and adherence to components of diabetes care, although there was no improvement in the use of advanced care directives and a lesser likelihood of controlled hypertension in those attending team based care practices. Measures of acute health care resource utilisation were also reduced in the team care approach including a reduction in emergency department visits and hospitalisations, in addition to a reduction in primary care physician visits.[208]

4.1.2 Models of care delivery for chronic cardiovascular conditions

Whilst a multitude of evidence exists for the use of co-ordinated systems of care in other chronic cardiovascular conditions including heart failure[270] and acute coronary syndromes,[186] there is comparatively less in the AF field. Recently, several studies have been undertaken examining the use of integrated care in the AF population [209,271] but to date a synthesis of the available literature has not been undertaken.

4.2 METHODS

This systematic review and meta-analysis was conducted in accordance with the PRISMA guidelines.[272] The aim of our study was to examine the impact of the integrated care approach in the AF population, compared to usual care, on outcomes including mortality, hospitalisations, emergency department presentations, cerebrovascular outcomes and patient reported outcomes including quality of life, anxiety and depression.

4.2.1 Literature search

PubMed, Embase and CINAHL databases were searched from inception to February 2016 with keywords including 'atrial fibrillation', 'integrated health care', 'multidisciplinary', 'ambulatory care', 'ambulatory monitoring', 'outpatient', 'interdisciplinary communications', 'outcome', 'treatment failures', 'death', 'mortality', 'fatal', 'hospitalisation', 'hospital admissions', 'quality of life' and 'symptom burden'. See Table 1 for an outline of the full search strategy in PubMed.

4.2.2 Inclusion and exclusion criteria

Inclusion criteria were the use of an integrated care approach, focus on holistic and comprehensive AF management, presence of a control group and a minimum six month follow up period. Randomised and non-randomised studies were eligible for inclusion. Exclusion criteria were studies that focussed on one area of AF management (e.g. anticoagulation), were not published in English or had less than 50 participants. A previously published description of integrated care was used and was defined as 'the

provision of multidisciplinary care at different stages of the care process in different institutional areas'.[273]

4.2.3 Data extraction

Two investigators independently reviewed all relevant articles to identify studies meeting criteria for inclusion. Any discrepancies were discussed, and a consensus decision reached. Data extracted from relevant publications included: first author, years of data collection, year of publication, number of participants, gender balance, mean age, follow up period, outcomes reported, and covariates adjusted for. Risk of bias in each study was assessed using the Cochrane tool.[274] See Table 2 for assessment of risk of bias for included studies. The authors of one study were contacted and provided information concerning all-cause mortality to facilitate report of this as an outcome measure.[209]

4.2.4 Statistical analysis

The risk estimate for the development of the outcome was extracted from each study. The most adjusted model in each study was utilised. Heterogeneity across studies was assessed using the I^2 statistic. The presence of publication bias was visually assessed using funnel plots of effect size against standard error. A 2-tailed value of $p<0.05$ was considered statistically significant and all analyses were performed using a random effects model in RevMan Version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

4.3 RESULTS

The search yielded a total of 1219 articles that were assessed by title and abstract. Of those, 1180 were excluded as they did not meet the inclusion criteria. The remaining 39 articles were retrieved for full text assessment with three meeting criteria for inclusion in our meta-analysis.[209,211,212] A study flow chart is depicted in Figure 1. Risk of bias was assessed as low in two of the included studies and moderate in one study. The total study population was 1383 participants of which 43% were female. Mean age was 66.9±15.4 years. Characteristics of the three studies included in the meta-analysis are outlined in Table 3. Outcomes that were able to be extracted from two or more of the included studies included all-cause mortality, cardiovascular hospitalisations, AF related hospitalisations and cerebrovascular events. A meta-analysis of results regarding AF related ED presentations was not performed as this data was not available in the included studies or quality of life due to heterogeneity in assessment tools used for this outcome. Similarly, there was a lack of original data on other patient reported outcomes including anxiety, depression and symptom burden. Visual assessment of funnel plots did not reveal any evidence of publication bias.

4.3.1 All-cause mortality

Based on two studies reporting on this outcome, an integrated care approach resulted in a significant 49% reduction in all-cause mortality (OR 0.51, 95% CI 0.32-0.80, p=0.003; see Figure 2). There was no evidence of significant heterogeneity (I^2=0%, p=0.51). The absolute event rate for the intervention group was 3.0 per 100-person years (95% CI 1.37-6.76) compared to 5.7 per 100-person years in the control arm (95% CI 3.55-9.0).

4.3.2 Cardiovascular related hospitalisations

Integrated care was associated with a significant 42% reduction in cardiovascular hospitalisations (OR 0.58, 95% CI 0.44-0.77, p=0.0002; see Figure 3) based on three studies, without any evidence of significant heterogeneity (I^2=6%, p=0.35). The absolute event rate was 8.0 per 100-person years in the integrated care arm (95% CI 2.56-25.02) compared to 11.87 in the control group (95% CI 4.59-30.71). Analysis of this outcome with the exclusion of one study[212] ,due to a higher risk of bias, did not significantly alter the outcome (OR 0.58, 95% CI 0.38-0.89, p=0.01).

4.3.3 AF related hospitalisations

The integrated care approach did not have a statistically significant impact on AF related hospitalisations (OR 0.82, 95% CI 0.56-1.19, p=0.29; Figure 4) based on two studies reporting on this outcome, without any evidence of significant heterogeneity (I^2=0%, p=0.38). An absolute event rate of 5.5 per 100-person years was demonstrated in the intervention arm (95% CI 1.02-29.59) compared to 7.0 per 100-person years in the control group (95% CI 1.87-26.23).

4.3.4 Cerebrovascular events

Similarly, there was no evidence of any benefit of an integrated care approach on cerebrovascular events based on three studies reporting on this outcome (OR 1.00, 95% CI 0.48-2.09, p=1.00; Figure 5). There was no evidence of significant heterogeneity (I^2=0%, p=0.68). There were comparable absolute event rates in both arms of the study at 1.1 per 100-person years in both groups (95% CI 0.50-2.44 for the intervention group

and 0.66-1.82 for the control group). Exclusion of one study from this analysis [212], due to a higher risk of bias, did not significantly alter this result (OR 1.00, 95% CI 0.42-2.38, p=1.00).

4.3.5 Patient reported outcomes

A meta-analysis of results related to quality of life or anxiety and depression was not possible due to heterogeneity of assessment tools utilised across studies. Two studies reporting on quality of life outcomes did not report any statistically significant between group differences at final follow up and, similarly, no impact of an integrated care approach on either anxiety and/or depression was demonstrated.[147,211] None of the included studies reported on effect of the intervention on symptom burden.

4.3.6 Number needed to treat (NNT)

Statistically significant outcomes were further analysed to determine a NNT compared to published data for heart failure clinics [275]. For all-cause mortality, a NNT of 19 in an AF program was demonstrated to prevent one death, compared to 17 in heart failure clinics. With respect to hospitalisations, a NNT of 18 in AF care programs to prevent one cardiovascular related hospitalisation, compared to 11 in a heart failure clinic to prevent one heart failure related hospitalisation.

4.4 DISCUSSION

The integrated care approach has demonstrated enhanced patient outcomes in several chronic conditions. This meta-analysis of studies evaluating the role of an integrated care approach in atrial fibrillation demonstrates that integrated care is associated with:

- Enhanced patient outcomes including reduction in all-cause mortality and cardiovascular hospitalisations;
- No significant impact on AF related hospitalisations and cerebrovascular events;
- Insufficient original data to report on a synthesis of data related to patient reported outcomes;
- A highly efficacious NNT, which compares favourably to other approaches including co-ordinated heart failure care programs, for outcomes including all-cause mortality and hospitalisations.

These findings have significant implications regarding care delivery in the AF population and support the use of integrated care as an effective and efficacious intervention. However, many questions remain unanswered and further research is required to address the way in which delivery of this approach is optimally implemented.

4.4.1 Integrated care management for AF

Whilst each study included in this meta-analysis utilised an integrated care approach, there are significant differences in populations recruited and methodology employed for care delivery. The first study by Hendriks and colleagues was a single centre study undertaken in the Netherlands.[209] This study recruited participants who had been referred to the outpatient clinic for management of AF with the intervention group attending a

nurse led, cardiologist supervised clinic. The program incorporated protocoled diagnostic testing, patient education and recommendations for AF management based on current guidelines at the time. The study also employed a software decision support system to facilitate guideline adherence, guide treatment recommendations and support decision making. After a mean follow up of 22 months, there was a significant 35% reduction in the composite endpoint of cardiovascular mortality and hospitalisations (HR 0.65; 95% confidence interval (CI) 0.45–0.93; p=0.017).[209]

The Standard versus Atrial Fibrillation specific strategy (SAFETY) study was a multicentre Australian based study in which participants who were admitted to hospital primarily due to AF, were eligible for inclusion in the study.[271] The intervention was diverse and included a home visit undertaken by a specialised cardiac nurse 7-14 days post discharge, an education package, referral to other healthcare professionals including physician referral for those requiring urgent review at the home visit and recommendations to the medical team concerning optimal AF treatment. After a mean follow up of two and a half years there was proportionately more event free days in the intervention group (defined as days alive and out of hospital) but no significant difference in the co-primary composite outcome of all-cause mortality and hospitalisations (HR 0.97, 95% CI 0.76–1.23; p=0.851).[211]

The final study was a 'before and after' study undertaken in Canada with eligible participants having presented to the emergency department primarily due to symptoms arising from AF.[212] In the intervention phase, participants received a brief educational telephone call by a cardiac nurse following discharge, were invited to attend a group education session and undertook one clinic visit in a nurse led, cardiologist supervised clinic. In propensity matched groups, the primary composite endpoint of all cause death,

cardiovascular hospitalisations and AF related ED visits was statistically significant (OR 0.71; 95% CI 0.59-1.0; p=0.049).[212]

4.4.2 Impact of the integrated care approach in AF

Despite differences employed in each study, we did not find any evidence of statistically significant heterogeneity in any of our outcomes, strengthening the conclusions drawn from our results. However, it is of interest to further explore each of these studies to explore clinical applicability and direct areas for future research. Although none of the studies were appropriately powered for all-cause mortality as an outcome measure, it is encouraging that co-ordinating care through an integrated approach had a clear and consistent effect in the two studies reporting on this. Similarly, the positive impact on cardiovascular hospitalisations is also consistent although reasons for the impact on this outcome but not AF hospitalisations is of interest. Firstly, how much of the reduction in cardiovascular related hospitalisation is due to enhanced clinical surveillance and improvements in cardiovascular risk factor status is not well defined. Two of the three studies did not report on changes in cardiovascular risk factor status, whilst the SAFETY study did not find any significant difference in any cardiovascular risk factor measures between groups at final follow up. Recently, the role of intense management of cardiovascular risk factors in the AF population has gained significant momentum with the recognition that this approach is associated with reduced symptom burden and an enhanced likelihood of sinus rhythm post catheter ablation.[141,276,277] It is also possible that participants having access to specialist care when required could have prevented cardiovascular related hospital admissions. The lack of impact on AF related hospitalisations is somewhat surprising but perhaps reflects a generally sicker population

with co-morbidities accounting for the need for hospitalisation. It is also possible that this reflects a type 2 error due to a small sample size and a significant impact may be observed in a larger population.

Similarly, cerebrovascular events were not significantly reduced with the use of this approach. This perhaps belies the complex issue of anticoagulation, with numerous issues, including the informed decision of the patient, to take in to consideration. It may also reflect the need for enhanced surveillance and management of cardiovascular risk factors with increased recognition that both AF and stroke share common risk factors, and this may play a significant role in the pathogenesis of cerebrovascular ischaemic events in AF. Encouragingly, recent data has suggested a significant increase in appropriate use of anticoagulation based on CHA_2DS_2-VASc score, with the clinical adoption of novel oral anticoagulant therapy (NOAC),[278] which were not in widespread use at the time two of the three studies were undertaken. The importance of reassessment of stroke risk scores over time has also been highlighted with recent large registry data from Taiwan demonstrating that in almost 90% of individuals who experienced an ischaemic stroke, the CHA_2DS_2-VASc score had increased over time due to the development of comorbidity.[130] In this study 4103 individuals of a total cohort of 31 039 individuals with AF experienced an ischaemic stroke, many of which may be potentially preventable if appropriate oral anticoagulant therapy had been instituted in response to changing circumstances.[130]

4.4.3 Integrated care and appropriate anticoagulation use

Two of the studies reported on appropriate prescription of anticoagulation based on CHADS/CHA_2DS_2-VASc score [209,271] with a significantly greater rate in the study by

Hendriks et al warranting further exploration. Whilst it is clear from the baseline demographics that the SAFETY study had a generally sicker and co-morbid population, the method by which anticoagulation was addressed may also be relevant. As a clinic-based study, Hendriks and colleagues were able to initiate anticoagulation and discuss any relevant issues at subsequent visits, whilst the SAFETY study made recommendations to treating clinicians without being able to start appropriate antithrombotic therapy if it was indicated. This should be a consideration for future studies as it is a phenomenon other studies have also found with appropriate therapy often not initiated unless it is undertaken by the specialist clinic.[279] The importance of both integrated care in AF and cardiovascular risk factor management in this population has recently been highlighted with current guidelines recommending these approaches as part of standard care delivery.[115,128]

4.4.4 Integrated care and patient reported outcome measures

There was insufficient original data to undertake a meta-analysis on patient reported outcomes due to either lack of report on these outcomes or heterogeneity in assessment tool utilised. This is a point worthy of consideration in the design of future studies in this field. The use of standardised clinical and patient reported outcomes measures in AF, such as those recommended by the International Consortium for Health Outcomes Measurement (ICHOM) for coronary heart disease[280] and heart failure, [281] would be of significant benefit in both future research in this field and in design of optimal care delivery systems for clinical application and evaluation.

4.5 LIMITATIONS

The results of this meta-analysis point to integrated care as a highly effective method of care delivery, which is further strengthened by examining outcomes in studies which have a control group undertaking usual care, to provide the highest level of evidence in support of this approach. However, several limitations need to be considered with regards to the current study. Firstly, whilst it is clear that the integrated care approach is associated with enhanced patient outcomes, it is difficult to know which components of this approach, and to which AF subpopulations, it would be of most benefit. Secondly, the setting and personnel required varied between studies and may need to be individualised with the recognition of AF as a heterogeneous condition with patients often having complex and competing needs, making appropriate recommendations in this area difficult. A schematic of how the integrated care approach may be applied in the AF population has previously been described and is outlined in Figure 6.[282] This highlights the importance of the multidisciplinary team approach with the patient at the core, and decision support systems to facilitate delivery of best practice, guideline adherent care. The possibility that an impact of the integrated care approach on both AF related hospitalisations and cerebrovascular events may be observed in a larger sample size also needs to be taken in to consideration due to a type 2 error in the current study. Finally, the need for clearly described methodology to allow for replication of studies is difficult due to the nature of such interventions but would be of benefit to the clinical and research community in determining how best to apply this approach.

4.6 CONCLUSIONS

This meta-analysis of current evidence demonstrates integrated care as a highly effective intervention when applied to the AF population with associated reductions in all-cause mortality and cardiovascular related hospitalisations. The integrated care approach, now recommended by international AF guidelines, has a crucial role in improving outcomes in this rapidly increasing population and should be widely implemented in the clinical setting. However, further work is needed to refine the optimal settings, methods and components of care delivery in such approaches, with strong consideration given to standardised clinical and patient reported outcomes in the AF sphere.

Table 1: Search strategy for PubMed

"atrial fibrillation"	Delivery of Health Care, Integrated [mh:noexp] OR "integrated health care" OR multidisciplinary OR "ambulatory care" OR "ambulatory monitoring" OR Outpatient* OR "Interdisciplinary Communication" OR "Interdisciplinary Communications"	Outcome* OR "treatment failure" OR "treatment failures" OR ((cardiac OR cardiovascular OR heart) AND (death* OR mortalit*)) OR Fatal* OR Hospitalisation [mh] OR "hospital admission" OR "hospital admissions" OR "quality of life" OR HRQL OR "life quality" OR "quality adjusted life year" OR qaly OR "quality adjusted life years" OR "short form 12" OR SF-12 OR SF12 OR "short form 20" OR SF-20 OR SF20 OR "short form 36" OR SF-36 OR SF36 OR "short form 8" OR SF-8 OR SF8 OR "symptom burden" OR "burden of symptoms"

Table 2: Risk of bias in studies included in meta-analysis

	Selection bias – random sequence generation	Selection bias – allocation concealment	Performance bias - Blinding of participant and personnel	Detection bias – blinding of outcome assessment	Attrition bias – incomplete outcome data	Reporting bias – selective reporting
Hendriks et al[209]	Low	N/A	N/A	Low	Low	Low
Stewart et al[211]	Low	N/A	N/A	Low	Low	Low
Carter et al[212]	High	N/A	N/A	Low	Low	Low

Table 3: Characteristics of studies included in the meta-analysis

	Hendriks et al[209]	Stewart et al[211]	Carter et al[212]
Mean age	66.5±13	71.5±12	62.8±15.4
Total participants	712	335	336
% female	41	48	39
Study type	RCT	RCT	Before and after
Year of publication	2012	2015	2016
CHA_2DS_2-VASc score	2.4±1.7	3.6±1.8	2.2±1.8
Participant recruitment method	Referred to outpatient clinic with AF	Hospital admission with AF	Presented to ED with AF
Duration of follow up (years)	1.83	2.51	2.06
Primary outcome measure	CV hospitalisation and death	All-cause mortality and/or unplanned readmission, proportion of event free days	Death, CV hospitalisation, AF ED visit

(AF – atrial fibrillation, CV – cardiovascular, ED – emergency department)

Figure 1: Study flow chart

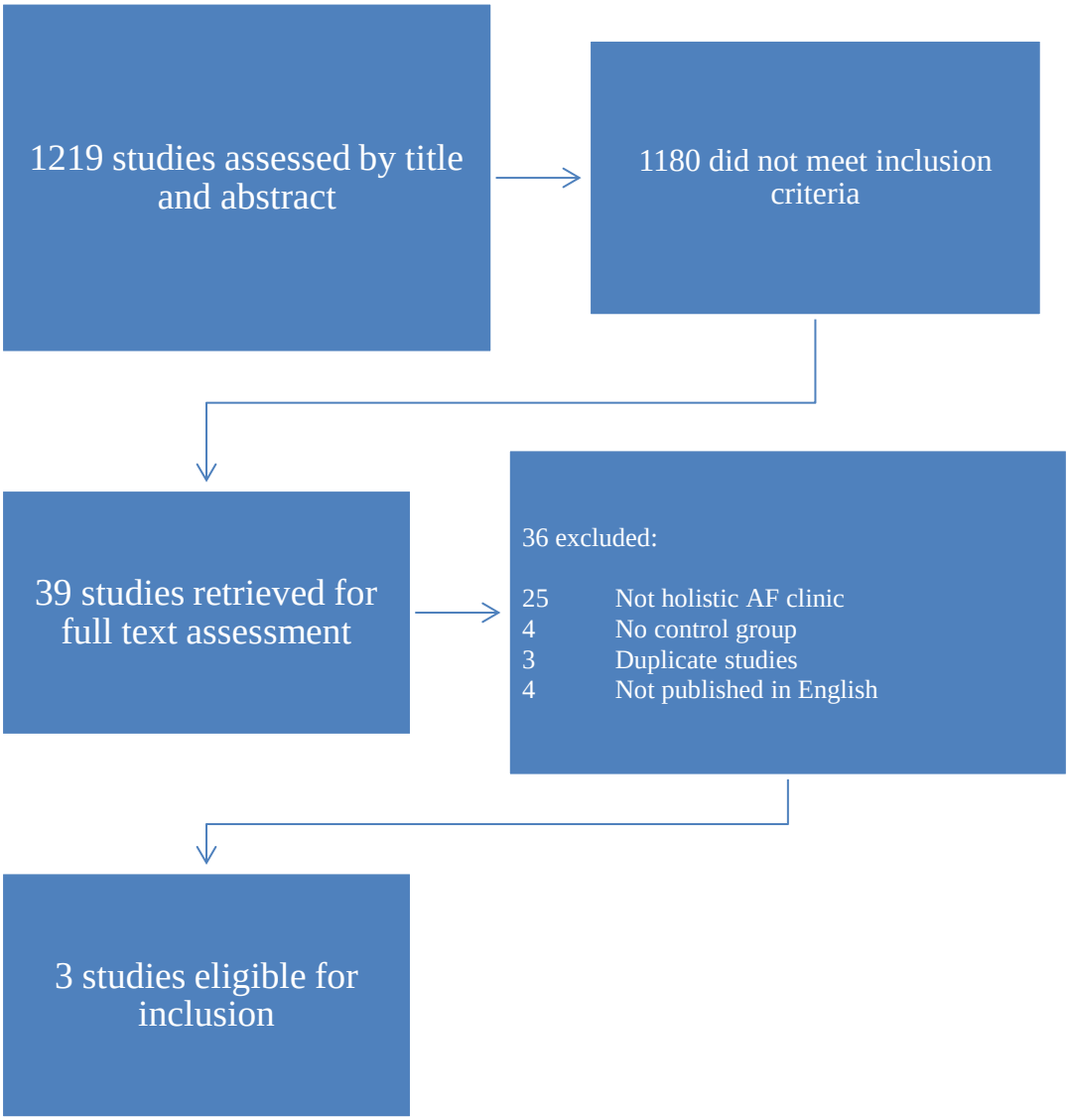


Figure 2: Impact of integrated care on all-cause mortality

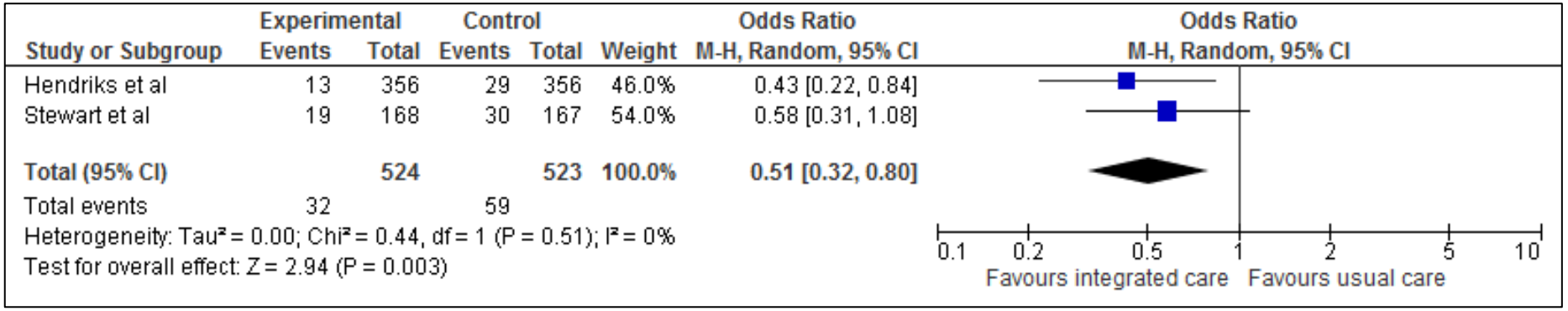


Figure 3: Impact of integrated care on cardiovascular hospital admissions

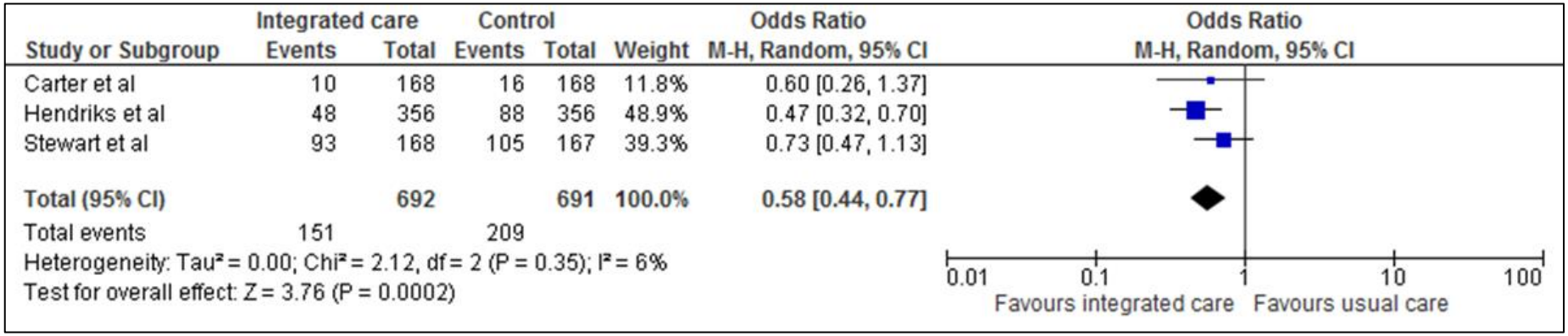


Figure 4: Impact of integrated care on AF related hospital admissions

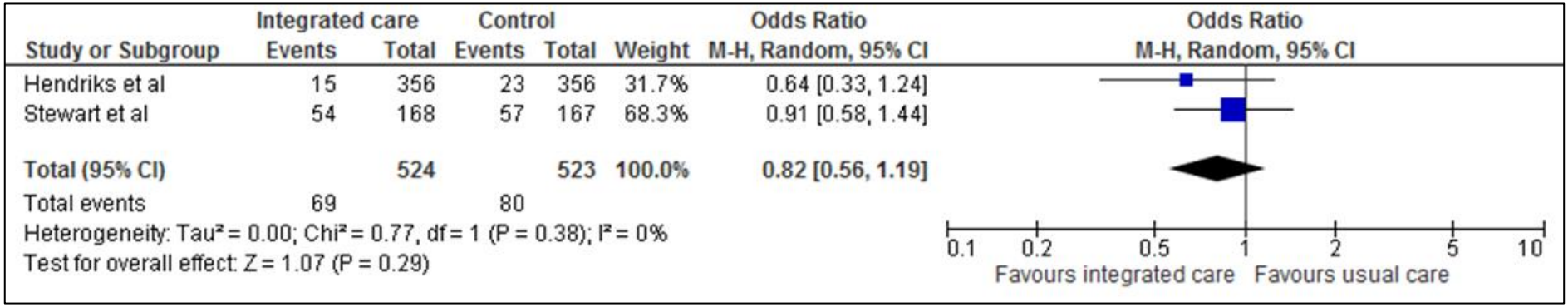


Figure 5: Impact of integrated care on cerebrovascular events

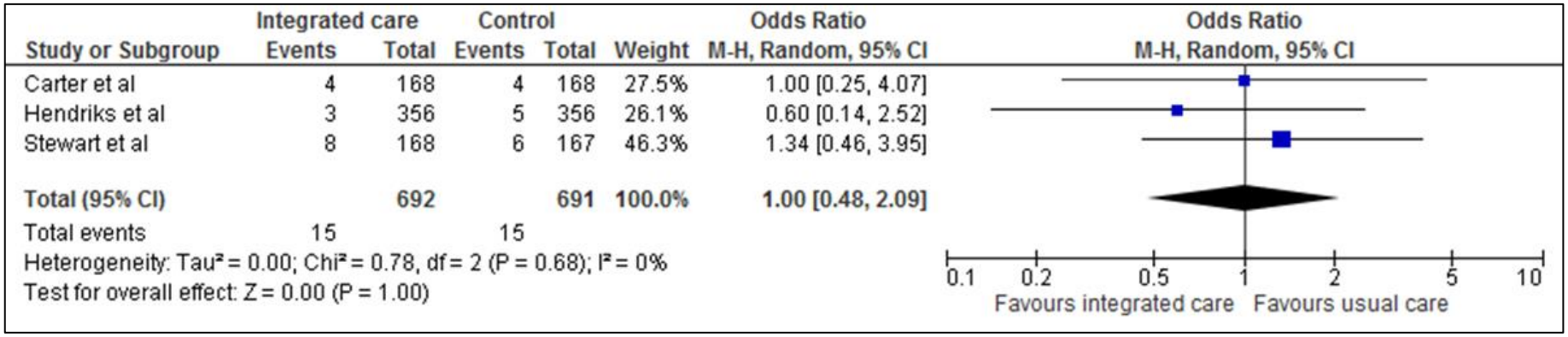
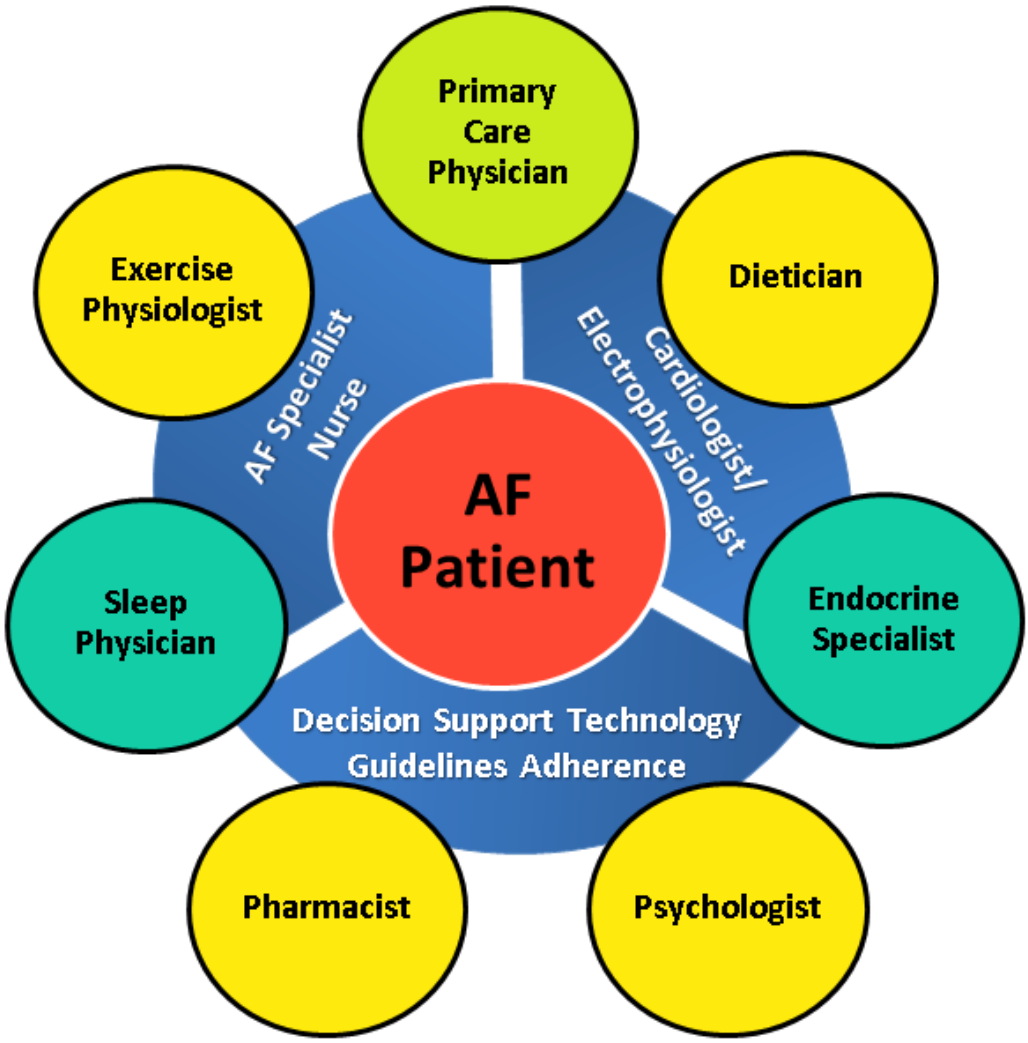


Figure 6: Suggested schematic of the integrated care approach[282]



Chapter 5: A Review of the Inpatient and Emergency Department Management of Atrial Fibrillation – the REVIEW AF Study

5.1 INTRODUCTION

Atrial fibrillation is an emerging global epidemic associated with significant morbidity and mortality. Numerous opportunities exist to improve outcomes in the AF population, including appropriate use of OAC to manage stroke risk, which remains suboptimal, and strategies to reduce associated mortality and other poor outcomes with this condition. Furthermore, health care resource utilisation due to AF has risen exponentially in recent decades. The main driver of AF costs are hospitalisations related to the condition itself, and its associated complications including stroke and heart failure.[24] Whilst increasing rates of AF related hospitalisations have been demonstrated globally, modifiable factors associated with these rising rates have not been well characterised. Although rising incidence and prevalence rates associated with AF and the ageing population are likely to be significant contributors, it is not known if other potentially modifiable factors are associated with increased health care resource utilisation in this condition.

5.1.1 The use of OAC for stroke risk in AF

The advent of DOAC therapy has led to improved rates of this therapy to manage stroke risk in AF.[131] The GARFIELD registry has demonstrated improved use of OAC in those at highest risk of stroke (CHA_2DS_2-VASc score of ≥2) from 2010 to 2015 with more than 70% of individuals prescribed this therapy.[278] The Global Registry on Long-Term Oral

Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF) has also demonstrated high rates of OAC use in those with a CHA_2DS_2-VASc score of ≥2, with 82.2% of individuals in this category appropriately treated.[283] Despite these improvements, Australian data has suggested that use of this therapy in individuals at high risk of stroke remains underutilised. In a single centre study of 19,613 individuals with AF from 1999-2012, 76.3% and 71.3% of Indigenous and non-Indigenous Australians with a CHA_2DS_2-VASc score of ≥2 were not prescribed anticoagulation.[132] Overuse of this therapy was also evident with 24% and 16.7% of those with a CHA_2DS_2-VASc score of 0 prescribed anticoagulation. More recently, a study of 609 individuals in rural Western Australia reported that approximately one third of all individuals with AF and a CHA_2DS_2-VASc score of ≥1 were not prescribed anticoagulation.[284]

5.1.2 Health care resource utilisation in AF

Hospitalisations remain the costliest component of AF care. Characterisation of ED re-presentations and hospitalisation readmissions in individuals with AF have demonstrated significant heterogeneity across studies. A retrospective sample of 6439 individuals with non-valvular AF in the USA demonstrated an 18% readmission rate at 30 days.[153] Readmissions were associated with significant health care burden with a mean length of stay of 7.4±8.0 days and occurred a mean of 9.7±9.0 days after admission with AF. In this cohort, AF remained the most common reason for re-presentation accounting for 10.2% of all readmissions. This was followed by congestive heart failure at 6.7% and coronary atherosclerosis at 3.1%.[153] In higher risk populations (individuals with AF ≥75 years of age or ≥70 years with one additional risk factor) re-hospitalisations are a significant burden.[154] In this cohort of 3498 individuals, 39.7% were hospitalised for any

reason over a 12 month follow up period. Of those that were hospitalised, 35% (1223 individuals) of the cohort were hospitalised for cardiovascular reasons of which AF or atrial flutter was the most common reason (47.5%). This was followed by congestive heart failure (9.9%), coronary artery disease (7.4%) and stroke/TIA (6.2%) related admissions.[154]

5.1.3 Predictors of rehospitalisation in AF

Prior studies have identified varying factors as predictors of AF related hospitalisations. Whilst numerous studies have described advanced age as a predictor of repeat hospitalisations[154,157], other potentially modifiable comorbid conditions have also been described. Both the $CHADS_2$ and CHA_2DS_2-VASc score were predictive of first cardiovascular hospitalisation in a large US based cohort.[159] Other factors associated with hospitalisations in a cohort of 9484 community dwelling individuals with AF included coronary artery disease, hypertension, cerebrovascular disease and peripheral vascular disease.[158] In this study, a higher symptom burden as determined by the EHRA score, was also predictive of hospitalisation. A high comorbid burden as characterised by the Charlson Comorbidity Index (CCI) score, a longer length of stay and admission to hospital through the emergency department was predictive of repeat all cause hospitalisations at 30 days in a US based cohort of 6439 individuals with AF listed as either a primary or secondary diagnosis.[153] Interestingly, in this cohort individuals with AF listed as a secondary diagnosis had a significantly higher rate of readmission than individuals with a primary diagnosis of AF. In the 1161 individuals who were readmitted to hospital within 30 days, 82.5% had AF listed as a secondary diagnosis at their index presentation, compared to 17.5% of those who had AF listed as a primary diagnosis.[153]

Other predictors of rehospitalisation in individuals with AF from another retrospective cohort include hypertension, peripheral vascular disease, coronary artery disease, valvular heart disease and female gender.[154] The cost of repeat admissions for AF in this study was also significantly greater than initial presentations ($3589 [SD $4194] vs $4418 [SD $6294] for index and repeat hospitalisations for AF respectively).[154]

5.1.4 Mortality in AF

Mortality associated with AF has increased globally in recent decades and has demonstrated a 2-fold and 1.9-fold increase for males and females respectively between 1990 and 2010.[2] A study of 71,683 individuals from four large studies of the use of anticoagulation in AF demonstrated a mortality rate of 4.72% per year.[285] The most common causes of death were cardiac related including sudden cardiac death, heart failure and myocardial infarction. Significant differences in characteristics of individuals who died over follow up compared to those alive at final follow up were evident with higher rates of heart failure, diabetes, permanent/persistent AF, older age and a greater likelihood of death in males.[285] Similar results were also found in a study of 8,962 individuals with AF from four hospitals in France between 2000-2010.[286] Over a mean follow up of 929 ± 1082 days, 14% of individuals died with an annual mortality rate of 5.5% per year. Heart failure was the most common cause of death in this cohort with significant differences in clinical characteristics evident in those who died compared to those alive at final follow up. Individuals who died were more likely to be older, more likely to have permanent AF, and to higher rates of most cardiovascular risk factors including hypertension, diabetes, dyslipidaemia and current smoking.[286] A higher cardiovascular comorbidity burden was also evident with higher rates of heart failure, coronary artery disease and stroke/TIA.[286]

Given the growing health care burden and poor patient outcomes associated with AF contemporary factors associated with ongoing hospitalisations are of paramount importance. Furthermore, modifiable factors are of interest due to the possibility to structure interventions that may reduce subsequent health care resource utilisation. However, the nature of re-hospitalisations in individuals with AF in Australia have not been characterised. Additionally, factors associated with AF related hospitalisations have not been examined. The aim of this study is to characterise reasons for readmission in a contemporary cohort of individuals with AF, in addition to identifying factors associated with readmission to hospital. Guideline adherence to appropriate use of OAC according to stroke risk will also be examined. Mortality rates, and associated patient characteristics, will also be determined.

5.2 METHODS

5.2.1 Study design

This was a retrospective study of consecutive individuals presenting to the ED of three hospitals in Adelaide, South Australia over a 12-month period from 22 March 2013 to 22 March 2014, primarily due to AF. The study was undertaken by electronic health record review. The follow up period was three to four years. This study was registered with the Australian and New Zealand Clinical Trial Registry (ACTRN12618001890224). Ethical approval was obtained from the Royal Adelaide Hospital Human Research Ethics Committee (HREC/15/RAH/447) and the University of Adelaide.

5.2.2 Patient selection

Participants were recruited from an electronic database of individuals who had presented to the emergency department of three metropolitan hospitals in Adelaide, South Australia due to AF. A principal diagnosis of AF, by ICD-9 or ICD-10 coding, was required for study eligibility. Participants were excluded if their index presentation was an elective admission, they were an overseas or interstate visitor, or they were <18 years of age. For follow up events, elective day case admissions due to non-cardiovascular causes were not collected (e.g. haemodialysis, chemotherapy).

5.2.3 Study outcomes definitions

Sociodemographic information was obtained from each presentation to hospital including patient age, postcode (as a surrogate marker of socioeconomic status), date and time of presentation and length of stay. All ED presentations and hospital admissions were further categorised in to three groups: AF related, cardiovascular related (excluding AF and atrial flutter) and all other causes based on a combination of ICD coding and review of the electronic health record attached to each event. Any event was categorised as AF related if it pertained to episode management, admission for AF related complications or monitoring or procedures undertaken due to AF. Any atrial flutter event was categorised as AF related whilst all other arrhythmias were categorised as 'other cardiovascular' events. Other cardiovascular events were categorised based on coding and electronic health record review and included any other type of cardiovascular event excluding those related to AF or atrial flutter. All other events were categorised as 'all other causes. Further information was obtained from the 'AF related' group including the use of rate and rhythm control strategies to manage episodes, CHA_2DS_2-VASc score, HAS-BLED

score, appropriate use of oral anticoagulation, type of oral anticoagulation used, referral on to a cardiologist for outpatient care and the provision of a personalised plan to manage future AF episodes. In addition to this, for each participant's index presentation, a Charlson Comorbidity Index score was calculated based on listed comorbidities.[287] Deaths that occurred during the follow up period were obtained from two sources: the electronic health record (if death occurred in a metropolitan public hospital) or publicly available death notices published online. Cause of death was unable to be obtained from these records.

5.2.4 Appropriate use of oral anticoagulation

The appropriate use of oral anticoagulation to reduce stroke risk was assessed using the CHA_2DS_2-VASc score. As per the European Society of Cardiology 2012 AF management guidelines,[288] which were current at this time in clinical practice, any use of OAC or antiplatelet therapy (without vascular disease) was considered *inappropriate* for a CHA_2DS_2-VASc score of 0 (except in the context of undertaking cardioversion or AF ablation). Any type of therapy (no therapy, aspirin or other antiplatelet therapy or OAC) was considered *appropriate* for individuals with a CHA_2DS_2-VASc score of 1 and OAC was considered *necessary* in all individuals with a CHA_2DS_2-VASc score of ≥ 2 unless there was a documented contraindication. Documented contraindications included: high falls risk, previous haemorrhagic stroke or major bleeding, uncontrolled hypertension, unexplained anaemia, heavy alcohol use, and patient refusal.

5.2.5 Primary and secondary outcomes

The primary outcome measure was the number and type of hospital re-presentations in this cohort of individuals with an AF related index ED presentation. Secondary outcome measures include factors predictive of AF related ED re-presentation, factors predictive of AF re-hospitalisation, appropriate use of OAC according to stroke risk and differences in baseline characteristics for those who died during follow up, compared to those who were alive at final follow up date. Differences in length of stay for repeat hospital presentations for each type (AF related, other cardiovascular and all other causes) was also examined.

5.2.6 Endpoint adjudication

All data was collected by one investigator with independent adjudication of endpoints by two investigators. Any disagreements were resolved by consensus.

5.2.7 Statistical analysis

Baseline demographic and clinical variables were analysed using descriptive statistics (means and standard deviations for continuous variables and counts and percentages for categorical variables). The number of re-presentations and admissions to hospital that occurred over follow up were expressed as means and standard deviation.

Re-admission status: Differences in baseline and index presentation characteristics between patient groups defined by AF-related re-admission/re-presentation status (never re-admitted vs ever re-admitted) were analysed using the Mann Whitney U test and Chi Squared tests of association for continuous and categorical variables, respectively.

Factors associated with AF related re-admissions, and variables associated with admission to hospital for AF following an ED presentation were investigated using binary logistic regression modelling. Differences in characteristics between those who obtained advice for management of future AF episodes was examined by Fisher's exact test of association for categorical variables or Mann Whitney U Test for continuous variables.

Covariates considered in the multivariate model included: age, gender, baseline comorbidities (hypertension, heart failure, diabetes, vascular disease), CHA_2DS_2-VASc score, HAS BLED score, Charlson Comorbidity Index, treatment at initial presentation (rate controlling medications, rhythm controlling medications or electrical cardioversion), rhythm on discharge from hospital (sinus rhythm or not), provision of non standardised advice to manage future AF episodes and referral to a Cardiologist for follow up. Multivariable cox proportional hazards regression modelling was used to estimate hazard ratios and corresponding 95% confidence intervals. If a clinical plan was described by a treating physician to guide the patient in the event of future AF episodes, this was noted as a non-standardised AF action plan. The proportional hazards assumption was assessed graphically using Kaplan-Meier plots, and using a test based on Schoenfeld residuals.

Time to first repeat AF hospitalisation: Cox regression modelling was used to examine the crude and adjusted effects of selected variables on the time to first repeat AF hospitalisation.

Length of stay for repeat hospital presentations: A negative binomial regression model was used to estimate differences in length of stay (in hours) between AF-related presentations and presentations that were either cardiovascular-related or all-cause.

Rate of AF-related re-presentations: Negative binomial regression modelling was used to examine factors associated with the number (count) of repeat AF related presentations per patient that occurred during follow-up.

Mortality status: Differences in baseline and index presentation characteristics between patients who died during follow-up and those who were alive at the end of follow-up were assessed using Mann Whitney U tests and Chi-square tests for continuous and categorical predictors, respectively.

All statistical analyses were performed using Stata (version 15, StataCorp, College Station, Texas, USA). The level of statistical significance was set at 0.05.

5.3 RESULTS

The cohort comprised 437 individuals who had all presented to hospital with an index presentation that was primarily due to AF. See Figure 1 for the study flow chart. Mean follow up time, defined as time from index presentation, was 3.7±0.4 years. Males comprised 49.9% of the cohort (218 participants). Mean age was 68.7±14.5 years. See Tables 1 and 2 for other baseline characteristics. There were a total of 2741 events recorded (comprising emergency department presentations, planned and unplanned hospital admissions).

5.4 APPROPRIATE USE OF OAC FOR STROKE RISK

5.4.1 First AF presentations and OAC prescription

Of the 437 individuals from this study cohort, 193 (44.2%) presented with a first diagnosis of AF. A CHA_2DS_2-VASc score of 0 was recorded in 30 individuals with prescription of OAC occurring in 2 (6.7%) cases (Figure 2). A CHA_2DS_2-VASc score of 1 was recorded in 34 (17.6%) individuals with a first AF presentation. In 7 (20.6%) individuals OAC was prescribed, whilst this did not occur in 26 (76.4%) individuals. Use of OAC was not documented in one (2.9%) case.

In 129 (66.8%) of these cases a CHA_2DS_2-VASc score of ≥ 2 was recorded and in 119 (61.7%) individuals there were no documented contraindications to the use of OAC. In 74 (62.2%) of these presentations OAC was not commenced, whilst in 45 (37.8%) individuals OAC was prescribed (Figure 2). Of the 74 presentations in which OAC was not commenced, 54 (73%) presentations involved prior or new prescription of Aspirin, Clopidogrel or a combination of both therapies. In 11 individuals, commencement of OAC was recommended to the treating general practitioner without being initiated in the hospital setting.

5.4.2 Use of oral anticoagulation in established AF

There were 609 unplanned AF presentations over the entire study duration which occurred in individuals with a prior diagnosis of the condition. A CHA_2DS_2-VASc score of 0 was recorded in 56 (9.2%) presentations of which 3 (5.4%) were prescribed OAC during hospital presentation (Figure 2). A CHA_2DS_2-VASc score of 1 occurred in 79 (13.0%) presentations with a prior diagnosis of AF. Prescription of OAC occurred in 5

(6.3%) cases. There were 16 presentations in which an individual was already anticoagulated (20.3%). This was unknown due to lack of documentation in 5 cases.

The majority of these presentations (474 presentations - 77.8%) recorded a CHA_2DS_2-VASc score of ≥2. A total of 39 (8.2%) of these presentations had a documented contraindication to the use of OAC. In 248 (57.0%) of these presentations, OAC had previously been prescribed. Of the 190 presentations where OAC was not prescribed and there was no documented contraindication, prescription of OAC occurred in 34 cases (17.9%). In 143 (75.3%) presentations with no documented contraindications, OAC had not previously been prescribed and was not prescribed during hospital presentation (Figure 2). In the 143 cases where no OAC had been prescribed prior to ED presentation or during the ED visit and/or hospital admission, 73 (51.0%) presentations involved individuals taking either Aspirin alone, Clopidogrel alone or combination therapy. Commencement of OAC therapy was recommended, but not commenced, in 10 (5.3%) of these presentations.

5.5 HOSPITAL RE-PRESENTATIONS

5.5.1 Hospital re-presentation characteristics

There were a total of 2304 repeat hospital presentations that occurred in the cohort of 437 patients over follow up. The number of repeat presentations recorded per patient ranged from 0 (81 participants; 18.5%) to 101 (1 participant). Approximately 50% of the cohort had at least two re-presentations during follow up. Mean number of follow up events across the cohort was 5.3±9.1. The most common reasons for a follow up presentation (ED presentation or hospital admission) were those relating to causes other than AF or cardiovascular aetiology (mean number of events 3.3±7.0). This was followed by AF

related presentations (mean 1.2±2.2) and then cardiovascular related reasons (mean 0.8±1.9). Limiting the analysis to the cohort who re-presented on at least one occasion did not materially alter this result. Most individuals were admitted to hospital at their AF related index presentation (72.3%). See Figure 3 for the distribution of repeat hospital re-presentations.

5.5.2 First hospital re-presentation

AF presentations accounted for 37.6% of first hospital re-presentations. Other cardiovascular causes was attributable to 14.9% of first re-presentations whilst all other causes accounted for 47.2% of first re-presentations.

5.5.3 AF related re-presentations

Of the 356 individuals who had at least one hospital re-presentation, 202 (56.8%) had at least one event that was AF related over the follow up period. Most of this cohort (50.3%) had between 1 and 4 AF re-presentations in total during follow-up (Figure 4). In the first 12 months following the index presentation, AF accounted for 39% of all repeat hospital admissions and 30% of all repeat ED presentations. During the remaining follow up period AF accounted for 11-33% of all hospital readmissions and 16-25% of all ED presentations (Table 3).

5.5.4 Cardiovascular related re-presentations

Of those patients who re-presented to hospital, 148/356 (41.6%) experienced an emergency department presentation or hospital admission that was cardiovascular-

related. Of those who had at least one cardiovascular related re-presentation, 91.2% had between 1-4 follow up re-presentations (Figure 5). Annual rates of readmission for other cardiovascular causes ranged from 15-18%, with ED presentations accounting for 10 - 24% of all re-presentations annually (Table 3).

5.5.5 Re-presentations related to other causes

Re-presentation due to other causes occurred in 278 patients, representing 78.1% of the cohort who had at least one event during follow up. Most of this cohort (64.3%) had between 1-4 follow up presentations (Figure 6). This category accounted for 45-73% of all annual readmissions, and 50-75% of all repeat ED presentations per annum (Table 3).

5.5.6 Length of stay for re-presentations

The mean length of stay for ED re-presentations was 4.5±4.4 hours. There were no significant differences between length of stay for AF re-presentations compared to those for other cardiovascular reasons (IRR 1.05, 95% CI 0.89-1.24; p=0.19); nor for AF re-presentations compared to those for other causes (IRR 0.92, 95% CI 0.82-1.04; p=0.19).

For hospital admissions, no difference was observed between length of stay for admissions due to AF reasons and admissions for other cardiovascular reasons (IRR 1.34, 95% CI 0.96-1.87; p=0.09). Hospital admissions relating to other causes were significantly longer than those of AF aetiology (IRR 1.59, 95% CI 1.17-2.16; p=0.003).

5.6 FACTORS PREDICTIVE OF AF RE-PRESENTATIONS

5.6.1 Impact of age and gender

Increasing age was associated with a decrease in the likelihood of an AF re-presentation (AF related ED presentation or hospital admission). Each one-year increase in age was associated with a 2% reduction in risk of AF related re-presentations (OR 0.98, 95% CI 0.98-0.99; p<0.0001). For each 5-year age increase, the associated risk of AF re-presentation decreased by 7% (OR 0.93, 95% CI 0.89-0.97; p<0.0001).

Males had a greater likelihood of re-presentation for AF over follow up. In the age and gender adjusted model, males were approximately 30% more likely to re-present during follow up compared to females (OR 1.29, 95% CI 1.03-1.60; p=0.025).

5.6.2 Factors associated with AF related ED re-presentations

Of 437 individuals, 82 (18.8%) presented to ED over the follow up period at least once for an AF related reason, whilst 355 did not. The group who re-presented to ED were less likely to have heart failure (6.1% vs 16.1%, p=0.020), were less likely to have been admitted to hospital at their index presentation (50.0% vs 77.5%, p<0.0001) and had a shorter length of stay at index presentation (23.5±30.2 hours vs 59.5±107.4 hours for repeat vs non-repeat ED presenters respectively). The repeat ED presenters were less likely to be in sinus rhythm on discharge from hospital at their index presentation (Table 4).

Univariate analysis demonstrated that heart failure was associated with a significant reduction in the risk of repeat ED presentation. Admission to hospital at index presentation (OR 0.29, 95% CI 0.18-0.48; p<0.0001) and each one hour increase in the

index length of stay (OR 0.98, 95% CI 0.98-0.99; p<0.0001) were both associated with a reduction in the risk of ED re-presentation in the univariate model. Documented evidence of an ad hoc non-standardised AF action plan for management of future AF episodes was associated with a significant increase in the risk of repeat ED re-presentations (OR 6.91, 95% CI 2.90-16.4; p<0.0001). In the multivariable model, the non-standardised AF action plan remained a significant predictor of repeat ED presentation (OR 6.66, 95% CI 2.4-18.3; p<0.0001; see Table 5). Admission to hospital at index presentation was associated with a significant reduction in risk of ED re-presentation for AF (OR 0.39, 95% CI 0.19-0.80; p=0.01).

Predictors of the total number of AF related ED presentations over follow up were also examined (Table 6). In the univariate model, heart failure was predictive of the total number of repeat ED presentations for AF (IRR 0.12, 95% CI 0.02-0.91; p=0.04), but was not significant in the multivariate model. Hypertension was of borderline significance in the univariate model and remained predictive in the multivariate model (IRR 10.2, 95% CI 1.61-64.4; p=0.014). In the univariate and multivariate model, each one hour increase in the index presentation length of stay was predictive of the number of AF related ED presentations over follow up (IRR 0.97, 95% CI 0.96-0.99; p<0.0001 and IRR 0.98, 95% CI 0.96-0.99, p=0.037 for univariate and multivariate respectively; Table 6).

5.6.3 Factors associated with AF related hospitalisations

In the cohort of 437 individuals, 125 (28.6%) were readmitted for an AF related cause whilst 312 did not experience a readmission for AF. The cohort who were readmitted were more likely to have hypertension (63.2% vs 43.9%, p<0.0001) and had a higher CHA_2DS_2-VASc (3.2±1.8 vs 2.7±1.9, p=0.0023) and HAS-BLED score (2.0±1.0 vs

1.5±1.1, p<0.00001) at their index presentation (see Table 7). Factors predictive of readmission for AF in a univariate model included hypertension (OR 2.19, 95% CI 1.43-3.36; p<0.0001) and each one unit increase in the CHA_2DS_2-VASc and HAS-BLED scores (OR 1.18, 95% CI 1.06-1.32; p=0.003 and OR 1.58, 95% CI 1.29-1.94; p<0.0001 for CHA_2DS_2-VASc and HAS-BLED scores respectively; Table 8). However, after adjustment for other variables in a multivariable model, the only factors significantly predictive of readmission was the non standardised AF action plan and each unit increase in the HAS-BLED score (OR 2.76, 95% CI 1.00-2.01; p=0.05 and OR 1.42, 95% CI 1.00-7.63; p=0.05 respectively; Table 8).

In univariate analysis, each one unit increase in the HAS-BLED score was predictive of the number of repeat AF hospitalisations over follow up (IRR 1.87, 95% CI 1.17-2.98; p=0.009). Multivariate analysis demonstrated that the presence of heart failure was associated with a reduction in total number of repeat AF hospitalisations over follow up (IRR 0.14, 95% CI 0.02-0.98; p=0.018) Each one unit increase in the HAS-BLED score was associated with increasing numbers of AF hospitalisations over follow up (IRR 2.24, 95% CI 1.01-4.98; p=0.05; Table 9).

5.6.4 Time to first AF related ED presentation

The Kaplan Meier curve for time to first AF related ED presentation following discharge from the index presentation demonstrates that the probability of AF related ED presentation rises steeply in the first year after discharge to approximately 10% and continues to increase steadily over time to approximately 20% after four years (Figure 7).

5.6.5 Time to first AF related hospitalisation

Similar trends were demonstrated in the Kaplan Meier curve for time to first AF related hospital readmission. The probability of readmission rose most sharply in the first 12 months after the index presentation to approximately 10% with a more gradual increase to approximately 30% after four years (Figure 8). Factors associated with time to first AF related hospital readmission were increasing age at index presentation, the presence of baseline hypertension and higher CHA_2DS_2-VASc and HAS-BLED scores at index presentation in a univariate model. However, in the multivariate model the only factor that remained predictive was the HAS-BLED score at index presentation (HR 1.41, 95% CI 1.05-1.89; p=0.02; Table 10).

5.6.6 Factors predictive of admission to hospital for unplanned AF re-presentations

Over follow up, a total of 366 repeat unplanned AF re-presentations occurred in 164 individuals. This resulted in admission to hospital in 62.8% of all AF related re-presentations. In univariate analysis, heart failure (OR 3.34, 95% CI 1.26-8.83; p=0.015), admission at index presentation (OR 2.44, 95% CI 1.47-4.06; p=0.001), each one hour increase in the index presentation length of stay (OR 1.01, 95% CI 1.47-4.06; p=0.002) and the use of rate controlling medications at the index presentation (OR 2.07, 95% CI 1.24-3.48; p=0.006) were all associated with an increased risk of admission to hospital for subsequent AF related ED re-presentations. In the multivariate model, only admission to hospital at the index presentation (OR 2.45, 95% CI 1.24-4.84; p=0.010) and the non-standardised AF action plan were associated with an increased risk of admission to

hospital for unplanned AF re-presentations over follow up (OR 3.11, 95% CI 1.09-8.87; p=0.034; Table 11).

5.6.7 Characteristics of individuals with a non-standardised AF action plan

Notable differences in baseline characteristics were evident in those who obtained a non-standardised AF action plan compared to individuals who did not receive this plan. Those who had a plan were younger (69.6±14.4 years vs 60.6±14.7 years; p=0.008), had a lower Charlson Comorbidity Index (4.1±2.0 vs 2.8±1.8; p=0.006), were less likely to be admitted to hospital at their index presentation (73.6% vs 40.0%; p=0.003), had a shorter length of stay at index presentation (55.7±101.5 hours vs 6.6±6.5 hours; p<0.0001, were more likely to receive electrical cardioversion at index presentation (13.8% vs 35%; p=0.052), were less likely to be treated with a rate control strategy at index presentation (60.6% vs 25.0%; p=0.006), were more likely to be referred to a Cardiologist (53.0% vs 80.0%; p=0.045) and had lower CHA_2DS_2-VASc (2.9±1.9 vs 1.6±1.5; p=0.003) and HAS-BLED scores (1.7±1.1 vs 1.2±1.4; p=0.050; all non AF action plan vs action plan recipients respectively; Table 12).

5.6.8 Mortality

There were 71 deaths recorded out of the study population of 437 individuals (16.2%). Cause of death was unable to be ascertained in this study. Patients who died during follow up were older at index presentation (79.8±10.7 years vs 66.6±14.1 years; p<0.00001). They were also more likely to have heart failure (31.0% vs 10.9%) and had higher Charlson Comorbidity Scores at baseline (6.0±2.0 vs 3.6±1.8; p<0.001). Compared to patients who were alive at the end of follow-up, those who died were more likely to have

admitted to hospital at index presentation (83.1% vs 70.2%) and a longer length of stay (76.0±161.4 hours vs 48.3±80.6 hours). Mortality during follow up was also associated with a decreased likelihood of sinus rhythm at discharge from index presentation, a reduced likelihood of referral to a Cardiologist and higher CHA_2DS_2-VASc and HAS-BLED scores at index presentation (Table 13). The Kaplan Meier curve demonstrates a relatively constant increase in risk of death over the follow up period (Figure 9). Over follow up the average mortality rate was 3.78% per annum. This ranged from 2.28% to 4.66% per year.

5.7 DISCUSSION

AF is associated with significant and growing health care burden with our study demonstrating numerous opportunities for improvement. Factors associated with repeat hospitalisations in this population have been poorly characterised with resultant missed opportunities to reduce this burden. Furthermore, appropriate use of oral anticoagulation remains suboptimal with both under and overuse of this therapy. Our results demonstrate that AF is associated with:

- Underuse of anticoagulation in 62% of those at high risk of stroke with a first AF presentation;
- Ongoing underuse of anticoagulation with 75% of repeat AF presentations in individuals at high risk of stroke not prescribed OAC despite tertiary hospital review;
- Significant ongoing rates of repeat hospitalisations, of which AF alone is accountable for 22%;

- Admission to hospital for AF in more than 72% of cases at index presentation and more than 62% of occasions over follow up;
- An increased risk of AF related hospitalisation in the first 12 months following an ED presentation, with this condition alone accounting for almost 40% of all hospital admissions;
- A 7-fold increase in risk of repeat ED presentations, a 3-fold increase in risk of hospitalisations and a more than 3-fold increase in risk of admission to hospital following repeat ED presentations for AF in those given non-standardised advice for management of future AF episodes;
- An average annual mortality rate of 3.78% per annum.

These results demonstrate that AF is associated with significant ongoing health care burden and urgent action is required to stem the growing tide of hospitalisations associated with AF. Whilst most re-presentations are not AF related, this condition alone accounts for a significant proportion of ongoing health care resource utilisation. Furthermore, significant opportunity exists to improve the appropriate use of oral anticoagulation in this population.

5.7.1 Appropriate use of oral anticoagulation

OAC is an effective therapy for the mitigation of stroke risk. Recent data from the GARFIELD and ORBIT AF registries demonstrated that in those with a CHA_2DS_2-VASc score ≥2, rates of appropriate OAC use were 69% and 87% respectively,[131] which is significantly better than rates observed in this study. However, data from earlier time periods has demonstrated much lower use of this therapy. Previous Australian data has

demonstrated that in the fourteen-year period leading up to 2012, 76.3% and 71.3% of Indigenous and Non Indigenous Australians were not prescribed OAC despite elevated risk scores[132]. A single centre retrospective analysis in Australia of 2118 individuals with non valvular AF demonstrated that whilst the introduction of DOAC therapy improved rates of OAC from 52.5% in the pre DOAC era to 60.7% in the post OAC period, OAC therapy was still not prescribed in 37% of the cohort with a CHA_2DS_2-VASc score of ≥2.[289] In the American College of Cardiology National Cardiovascular Data Registry's Practice Innovation and Clinical Excellence (PINNACLE) Registry of 429,417 outpatients with AF from 2008-2012, whilst increasing CHA_2DS_2-VASc scores were associated with an increased likelihood of prescription of OAC, this still remained poor overall.[290] In those at considerable stroke risk (CHA_2DS_2-VASc score >4), less than 50% of eligible participants were prescribed anticoagulation.[290]

Despite tertiary hospital review, 62% of individuals with a first AF presentation were not prescribed OAC despite a CHA_2DS_2-VASc score of ≥2 in our study. This is comparable to other datasets in which more than 50% of eligible patients are not prescribed this therapy despite hospital review.[291] Furthermore, our dataset has demonstrated that this effect continued over time where, although 57% of AF presentations were appropriately anticoagulated prior to presentation, only a minority of eligible presentations (17.9%) involved prescription of this therapy in hospital. In more than half of the cases in which OAC was not prescribed, this involved the use of other antithrombotic therapy including aspirin, clopidogrel or combination therapy. This may reflect physician uncertainty about appropriate therapy or concern about excess bleeding risk. In the GARFIELD registry, ‘physician choice’ was cited as the most common reason for withholding OAC therapy in those at high risk of stroke (48.3%) and may be reflective of concern about heightened bleeding risk in these individuals.[292]

5.7.2 Rates of hospital admission for AF

Notably our results demonstrate a rate of admission to hospital for AF that exceeds that of other published data. The index ED presentation for AF in our dataset resulted in hospital admission in more than 72% of cases. Over the follow up period, unplanned ED presentations with AF resulted in hospital admission in more than 62% of cases. Comparable datasets have demonstrated much lower rates of admission with a study examining hospitalisations in a large cohort of 33,699 individuals in Ontario, Canada resulting in admission to hospital in 48.3% of presentations.[293] Wide practice variations were evident in this study with admission rates ranging from 3% to 91% across geographical locations. Propensity matched analysis in this study demonstrated that mortality and repeat all cause ED visits and hospitalisations were higher in the group admitted at index presentation whilst other adverse outcomes including any stroke or major or minor bleeding did not differ between groups at one year irrespective of initial admission status.[293] From an earlier timepoint, US data over the 12 year period leading up to the end of 2004 demonstrated a significant increase in the population adjusted rate of ED presentation for AF, whilst the admission rate remained relatively constant over the study period at approximately 64%.[294] These variations in rates of admission to hospital suggest that factors beyond clinical need may play a role in decisions to admit and may offer an opportunity to intervene to reduce the costliest component of AF care. Indeed, this was supported by our multivariate model which was unable to delineate any clinical factors associated with risk of admission to hospital for repeat ED presentations with AF over follow up.

5.7.3 Readmission type in AF

AF accounted for 22% of all hospital readmissions in our dataset. This is in line with other studies which have also demonstrated high rates of readmission in AF cohorts, with many of these events related to AF, even over shorter follow up duration. In a multi-centre study examining the impact of an antiarrhythmic medication (dronedarone) on cardiovascular hospitalisations in AF, rates of readmission at one year approached 40% for all causes, with AF and atrial flutter accounting for the majority of all cardiovascular hospitalisations at 47.5%.[154] This is comparable to our dataset where, in the first year following an unplanned presentation to ED with AF, almost 40% of all hospital readmissions were due to AF. In another cohort of individuals with AF, readmission rates to hospital at 30 days were 18%.[153] Of the cohort who were readmitted, the most common reasons were general and non-specific symptoms (12.8%) followed by AF at 10.2%.[153] Similarly, in a large US based study of 388,340 with a principal diagnosis of AF rates of readmission at 30 days, utilising the National Readmissions Database, was 15%. The most common reason for readmission were AF and heart failure.[295] Together, these studies support our data suggesting an early higher risk of representation to hospital for AF related reasons, with our long term data reflecting an ongoing, although somewhat tempered, increase in risk.

Whilst admissions related to AF were shorter than those related to other causes, there was no difference between those of AF or cardiovascular causes. As the burden of AF hospitalisations in Australia has exponentially risen in recent times, and at a significantly greater rate than that of other cardiovascular conditions including HF and MI, factors associated with this rise and strategies to address the growing burden of AF related health care burden should be urgently addressed.

5.7.4 Predictors of AF related readmissions

Our multivariate model was unable to delineate many factors associated with readmissions for AF. Whilst other studies have varied in this regard there have been few consistently identified predictors of readmission. In Australia higher rates of AF related hospitalisations have been observed in older age groups.[156] In a US based study geographical variations in rates of admission to hospital following an ED presentation for AF were noted, with congestive heart failure the only significant clinical predictive factor (OR 6.44, 95% CI 2.49-16.63).[294] Congestive heart failure has also been identified as a predictive factor for all cause hospitalisation in other studies in AF populations.[10,160] Other significant predictors of readmission have included a longer length of stay at index presentation and a higher Charlson comorbidity index score, reflective of a generally sicker population.[153] Older age and greater comorbid burden in addition to female gender were associated with a higher risk of all cause 30 day readmissions in another study.[295] In an anticoagulated community based cohort in the Netherlands, factors associated with hospitalisation included older age, vascular disease and heart failure.[157] Whilst other studies have demonstrated comorbidities predictive of admission to hospital in AF including hypertension, vascular disease and diabetes, we were unable to elicit any predictive clinical factors in our dataset. This may be due to a smaller sample size but potentially highlights that many AF related admissions are not necessarily based on clinical need and could be preventable with strategies including improved outpatient management of the condition. Our data demonstrates a higher risk of AF related presentations in males and younger patients with a steep rise in this risk in the first year following presentation. It is plausible that improved early outpatient management following discharge from hospital could significantly impact on rates of subsequent ED presentations and hospitalisations. The potential benefit of this strategy was also

highlighted in a recently published study which demonstrated an early increased mortality rate, largely attributable to cardiovascular causes including heart failure, sudden cardiac death and acute coronary syndrome, in the one month following newly diagnosed AF in the hospital setting. Stroke and systemic embolism and major bleeding rates were also significantly elevated in the month following diagnosis with a reduction over the subsequent one-year period.[296] Early outpatient follow up after hospital presentation could possibly prevent or allow for earlier identification of adverse events.

5.7.5 Education and action plan

This study is the first to examine the impact of non-standardised clinician advice for the management of future AF episodes on the impact of repeat ED presentations and hospitalisations for AF. Significant differences were noted between individuals who received this AF action plan compared to those who did not, and generally suggest that this plan was more likely to be utilised in a 'lower risk' population as was evident by younger age and lower comorbidity burden. However, this non-standardised AF action plan was the only factor predictive of both repeat ED presentations and hospitalisations for AF. Furthermore, the presence of this plan was also predictive of an increased risk of repeat admissions to hospital for unplanned AF presentations. Whilst this was a surprising and unexpected finding it can perhaps be explained by several possibilities. Whilst individuals are given an action plan they may neither understand nor recall details of this plan when required. We were unable to determine if action plans were written down or verbally conveyed which may also impact on an individual's ability to implement their plan. The content and the quality of the information provided in the plan was also unable

to be assessed in detail and may include provision to go to hospital if symptoms did not improve and could contribute to increasing ED presentations.

The impact of personalised plans as part of chronic condition management was explored in a recent Cochrane systematic review examining their use in asthma. Due to significant heterogeneity across the 15 studies identified in relation to both interventions and study outcomes, there was no definitive evidence to support either benefit or harm with the use of action plans in asthma.[297] Although action plans are also widely used in heart failure, similarly there is no definitive evidence to support their role in improving patient outcomes or reducing hospitalisations.[298] In a sicker population with chronic respiratory diseases (predominantly chronic obstructive pulmonary disease – 78.7%) requiring long term oxygen therapy the use of an action plan, as part of a structured educational visiting approach for both patients and carers, was associated with increased mortality. After 12 months of follow up mortality was 31% in the intervention group compared to 11% in controls ($p=0.0008$).[299]

Health literacy may also play a significant part in an individual's ability to comprehend an action plan. A recently published study which examined the impact of improving the readability and reducing the level of difficulty in patient discharge instructions following trauma surgery resulted in a 50% reduction in the monthly readmission rate.[300] Rates of patient phone calls were also significantly reduced following implementation.[300] This study highlights the importance of ensuring that individuals have a written copy of their action plan and can adequately comprehend and implement the instructions it conveys.

However, written and electronic material, in the context of ongoing support and monitoring from health care professionals, has demonstrated benefit in other studies as part of a comprehensive chronic condition program. This was evident in a study in a

hypertensive population where significant improvements in home and office blood pressure readings, improvements in diet, physical activity levels and weight reduction were observed in 149 individuals with the use of smartphone apps and a web based patient portal.[301] Based on home BP readings a nurse or pharmacist was able to adjust each individuals medication regime. Each study participant set two to three lifestyle goals with progress monitored through the patient applications and web-based portal. In AF, a nurse led integrated care approach which included the provision of educational counselling sessions by a nurse and standardised written material, protocol driven diagnostic testing and an electronic decision support decision for the health care provider resulted in a significant reduction in cardiovascular hospitalisations and mortality in a single centre study of 712 participants in the Netherlands.[209] Based on these and other chronic condition studies undertaken to date it is likely that a combination of factors contributes to improved outcomes including written/electronic instructions, re-enforcement of these instructions at subsequent appointments and intensive and comprehensive follow up by a multidisciplinary team. The ability to access urgent support in between scheduled appointment times is also likely to be an important factor.

5.7.6 Strategies to reduce AF admissions

Other strategies to reduce hospital admissions due to AF have been examined including the use of ED management protocols to standardise AF treatment. In a recently published US study, the use of such a protocol, in addition to next day follow up at an AF clinic, resulted in a 24% reduction in the rate of admission to hospital for individuals presenting with AF.[164] Similarly, the use of an ED protocol in another study also resulted in a 64% reduction in the admission rate in another US based study of 359 individuals presenting

to ED with AF.[165] Individuals who were admitted to hospital also experienced a shorter length of stay, although the time spent in ED was significantly greater with the use of the ED protocol compared to the control period.[165] Despite the observed improvements with ED management protocols, their use in clinical practice is limited and has never been tested in an Australian health care setting.

5.7.7 Mortality

AF has an established association with increased all cause and cardiovascular mortality with a recent meta-analysis demonstrating a 46% increase in all-cause mortality risk (RR 1.46, 95% CI 1.39-1.54) and a more than 2 fold increased risk of cardiovascular mortality (RR 2.03, 95% CI 1.79-2.30).[302] Although we were unable to ascertain the causes of death in our cohort, the overall mortality rate at more than 16% over follow up is significant and highlights the poor outcomes associated with the condition. The baseline characteristics of those who died differed from the rest of the cohort and are reflective of a generally sicker population with a higher comorbid burden. This is similar to results of other studies,[285,286] and highlights the need for management of other comorbid risk factors and conditions as a potential avenue for improving outcomes in AF. The impact of improved care of other conditions in the AF population such as heart failure, hypertension and vascular diseases on risk of mortality is however, not known.

5.8 LIMITATIONS

Our study has several limitations worthy of discussion. Firstly, this is likely to be an under-representation of all repeat events as this study was only able to identify events

occurring in the public health system. It is possible that factors may not have been recorded in the electronic health record and therefore not accurately recorded in the database e.g. an individual could have had a personalised AF action plan, but this was not identified as it was not recorded in the electronic health record. As our study population is based on individuals presenting to hospital primarily due to AF, the results may not be reflective of other AF populations. Finally, there were several important factors that we were unable to identify from the electronic health record including depression, anxiety and symptom burden (e.g. EHRA class) as these were not routinely screened for and recorded in the electronic health record. It is possible that these and other demographic and clinical factors that we were unable to collect could be associated with repeat ED presentations and hospitalisations for AF.

5.9 CONCLUSIONS

AF is associated with significant health burden. Hospitalisations are the main driver of AF related cost and occur frequently in this population. AF related ED presentations and hospitalisations are more likely to occur in males and younger individuals and attention should be directed at these populations to prevent growing health care burden. Admission to hospital frequently occurs in the setting of unplanned ED presentations for AF and may often be inappropriate with our study suggesting that this is largely driven by factors beyond that of clinical need. The use of a non-standardised AF action plan is associated with an increased risk of both repeat ED presentations and hospitalisations with further research needed to understand this unexpected finding. Strategies to reduce the burgeoning numbers of the AF population and subsequent increase in associated health care resources may include the use of ED protocols and enhanced outpatient management

of the condition. These may also contribute to improved appropriate use of OAC which remains suboptimal in our cohort. Given the heterogenous nature of AF and of repeat hospitalisations, the need for a new paradigm in care delivery through a comprehensive, individualised and integrated approach to AF management has never been stronger.

Table 1: Baseline characteristics

Patient characteristics	
Sex: male, n (%)	218 (49.9)
Age at initial presentation (years), mean±SD	68.7 ± 14.5
SES: IRSAD[1] quintile, n (%)	
1 (lowest)	69 (15.9)
2	62 (14.3)
3	74 (17.0)
4	111 (25.5)
5 (highest)	119 (27.4)
Index presentation details	
Admitted: yes, n(%)	316 (72.3)
Length of stay (hours), mean±SD	52.8 ± 98.6
Treatment at initial presentation: yes, n (%)	
Electrical cardioversion	64 (14.7)
Rate control medication administered	255 (58.5)
Rhythm control medication administered	97 (22.3)
Reverted to SR on discharge	246 (56.4)
AF action plan	20 (4.6)
Cardiologist referral	275 (62.9)
Risk Assessments	
CHA_2DS_2-VASc score documented: yes, n (%)	52 (11.9)
CHA_2DS_2-VASc score, mean±SD	2.83 ± 1.88
HAS-BLED score documented: yes, n (%)	0 (0)
HAS-BLED score, mean±SD	1.66 ± 1.08
Comorbidities: yes, n (%)	
Heart failure	62 (14.2)
Hypertension	216 (49.4)
Diabetes	75 (17.2)
Prior stroke/TIA/TE	48 (11.0)
Vascular disease	101 (23.1)
Renal disease	13 (3.0)
Liver disease	7 (1.6)
Prior major bleeding	6 (1.4)

Postcodes were matched to Index of Relative Socio-Economic Advantage and Disadvantage (IRSAD) ranks. IRSAD quintiles were generated based on IRSAD rankings within Australia using Socio-Economic Indexes for Areas (SEIFA) for 2016 from the Australian Bureau of Statistics (http://www.abs.gov.au/ausstats/abs@.nsf/mf/2033.0.55.001)

(SES – socioeconomic status, TIA – transient ischaemic attack, TE –thromboembolism)

Table 2: Baseline Charlson Comorbidity Index Scores

Charlson Comorbidity Index	n (%)
0	21 (4.8)
1	16 (3.7)
2	53 (12.1)
3	84 (19.2)
4	111 (25.4)
5	67 (15.3)
6	36 (8.2)
7	21 (4.8)
8	10 (2.3)
≥ 9	13 (3.0)
Unknown	5 (1.1)

Table 3: Distribution of repeat hospital admission and ED presentations per annum

	Hospital admissions			ED presentations		
	AF related n (%)	**Other CV n (%)**	**All other causes n (%)**	**AF related n (%)**	**Other CV n (%)**	**All other causes n (%)**
March 2013-March 2014	104(38.8)	44(16.4)	120(44.8)	54(30.3)	26(14.6)	95(53.4)
March 2014-March 2015	82(22.1)	69(18.6)	220(59.3)	64(20.9)	30(9.8)	207(67.7)
March 2015-March 2016	52(16.0)	59(18.2)	213(65.5)	31(16.06)	23(11.9)	134(69.4)
March 2016-March 2017	30(11.3)	42(15.8)	194(72.9)	40(25.6)	18(11.5)	98(62.8)
March 2017-March 2018	19(14.2)	23(17.2)	92(68.7)	20(22.7)	21(23.9)	44(50.0)
March 2018-July 2018	5(33.3)	0(0.0)	10(66.7)	1(25.0)	0(0.0)	3(75.0)
Total follow up duration	292(21.2)	237(17.2)	849(61.6)	210(22.7)	118(12.8)	581(62.8)

(ED – emergency department, CV – cardiovascular)

Table 4: Characteristics of individuals who re-presented to ED for AF compared to non-re-presenters

	Repeat ED presentation group (n=82)	Non-repeat ED presentation group (n=355)	P-value^
Female **Male**	40 (48.8) 42 (51.2)	179 (50.4) 176 (49.6)	0.789
Age at index presentation (years), mean±SD	68.6±11.9	69.1±15.0	0.378
Baseline comorbidities			
Heart failure: n (%)	5 (6.1)	57 (16.1)	**0.02**
Hypertension, n (%)	48 (58.5)	168 (47.3)	0.067
Diabetes, n (%)	15 (18.3)	60 (16.9)	0.763
Prior stroke/TIA/TE: n (%)	5 (1.2)	43 (12.1)	0.270
Charlson Comorbidity Index score (mean±SD)	3.75±1.72	4.05±2.12	0.187
INDEX PRESENTATION CHARACTERISTICS			
Admitted, n (%)	41 (50.0)	275 (77.5)	**<.001**
Length of stay (hours), mean±SD	23.5±30.2	59.5 ± 107.4	**<.001**
Treatment			
Electrical cardioversion: n (%)	14 (17.1)	50 (14.1)	0.722
Rate control, n (%)	45 (54.9)	210 (59.1)	0.374
Rhythm control, n (%)	81 (98.8)	343 (96.6)	0.299
Sinus rhythm on discharge, n (%)	44 (53.7)	191 (53.8)	**0.001**
AF action plan, n (%)	13 (15.9)	10 (2.8)	**<.001**
Cardiologist referral, n (%)	52 (63.4)	221 (62.3)	**0.001**
CHA_2DS_2-VASc score, mean±SD	2.66±1.69	2.86±1.92	0.462
HAS-BLED score, mean±SD	1.74±1.04	1.64±1.09	0.415

^ P-value for chi-square test of association for categorical predictors, or Mann-Whitney U test for continuous predictors

(ED – emergency department, TIA – transient ischaemic attack, TE – thromboembolism)

Table 5: Predictors of AF related ED re-presentations

Predictor	Univariable			Multivariable[a]		
	Odds Ratio	(95% CI)	P-value	Odds Ratio	(95% CI)	P-value
Female (ref) **Male**	1.00 1.07	(0.66-1.73)	0.789	1.00 1.04	(0.47-2.29)	0.931
Age at index presentation, per year increase	0.998	(0.98-1.01)	0.785	1.04	(0.995-1.089)	0.079
Heart Failure	0.34	(0.13-0.88)	0.025	1.11	(0.31-3.98)	0.868
Hypertension	1.57	(0.97-2.56)	0.068	2.15	(0.82-5.62)	0.120
Diabetes	1.10	(0.59-2.06)	0.763	1.86	(0.70-4.94)	0.211
Prior stroke/TIA/TE	0.74	(0.18-1.24)	0.128	1.33	(0.29-6.03)	0.710
Charlson Comorbidity Index, per unit increase	0.93	(0.82-1.05)	0.238	0.96	(0.75-1.22)	0.735
Admitted at index presentation	0.29	(0.18-0.48)	<.0001	0.39	(0.19-0.80)	0.011
Index presentation LOS, per hour increase	0.986	(0.979-0.994)	<.0001	0.992	(0.983-1.002)	0.108
Electrical cardioversion	1.26	(0.66-2.40)	0.491	1.03	(0.42-2.49)	0.953
Rate control medication	0.79	(0.49-1.29)	0.349	1.69	(0.86-3.31)	0.126
Rhythm control medication	2.83	(0.36-22.1)	0.320		[b]	
Sinus rhythm at discharge	1.18	(0.69-2.01)	0.546	1.30	(0.68-2.48)	0.431
AF action plan	6.91	(2.90-16.4)	<.0001	6.67	(2.42-18.3)	**<.001**
Cardiologist referral	1.32	(0.77-2.26)	0.311	1.36	(0.72-2.60)	0.345
CHA_2DS_2-VASc score, per unit increase	0.94	(0.83-1.07)	0.371	0.66	(0.39-1.11)	0.116
HAS-BLED score, per unit increase	1.09	(0.87-1.36)	0.444	1.30	(0.83-2.03)	0.249

[a] ORs are adjusted for all other variables in the table
[b] Variable omitted from multivariable model due to collinearity

(LOS - length of stay, TIA – transient ischaemic attack, TE - thromboembolism)

Table 6: Predictors of the number of AF related ED re-presentations

Predictor	Univariable			Multivariable[a]		
	IRR	(95% CI)	P-value	IRR	(95% CI)	P-value
Female (ref) **Male**	1.00 0.62	(0.20-1.95)	0.416	1.00 0.62	(0.13-2.98)	0.551
Age at index presentation, per year increase	0.98	(0.93-1.04)	0.578	0.99	(0.90-1.08)	0.810
Heart failure	0.12	(0.02-0.91)	0.040	2.26	(0.21-23.8)	0.497
Hypertension	3.30	(0.96-11.3)	0.058	10.2	(1.61-64.4)	**0.014**
Diabetes	0.44	(0.11-1.76)	0.244	0.48	(0.08-2.85)	0.418
Prior stroke/TIA/TE	0.32	(0.02-5.33)	0.425	0.45	(0.02-10.5)	0.617
Charlson Comorbidity Index, per unit increase	0.72	(0.51-1.02)	0.064	1.32	(0.79-2.20)	0.291
Admitted at index presentation	0.18	(0.05-0.62)	0.007	0.16	(0.03-0.77)	**0.022**
Index presentation LOS, per hour increase	0.97	(0.96-0.99)	<0.0001	0.98	(0.961-0.999)	**0.037**
Electrical cardioversion	1.09	(0.26-4.56)	0.901	1.39	(0.26-7.34)	0.698
Rate control medication	0.56	(0.17-1.84)	0.341	3.11	(0.70-13.8)	0.136
Rhythm control medication	1.20	(0.07-19.9)	0.899		[b]	
Sinus rhythm at discharge	2.31	(0.70-7.57)	0.167	2.39	(0.58-9.91)	0.228
AF action plan	4.63	(0.49-44.0)	0.182	4.72	(0.65-34.5)	0.120
Cardiologist referral	2.09	(0.63-6.93)	0.226	1.51	(0.44-5.17)	0.511
CHA_2DS_2-VASc score, per unit increase	1.02	(0.73-1.43)	0.918	0.53	(0.19-1.49)	0.232
HAS-BLED score, per unit increase	1.02	(0.56-1.86)	0.946	1.28	(0.60-2.73)	0.516

[a] ORs are adjusted for all other variables in the table
[b] Variable omitted from multivariable model due to collinearity

(LOS - length of stay, TIA – transient ischaemic attack, TE - thromboembolism)

Table 7: Characteristics of individuals who were readmitted for AF compared to non-re-admitters

Variable	Readmission group (n=125)	Non-readmission group (n=312)	P-value^
Female **Male**	64(51.2) 61(48.8)	155(49.7) 157(50.3)	0.774
Age at index presentation (years), mean±SD	70.6±12.6	68.0±15.1	0.165
Heart failure	15 (12.0)	47 (15.1)	0.407
Hypertension	79 (63.2)	137 (43.9)	**<.001**
Diabetes, n (%)	28 (22.4)	47 (15.1)	0.066
Prior stroke, TIA, TE: n (%)	17 (13.6)	31 (9.9)	0.554
Charlson Comorbidity Index score (mean±SD)	4.3±1.9	3.9±2.1	0.078
Admitted	91 (72.8)	225 (72.1)	0.885
Length of stay (hours), mean±SD	54.8±89.2	52.0±102.3	0.573
Electrical cardioversion	16 (12.8)	48 (15.4)	0.760
Rate control medication: n (%)	81 (64.8)	174 (55.8)	0.223
Rhythm control medication: n (%)	122 (97.6)	302 (96.8)	0.654
Sinus rhythm on discharge: n (%)	76 (60.8)	170 (54.5)	0.622
AF action plan: n (%)	9 (7.2)	11 (3.5)	0.233
Cardiologist referral: n (%)	83 (66.4)	192 (61.5)	0.609
CHA_2DS_2-Vasc score, mean±SD	3.2±1.8	2.7±1.9	**0.0023**
HAS-BLED score, mean±SD	2.0±1.0	1.5±1.1	**<.001**

^ P-value for chi-square test of association for categorical predictors, or Mann-Whitney U test for continuous predictors

(TIA – transient ischaemic attack, TE – thromboembolism)

Table 8: Predictors of AF related readmissions

Predictor	Univariable			Multivariable[a]		
	Odds Ratio	(95% CI)	P-value	Odds Ratio	(95% CI)	P-value
Female (ref)	1.00			1.00		
Male	0.94	(0.62-1.43)	0.774	1.24	(0.66-2.30)	0.503
Age at index presentation, per year increase	1.01	(0.997-1.028)	0.102	1.00	(0.96-1.03)	0.900
Heart Failure	0.77	(0.41-1.43)	0.408	0.72	(0.30-1.72)	0.466
Hypertension	2.19	(1.43-3.36)	<.0001	1.35	(0.63-2.86)	0.439
Diabetes	1.63	(0.97-2.74)	0.068	1.10	(0.52-2.34)	0.797
Prior stroke/TIA/TE	1.43	(0.76-2.69)	0.268	0.86	(0.29-2.50)	0.776
Charlson Comorbidity Index score, per unit increase	1.09	(0.99-1.21)	0.083	1.01	(0.84-1.21)	0.952
Admitted at index presentation	1.03	(0.65-1.65)	0.885	0.90	(0.50-1.62)	0.721
Index presentation length of stay, per hour increase	1.00	(0.998-1.002)	0.785	1.00	(0.997-1.002)	0.879
Electrical cardioversion	0.81	(0.44-1.48)	0.490	0.94	(0.46-1.91)	0.863
Rate controlling medication	1.45	(0.94-2.26)	0.096	1.44	(0.83-2.52)	0.195
Rhythm control medication	1.35	(0.36-4.98)	0.655		[b]	
Sinus rhythm at discharge	1.29	(0.82-2.02)	0.274	1.56	(0.92-2.64)	0.097
AF action plan	2.11	(0.85-5.23)	0.106	2.76	(1.00-7.63)	**0.051**
Cardiologist referral	1.22	(0.79-1.90)	0.369	1.36	(0.82-2.27)	0.231
Index presentation CHA_2DS_2-VASc score, per unit increase	1.18	(1.06-1.32)	0.003	1.11	(0.74-1.66)	0.603
Index presentation HAS-BLED score, per unit increase	1.58	(1.29-1.94)	<.0001	1.42	(1.00-2.01)	**0.051**

[a] ORs are adjusted for all other variables in the table
[b] Variable omitted from multivariable model due to collinearity

(TIA – transient ischaemic attack, TE – thromboembolism)

Table 9: Predictors of the number of AF related readmissions

Predictor	Univariable			Multivariable[a]		
	IRR	95% CI	P-value	IRR	95% CI	P-value
Female (ref) **Male**	1.00 0.80	(0.31-2.03)	0.631	1.00 0.57	(0.14-2.38)	0.440
Age at index presentation, per year increase	0.99	(0.95-1.03)	0.601	0.93	(0.86-1.02)	0.130
Heart failure	0.35	(0.10-1.23)	0.101	0.14	(0.02-0.98)	**0.018**
Hypertension	3.50	(1.32-9.28)	0.012	2.65	(0.42-16.7)	0.918
Diabetes	1.24	(0.37-4.11)	0.729	0.72	(0.10-5.10)	0.869
Prior stroke/TIA/TE	1.17	(0.29-4.81)	0.823	0.89	(0.05-16.9)	0.511
Charlson Comorbidity Index, per unit increase	0.88	(0.69-1.12)	0.295	1.16	(0.69-1.97)	0.486
Admitted to hospital	0.79	(0.29-2.14)	0.638	1.40	(0.36-5.49)	0.633
Index presentation LOS, per hour increase	0.998	(0.994-1.003)	0.445	1.003	(0.997-1.008)	0.394
Electrical cardioversion	0.67	(0.18-2.43)	0.540	0.78	(0.12-4.88)	0.790
Rate control medication	2.03	(0.77-5.39)	0.153	1.89	(0.48-7.36)	0.361
Rhythm control medication	0.63	(0.06-6.47)	0.695		[b]	
AF action plan	0.86	(0.13-5.75)	0.870	3.87	(0.33-45.3)	0.280
Cardiologist referral	0.89	(0.33-2.42)	0.820	0.62	(0.18-2.12)	0.447
CHA_2DS_2-VASc score, per unit increase	1.12	(0.87-1.44)	0.394	1.32	(0.51-3.46)	0.566
HAS-BLED score, per unit increase	1.87	(1.17-2.98)	0.009	2.24	(1.01-4.98)	**0.047**

[a] ORs are adjusted for all other variables in the table
[b] Variable omitted from multivariable model due to collinearity

(LOS - length of stay, TIA – transient ischaemic attack, TE - thromboembolism)

Table 10: Predictors of the time to first AF hospitalisation

Predictor	Univariable			Multivariable[a]		
	Hazard Ratio	(95% CI)	P-value	Hazard Ratio	(95% CI)	P-value
Female (ref) **Male**	1.00 0.96	(0.68-1.37)	0.842	1.00 1.21	(0.71-2.07)	0.480
Age at index presentation, per year increase	1.01	(1.001-1.027)	0.031	1.001	(0.971-1.032)	0.954
Heart failure	0.80	(0.46-1.37)	0.408	0.80	(0.37-1.74)	0.568
Hypertension	1.93	(1.34-2.77)	<.0001	1.25	(0.65-2.41)	0.504
Diabetes	1.50	(0.98-2.28)	0.059	1.19	(0.64-2.21)	0.590
Prior stroke/TIA/TE	1.34	(0.80-2.24)	0.260	0.89	(0.35-2.26)	0.802
Charlson Comorbidity Index, per unit increase	1.08	(0.99-1.17)	0.077	0.98	(0.84-1.14)	0.814
Admitted to hospital	0.99	(0.67-1.47)	0.966	0.88	(0.52-1.48)	0.628
Index presentation LOS, per hour increase	1.00	(0.999-1.002)	0.652	1.00	(0.999-1.003)	0.368
Electrical cardioversion	0.79	(0.46-1.33)	0.366	0.90	(0.48-1.67)	0.736
Rate control medication	1.36	(0.93-1.98)	0.109	1.26	(0.79-2.01)	0.330
Rhythm control medication	1.25	(0.40-3.92)	0.706		[b]	
Sinus rhythm at discharge	1.14	(0.77-1.70)	0.507	1.33	(0.86-2.01)	0.206
Cardiologist referral	1.02	(0.70-1.49)	0.899	1.41	(0.89-2.23)	0.146
CHA_2DS_2-VASc score, per unit increase	1.14	(1.05-1.25)	0.004	1.05	(0.74-1.48)	0.792
HAS-BLED score, per unit increase	1.49	(1.26-1.76)	<.0001	1.40	(1.04-1.89)	**0.027**

[a] HRs are adjusted for all other variables in the table
[b] Variable omitted from multivariable model due to collinearity

(LOS - length of stay, TIA – transient ischaemic attack, TE - thromboembolism)

Table 11: Predictive factors for admission to hospital for unplanned AF re-presentations

Predictor	Univariable			Multivariable[a]		
	Odds Ratio	(95% CI)	P-value	Odds Ratio	(95% CI)	P-value
Female (ref) **Male**	1.00 1.20	(0.72-2.01)	0.842	1.00 1.39	(0.71-2.72)	0.342
Age at index presentation, per year increase	1.00	(0.98-1.03)	0.670	0.99	(0.95-1.03)	0.566
Heart Failure	3.34	(1.26-8.83)	0.015	1.00	(0.29-3.45)	0.997
Hypertension	0.96	(0.58-1.58)	0.859	0.62	(0.26-1.49)	0.284
Diabetes	1.06	(0.51-2.23)	0.868	1.27	(0.46-3.49)	0.647
Prior stroke/TIA/TE	2.42	(0.85-6.85)	0.097	1.24	(0.25-6.04)	0.26
Charlson Comorbidity Index score, per unit increase	1.08	(0.02-1.25)	0.346	0.88	(0.65-1.19)	0.416
Admitted at index presentation	2.44	(1.47-4.06)	0.001	2.45	(1.24-4.84)	**0.010**
Index presentation length of stay, per hour increase	1.01	(1.00-1.02)	0.002			
Electrical cardioversion	0.79	(0.42-1.46)	0.450	1.03	(0.50-2.14)	0.935
Rate control medication	2.07	(1.24-3.48)	0.006	1.44	(0.79-2.61)	0.229
Rhythm control medication	0.94	(0.40-2.21)	0.882		[b]	
AF action plan	0.98	(0.44-2.18)	0.969	3.11	(1.09-8.87)	**0.034**
Cardiologist referral	0.93	(0.58-1.49)	0.752	1.02	(0.60-1.75)	0.937
Index presentation CHA_2DS_2-VASc score, per unit increase	1.08	(0.92-1.26)	0.348	1.29	(0.82-2.03)	0.262
Index presentation HAS-BLED score, per unit increase	1.13	(0.90-1.41)	0.280	1.19	(0.82-1.73)	0.360

[a] ORs are adjusted for all other variables in the table
[b] Variable omitted from multivariable model due to collinearity

(TIA – transient ischaemic attack, TE – thromboembolism)

Table 12: Baseline characteristics for those with and without a non-standardised AF action plan

Variable	No AF action plan (n=406)	AF action plan (n=20)	P-value^
Sex (n, %)			
Female	206 (50.7)	8 (40.0)	0.370
Male	200 (49.3)	12 (60.0)	
Age at index presentation (years), mean±SD	69.6±14.4	60.6±14.7	**0.008**
Heart failure: n (%)	60 (14.8)	0 (0.0)	0.092
Hypertension: n (%)	203 (50.0)	7 (35.0)	0.253
Diabetes: n (%)	72 (17.7)	1 (5.0)	0.222
Prior stroke/TIA/TE: n (%)	48 (11.8)	0 (0.0)	0.263
Charlson Comorbidity Index score (mean±SD)	4.1±2.0	2.8±1.8	**0.006**
Admitted: n (%)	299 (73.6)	8 (40.0)	**0.003**
Length of stay (hours), mean±SD	55.7±101.5	6.6±6.5	**<.001**
Treatment			
Electrical cardioversion: n (%)	56 (13.8)	7 (35.0)	**0.052**
Rate control medication administered: n (%)	246 (60.6)	5 (25.0)	**0.006**
Rhythm control medication administered: n (%)	88 (21.7)	7 (35.0)	0.383
Reverted to SR on discharge: n (%)	220 (54.2)	15 (75.0)	0.156
Cardiologist referral: n (%)	215 (53.0)	16 (80.0)	**0.045**
CHA_2DS_2-Vasc score, mean±SD	2.9±1.9	1.6±1.5	**0.003**
HAS-BLED score, mean±SD	1.7±1.1	1.2±1.4	**0.050**

^P-value for Fisher's exact test of association for categorical predictors, or Mann-Whitney U test for continuous predictors

(TIA – transient ischaemic attack, TE – thromboembolism)

Table 13: Baseline characteristics according to mortality status at end of study

Variable	Died during follow-up (n=71)	Alive at the end of follow-up (n=366)	P-value^
Demographics			
Female	33 (46.5)	186 (50.8)	0.503
Male	38 (53.5)	180 (49.2)	
Age at index presentation (years), mean±SD	79.79±10.71	66.63±14.15	**<.001**
Heart failure: n (%)	22 (31.0)	40 (10.9)	**<.001**
Hypertension: n (%)	34 (47.9)	182 (49.7)	0.777
Diabetes: n (%)	17 (23.9)	58 (15.8)	0.098
Prior stroke/TIA/TE: n (%)	12 (16.9)	36 (9.8)	0.172
Charlson Comorbidity Index score (mean±SD)	6.04±2.01	3.60±1.81	**<.001**
Presentation details			
Admitted: n (%)	59 (83.1)	257 (70.2)	**0.026**
Length of stay (hours), mean±SD	76.0±161.4	48.3±80.6	**0.003**
Electrical cardioversion: n (%)	2 (2.8)	62 (16.9)	**0.003**
Rate control medication: n (%)	49 (69.0)	206 (56.3)	0.074
Rhythm control medication: n (%)	68 (95.8)	356 (97.3)	0.498
Sinus rhythm at discharge	26 (36.6)	220 (60.1)	**<.001**
AF action plan: n (%)	1 (1.4)	19 (5.2)	0.370
Cardiologist referral: n (%)	29 (40.8)	246 (67.2)	**<.001**
CHA_2DS_2-VASc score, mean±SD	3.92±1.88	2.61±1.81	**<.001**
HAS-BLED score, mean±SD	2.08±0.95	1.58±1.09	**<.001**

^ P-value for chi-square test of association for categorical predictors, or Mann-Whitney U test for continuous predictor

(TIA – transient ischaemic attack, TE – thromboembolism)

Figure 1: Study flow chart

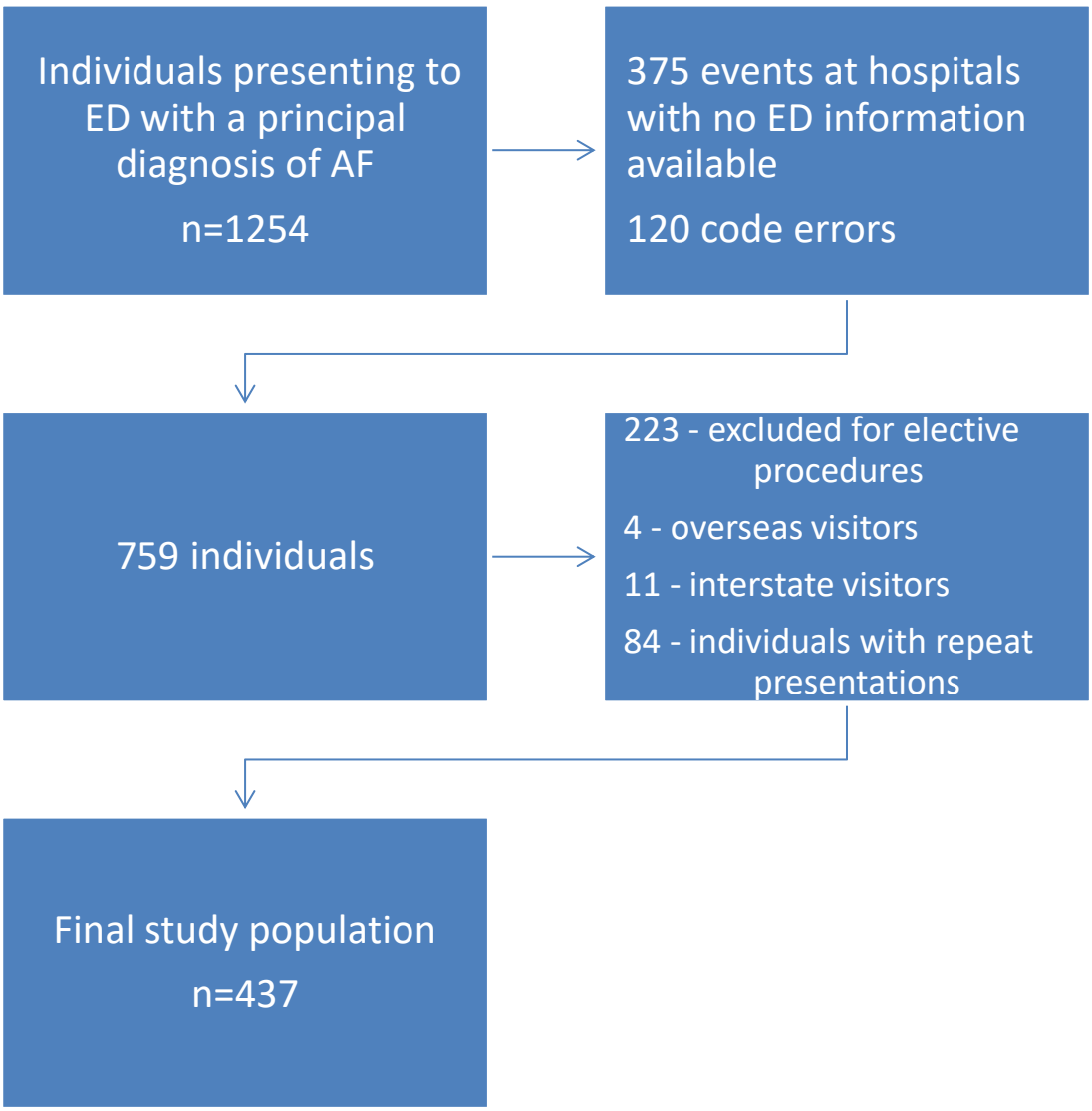


Figure 2: Use of OAC in hospital presentations stratified by first and prior AF diagnosis

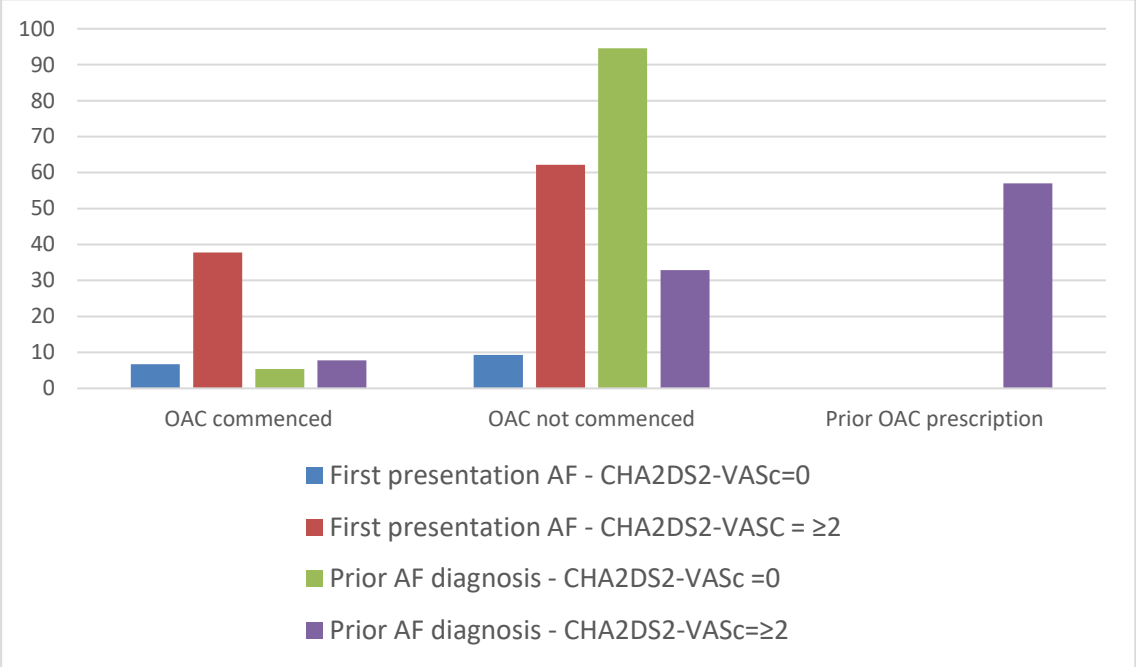


Figure 3: Distribution of type of hospital re-presentation

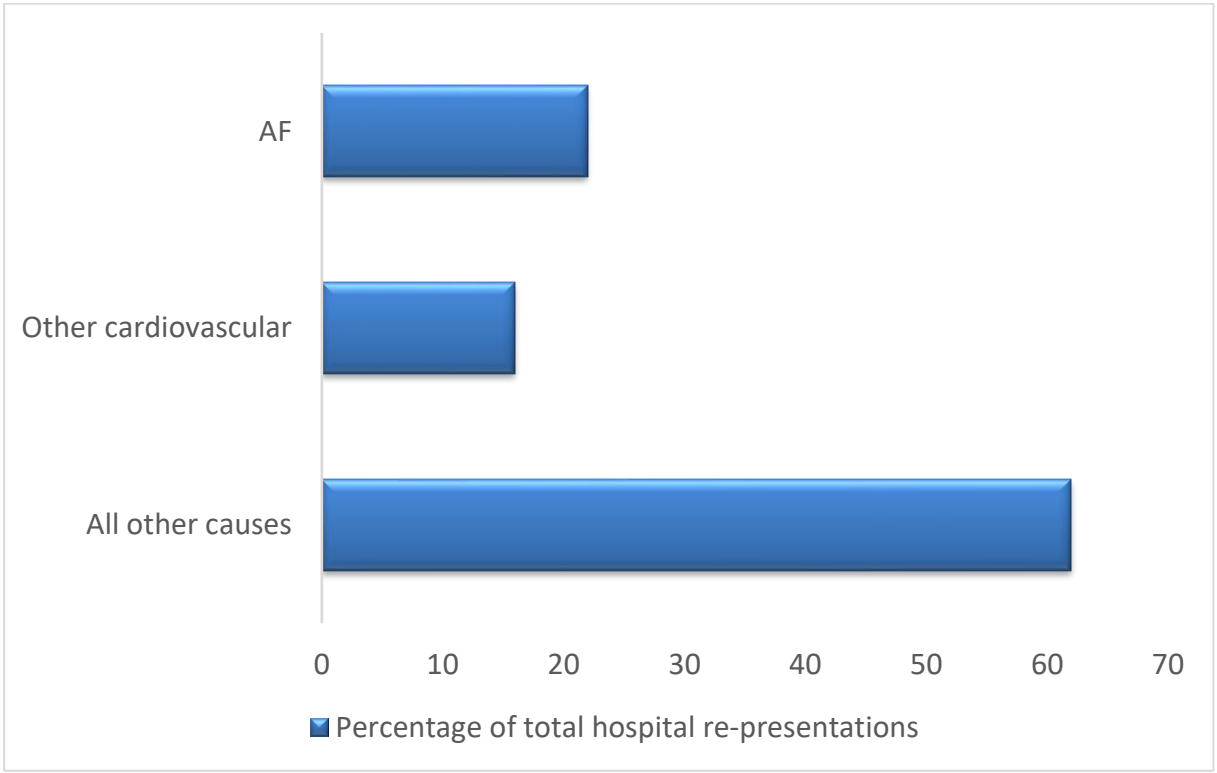


Figure 4: Distribution of repeat AF related re-presentations

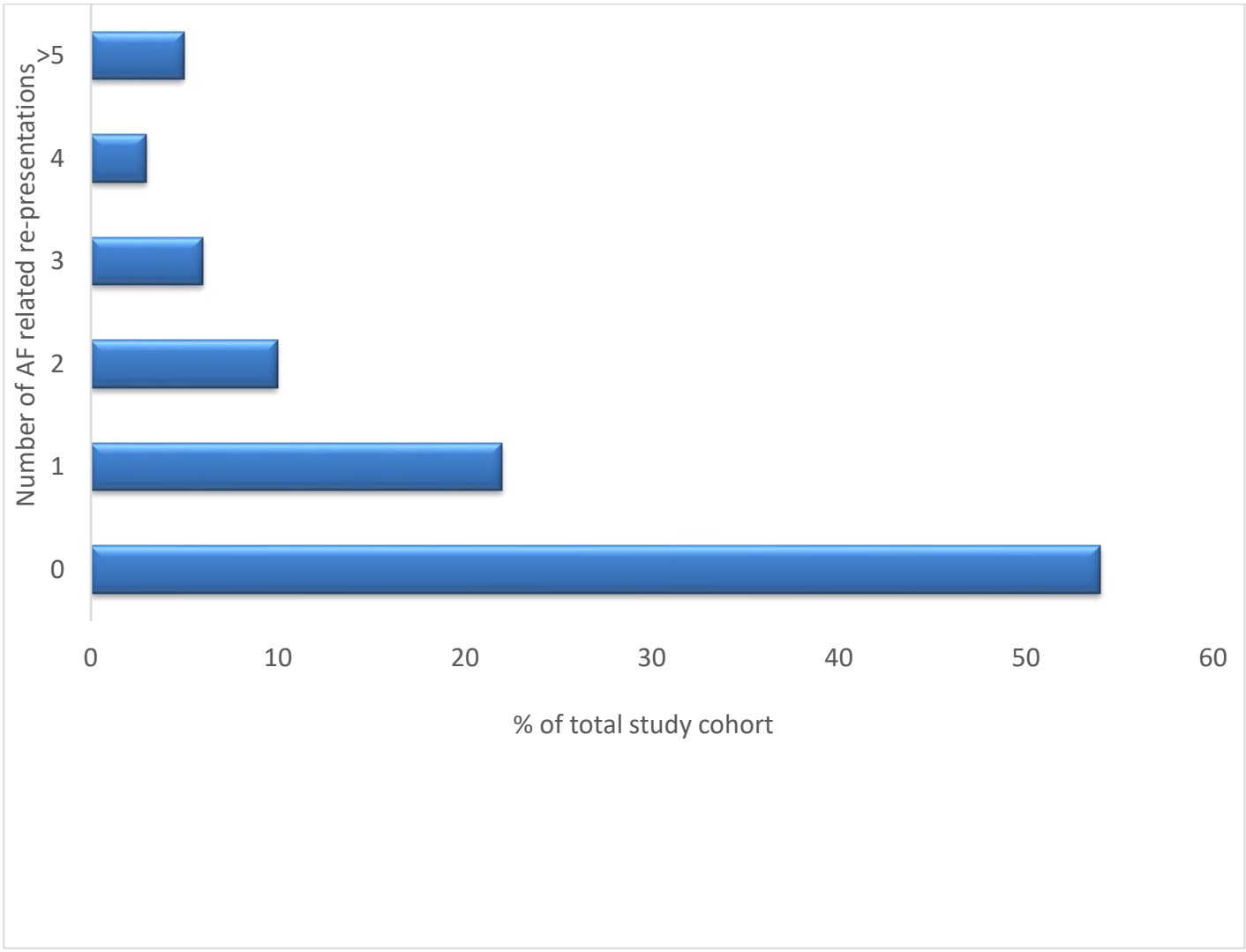


Figure 5: Distribution of other cardiovascular presentations

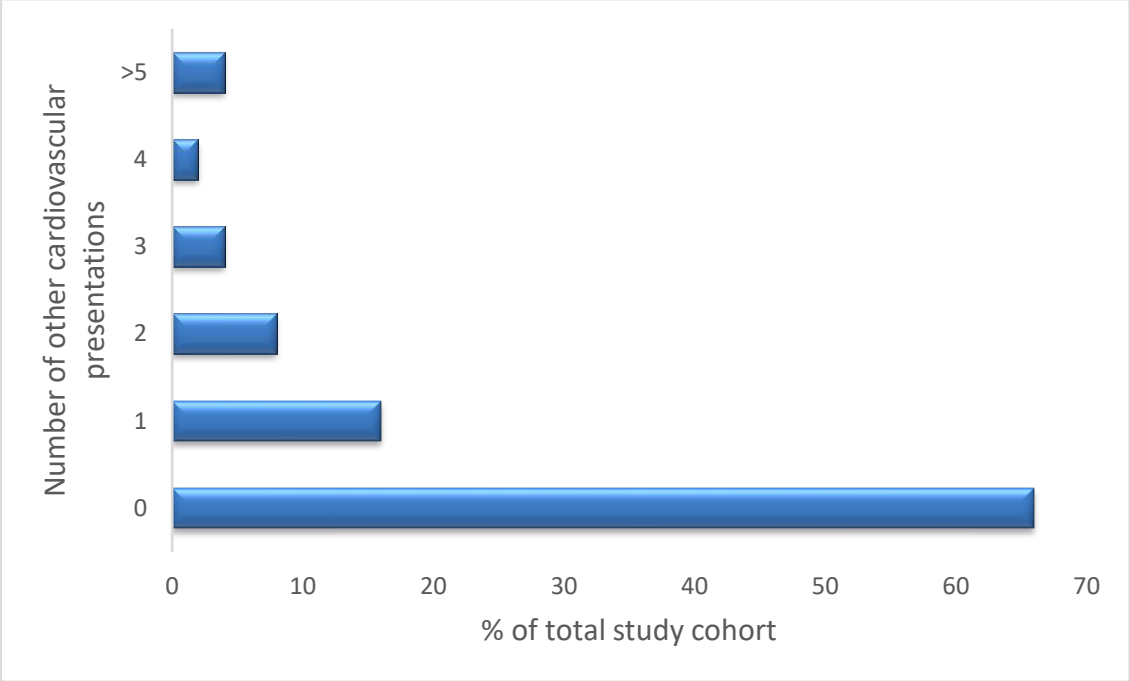


Figure 6: Distribution of presentations due to 'all other causes'

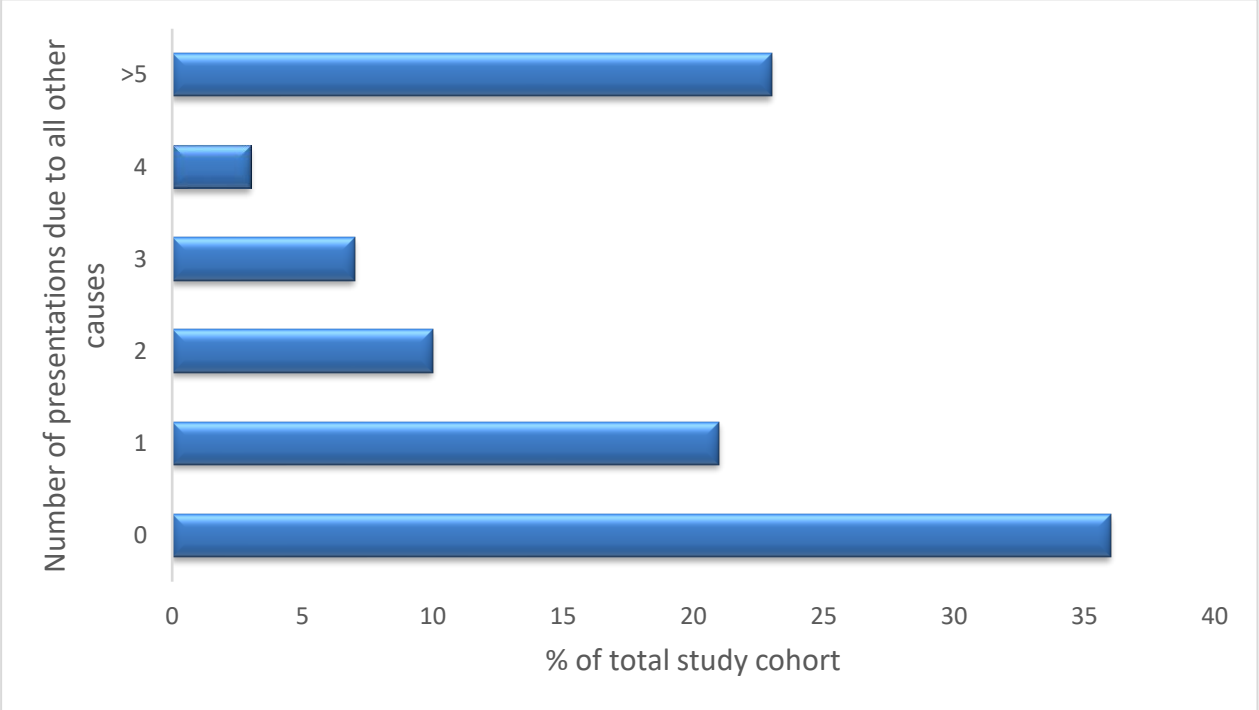


Figure 7: Kaplan Meier curve for time to first ED presentation for AF

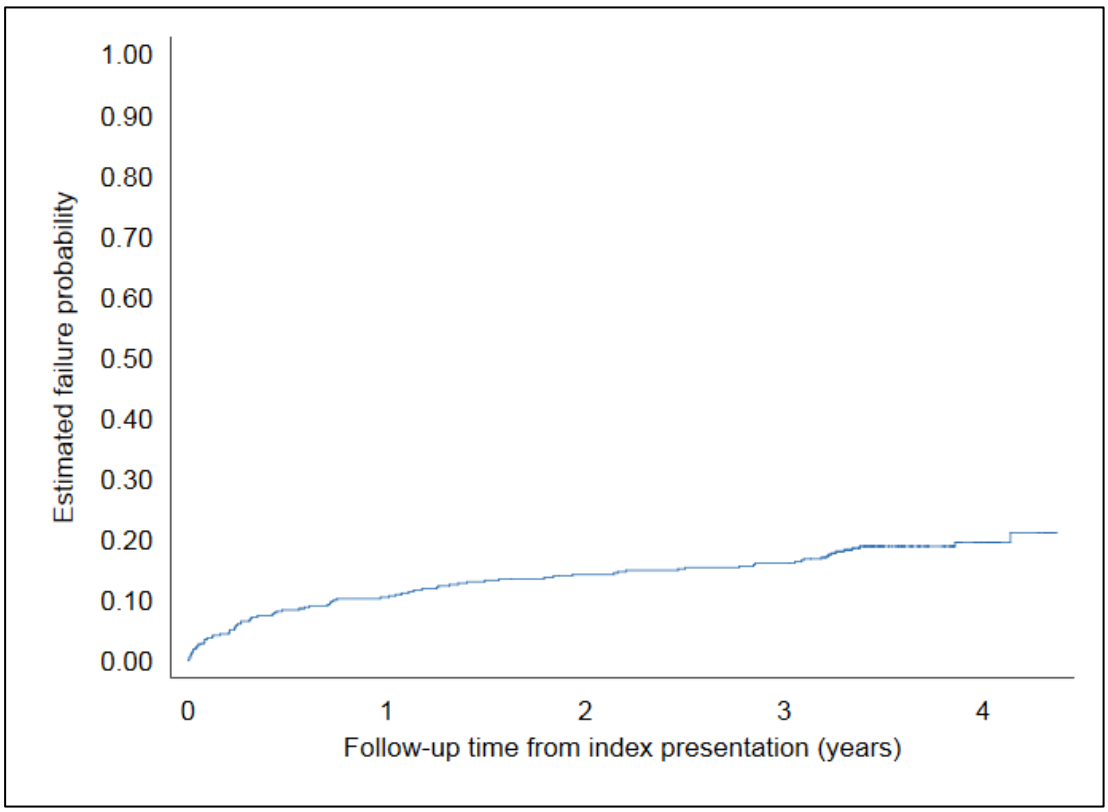


Figure 8: Kaplan Meier curve for time to first hospital admission for AF

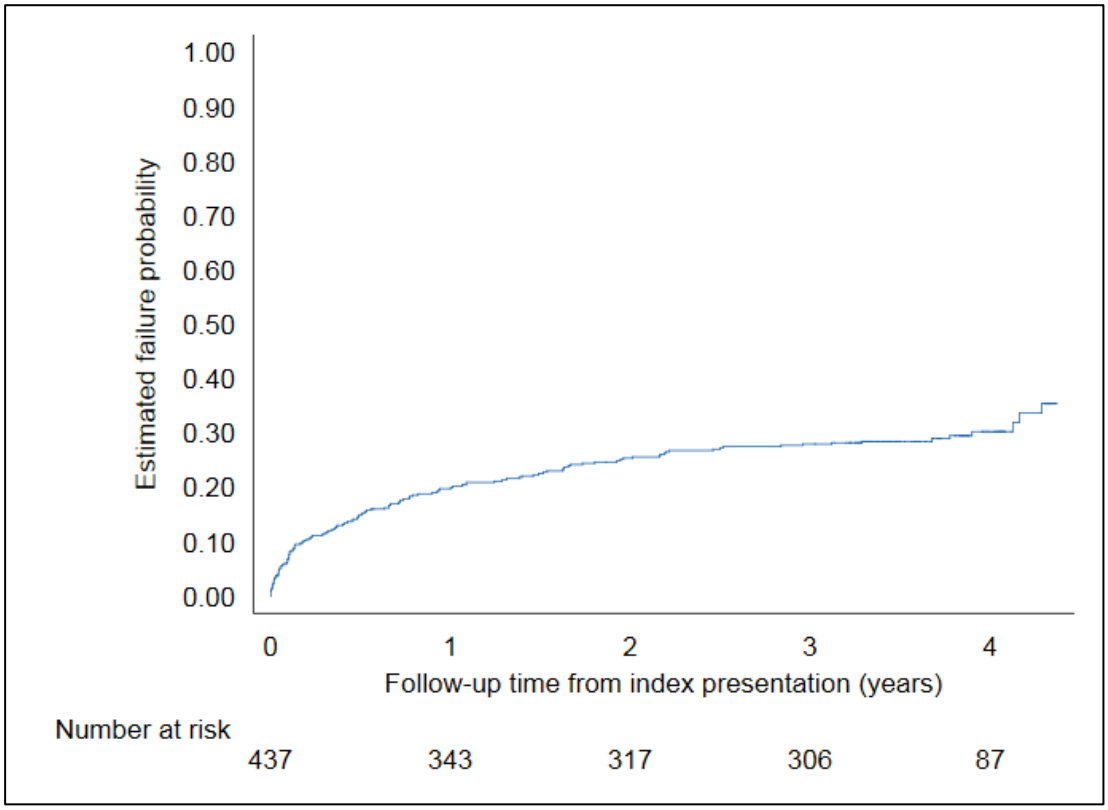
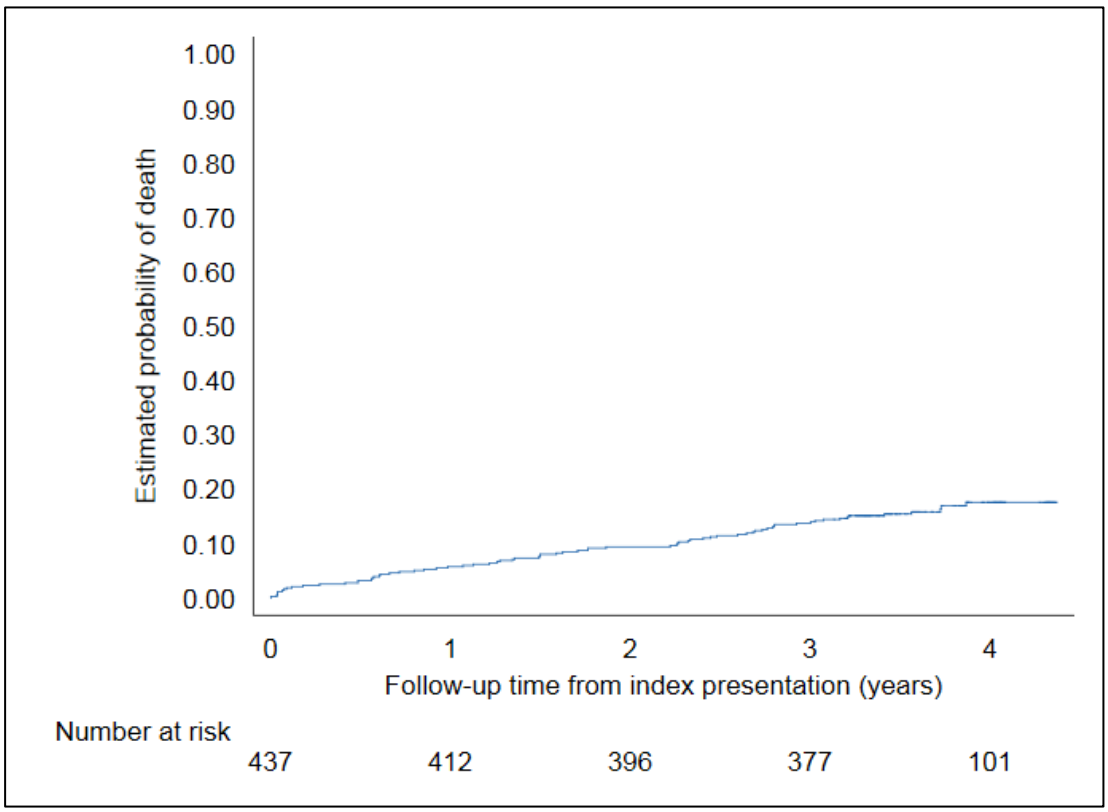


Figure 9: Kaplan Meier curve for risk of death following index hospital presentation



Chapter 6: Nurse Led Atrial Fibrillation Management – the NEAT study

6.1 INTRODUCTION

6.1.1 Background

AF has emerged as one of the greatest healthcare challenges of this century. Incidence and prevalence rates have exponentially risen over recent decades and show no sign of abate.[2] Age adjusted mortality rates associated with the condition have increased approximately two fold for both males and females.[2] Health care resource utilisation associated with AF is significant with hospitalisations the main driver of this.[24] Furthermore, impairment to health-related quality of life (HRQoL) in individuals with AF is considerably worse than the general population and those with other chronic cardiovascular conditions including post MI or percutaneous coronary intervention.[25] The degree of impairment to HRQoL in AF is akin to the heart failure population.[25] In large registry data from the USA lower quality of life, as assessed by the AFEQT in 10 132 individuals with AF, was associated with a higher risk of all cause hospitalisation (HR 1.49; 95% CI 1.2-1.84, $p \leq 0.001$).[31] In the older population (≥65 years of age), HRQoL was significantly lower across numerous studies in individuals with AF compared to control groups.[303] The use of both rate and rhythm control strategies was comparable in relation to improvement of quality of life measures. Factors predictive of poorer quality of life were examined across numerous studies and included being female, elderly, an earlier stage of the disease trajectory and higher symptom burden.[303]

6.1.2 The role of education in AF

Patient education and engagement is a key component of the chronic condition model.[202] Few studies have examined the impact of education on outcomes in the AF population. An RCT of a brief nurse delivered education program in 240 individuals presenting to ED primarily due to AF demonstrated a significant reduction in the primary composite endpoint of any AF related complication including stroke, heart failure and any bradycardia requiring treatment, in addition to other non-specific outcomes including ventricular tachycardia, any arrhythmia causing haemodynamic instability, any haemorrhage in anticoagulated individuals and all-cause mortality.[221] At 12 months, there were significantly less cumulative adverse events in the intervention group (31.9% vs 48.4%; p=0.005). There were no statistically significant differences for ED presentations or hospitalisations between the groups.[221]

The role of nurse delivered education in a post ablation cohort has been examined in a small single centre RCT of 41 individuals.[222] In this study, education about an individual's condition and their procedure was delivered both pre and post ablation during the hospital admission and by three telephone calls over a three month period post procedure. After a six month follow up period, significant improvements in symptomatology were evident in the intervention group compared to controls, in addition to improvements in some domains of the SF-36 including physical functioning and vitality. No differences were observed for AF related or all cause hospital admissions.[222]

6.1.3 Risk factor management in AF

Numerous studies have examined the impact of cardiovascular risk factor management in AF with varying results. Single centre physician led models have demonstrated the most significant outcomes to date. In a series of studies the use of an intensive model which simultaneously targets numerous cardiovascular risk factors including overweight and obesity, hypertension, dyslipidaemia, diabetes, obstructive sleep apnoea, smoking and alcohol intake in a dedicated clinic has demonstrated a reduction in both subjective and objective AF burden at both short and long term follow up.[140-142]

Other studies have examined the impact of exercise based cardiac rehabilitation programs on outcomes in the AF population. The Routine vs. Aggressive risk factor driven upstream rhythm Control for prevention of Early atrial fibrillation in heart failure (RACE 3) RCT enrolled 250 individuals with persistent AF and early heart failure who were scheduled to undertake electrical cardioversion.[148] The intervention arm of this study received four additional therapies which included: mineralocorticoid receptor antagonists, statins, ACE inhibitors or ARBs and cardiac rehabilitation. Cardiac rehabilitation consisted of 2-3 supervised exercise training sessions per week. In addition to this, participants attended a specialised clinic delivered by a nurse which included education and self-management strategies for both conditions. After 12 months of follow up, there was a greater likelihood of sinus rhythm in the intervention group compared to control as objectified by Holter monitoring. The intervention also resulted in a significant reduction in systolic and diastolic blood pressure, BMI, weight, total and LDL cholesterol. No impact on AF symptoms were observed.[148]

An RCT examining the impact of an exercise program in participants who had undertaken ablation for AF demonstrated improvements in peak VO_2 after four months

of follow up, although no impact on quality of life as assessed by the SF-36 was evident.[146]

A pilot study of a telephone-based intervention in 19 individuals with AF did not demonstrate any improvement in health related quality of life as assessed by the SF-12.[304] In this study, individuals attended an extensive baseline assessment with a nurse which also involved goal setting to improve overall cardiovascular risk factor status. However, after three months of follow up, this observational study did not demonstrate any differences in cardiovascular risk factor status in participants at baseline compared to follow up.[304]

The aim of this study was to determine if a brief nurse led clinic, facilitated by a guideline based electronic decision support tool to ensure appropriate oral anticoagulation to reduce stroke risk, can improve health related quality of life and cardiovascular risk factor status in individuals with AF.

6.2 METHODS

6.2.1 Study design

The Nurse Led Atrial Fibrillation Management (NEAT) study was a RCT undertaken collaboratively by the University of Sydney and the University of Adelaide. The study was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12615000928516). Ethics approval was received from the Sydney Local Health District Human Resources Ethics Committee with reciprocal agreement from the University of Adelaide Human Research Ethics Committee (HREC/15/CRGH/57).

6.2.2 Participants

Eligible participants were referred for participation in the study by cardiologists at the Royal Prince Alfred Hospital and Concord Repatriation Hospital in Sydney, and the Centre for Heart Rhythm Disorders at the University of Adelaide, Australia. Inclusion criteria was AF documented on electrocardiogram and ≥18 years of age. Both inpatient and outpatients were eligible for participation. Exclusion criteria were non-English speaking individuals or an inability to provide informed consent. Participants were allocated to the intervention group or usual care by a computer generated 1:1 randomisation schedule. The study conformed with the Declaration of Helsinki and informed consent was obtained from all participants.

6.2.3 Baseline visit and follow up assessment

All patients visited a nurse specialist for baseline assessment. This baseline visit included baseline socio-demographic and clinical data recorded in an electronic case record form. Information collected included demographic data such as age, gender and education level. Health related quality of life was assessed using the Short-form 12 questionnaire (SF-12). Cardiovascular risk factors recorded included smoking status, blood pressure measurement, alcohol consumption and physical activity level. Medication adherence was assessed with the Morisky Medication Adherence Scale and physical activity using the General Physical Activity Questionnaire (GPAC).

All participants attended a final assessment on exit from the study after three months of follow up. This was undertaken by a researcher blinded to group allocation. The final assessment included completion of the SF-12, Morisky Medication Adherence

Scale, the GPAC and cardiovascular risk factors including weight, waist, BMI, blood pressure, smoking status and alcohol intake. A current medication list was also recorded.

6.2.4 Intervention

Participants in the intervention arm of this study attended a brief nurse led educational and risk factor management program. The following components were incorporated in to the intervention:

1. An electronic decision support tool designed to ensure appropriate use of OAC based on stroke risk score and current AF guidelines;
2. Clinical profiling including medication adherence and cardiovascular risk factor status;
3. Health counselling and goal setting

At the baseline visit education was provided concerning basic AF pathophysiology, causes, potential complications, treatment options, appropriate stroke prevention therapies based on individual risk score and self-management of episodes. This session was facilitated by written educational material (Living with Atrial Fibrillation).[305]

Following this, and using the principles of motivational interviewing, participants were encouraged to set 3-4 realistic risk factor or behavioural goals in line with their priorities and motivation. Goals were set by participants according to what was deemed most important to them. The health care professional assisted in ensuring that these goals were realistic and achievable over the follow up time frame and identified ways in which each goal could be achieved. A printed summary of each participant's goals was given to

them. This also contained written information about each individual's stroke risk score and if the current antithrombotic regime was appropriate according to this score. Follow up consisted of telephone only support. Each participant received 3-4 telephone calls over the three month follow up period to monitor their progress and re-assess goals if necessary. The control group attended standard follow up with their cardiologist and/or GP. The frequency of this follow up and care provided was left to the discretion of the treating physician.

6.2.5 Outcomes measures

The primary outcome measure was health related quality of life as assessed by the SF-12. Secondary outcome measures included cardiovascular risk factors such as blood pressure, BMI, self-reported smoking status and physical activity as assessed by the GPAC. Blood pressure was taken via automated measurement (Omron healthcare, Lake Forest, IL). This was recorded with the participant in a seated position after at least five minutes resting. The first blood pressure measurement was utilised. Height and weight were recorded in light clothing with shoes removed and utilising the same tape measure and scales for each individual's baseline and follow up measurements. Medication adherence was assessed by the Morisky Medication Adherence Scale.

6.2.6 Power analysis

Based on the CHOICE-AF study, in which patients were encouraged to set individual goals to manage their risk factors, and international data for HR-QoL, the sample size for the study was calculated on a minimum clinically important difference of 8.1 in the SF-

12 physical function domain (effect size of 0.75) and alpha of 0.8 and critical level of 0.05 a minimal total sample size of 60 or 30 participants per group.[304,306] Allowing for 20% loss to follow up, 72 participants were recruited (36 per group).

6.2.7 Statistical analyses

Primary analyses were conducted using SPSS for Windows (Version 23.0). Continuous variables will be reported as mean±standard deviation (SD), and categorical variables as numbers and percentages. Within subject differences between baseline and follow-up was analysed using Wilcoxon signed ranks tests for non-parametric variables (two-tailed $p<0.05$ considered significant). Between group comparisons was analysed using Students t-test, the Mann-Whitney U test (for non-normally distributed continuous data), and the χ^2 test. SF-12 data will be analysed using software licensed and provided by Optum Insight. Analysis will be limited to complete cases to avoid artificially increasing precision around the estimates by imputing values or carrying baseline values forward.

6.3 RESULTS

A total of 72 participants were randomised. Mean age of the study cohort was 65±11 years and 43.7% were female. See Table 1 for baseline characteristics. One participant in the control group did not meet the inclusion criteria and was excluded from analysis. A total of 33 participants in each arm completed the three-month final follow up. See Figure 1 for the CONSORT diagram.

6.3.1 Goal setting

Participants in the intervention arm set a mean of 3 goals. The most commonly set goal related to improving physical activity levels (32%). Other frequently used goals set included self-monitoring and management of blood pressure (24%), closely followed by weight loss (22%). Less commonly set goals related to self-monitoring of cardiovascular risk factors (e.g. lipids, glucose monitoring) at 6% and pulse self-monitoring to facilitate recognition of AF episodes (4%). See Table 2 for a summary of goals set by participants.

6.3.2 Telephone follow up

Participants in the intervention arm received a mean of 3.4±1.1 phone calls over the follow up period. Mean duration of follow up phone calls was 8.8±4.9 minutes.

6.3.3 Health related quality of life

Significant differences were evident in baseline SF-12 scores between groups with the control group demonstrating a lower mean physical component summary score, physical functioning and role physical scores (Table 3). There was a significant improvement in the mental component summary (MCS) score in the control group from baseline to follow up (Table 2). No within group differences were evident from baseline to follow up with the physical component summary (PCS) score. An improvement in the bodily pain subscale of the SF-12 occurred for the intervention group over time. The control group demonstrated an improvement in the general health, social function and role emotional subscales over time. However, there were no between group differences at final follow

up for the PCS score, MCS score or any of the SF-12 subscales (Table 3 and Figures 2 and 3).

6.3.4 Cardiovascular risk factors

Blood pressure

At baseline, no significant differences in systolic or diastolic blood pressure were observed (128±21mmHg vs 130±21mmHg for systolic BP. p=0.65 and 71±11mmHg vs 73±11mmHg for diastolic BP. p=0.30 for intervention vs control respectively). There was no significant between group differences for systolic or diastolic blood pressure (125±21mmHg vs 124±15mmHg for systolic BP, p=0.80 and 71±11mmHg vs 73±11mmHg for diastolic BP, p=0.39 for intervention vs control respectively; Table 4 and Figures 4a and b) at final follow up.

Body mass index and waist circumference

BMI did not demonstrate any significant between group differences at baseline (30.3±6.9 kg/m^2 vs 30.1±5.8 kg/m^2, p=0.87 for intervention vs control respectively). At final follow up no significant between group differences were observed for BMI (30.0±6.7kg/m^2 vs 30.2±5.9kg/m^2, p=0.90 for intervention vs control respectively) or waist circumference (104±13cms vs 104±16cms, p=0.97 for intervention vs control respectively; Table 4 and Figures 5a and b).

Smoking status

Smoking status did not differ between groups at final follow up (6.1% vs 3.0% current smokers for intervention vs control respectively and 93.9% vs 97.0% for non-smokers, p=1.0 for intervention vs control respectively; Table 4).

Medication adherence

There were no significant between group differences for medication adherence as assessed by the Morisky Medication Adherence Scale at baseline or final follow up (p=0.81 for interaction; Table 4).

Physical activity

Physical activity levels, as assessed by the General Physical Activity Questionnaire score, did not differ between groups at final follow up (8.5±1.1 vs 8.4±1.2, p=0.60 for intervention vs control respectively; Table 4).

6.4 DISCUSSION

Education and empowering individuals to achieve self-care are important elements of chronic disease management. This prospective randomised study in patients with AF, demonstrates that a nurse-led education program did not significantly impact on quality of life or cardiovascular risk factor status in a cohort of individuals with AF. Furthermore, behavioural modification, including medication adherence and physical activity levels, was not significantly improved with this intervention. These findings highlight the

complexity and need for evaluation of interventions of service delivery to ensure optimal design of care models.

6.4.1 Impact of prior interventions for AF on quality of life

Several studies have examined the impact of various interventions on quality of life in AF populations. In a single centre RCT undertaken in the Netherlands of 712 newly diagnosed AF participants, an integrated care approach in a nurse led, cardiologist supported clinic, did not significantly impact on quality of life as assessed by the SF-36 at final follow up.[147] This occurred despite a significant reduction in the primary endpoint: a composite of cardiovascular mortality and hospitalisations.[209] In both the NEAT intervention and the RCT undertaken in the Netherlands, high baseline levels of quality of life were observed and may account for the lack of observed effect. A nurse delivered home based intervention for individuals who had been admitted to hospital due to AF which included education, clinical profiling, referral on to other members of the multidisciplinary team as required and recommendations to treating physicians about gold standard care delivery according to current AF guidelines, also did not significantly impact on quality of life as assessed by the SF-12.[211] An RCT which examined an exercise based rehabilitation program for individuals who had undertaken an ablation for AF did not demonstrate any impact of quality of life in individuals at short term follow up, despite an improvement in exercise capacity as demonstrated by peak VO_2.[146]

6.4.2 Cardiovascular risk factor management in AF

Numerous studies have examined the impact of cardiovascular risk factor management on outcomes in AF populations. Several studies have utilised a single centre physician led model in dedicated risk factor clinics. The first of these studies assessed the impact of a comprehensive risk factor management strategy on AF symptom burden as assessed by the AF symptom severity questionnaire (AFSS) in a RCT of 150 symptomatic overweight and obese individuals with AF.[140] After 15 months of follow up AF burden, symptoms and symptom severity significantly decreased in the intervention group compared to control.

In the RACE 3 study, a different approach to cardiovascular risk factor management was undertaken with a combination of pre-defined pharmacological therapy and lifestyle measures.[148] In this study of 245 individuals with persistent AF and early heart failure, the intervention consisted of three pharmacological therapies (MRAs, statins, ACE-I or ARBs) in addition to an exercise based cardiac rehabilitation program. Furthermore, participants in the intervention arm attended a specialist nurse led outpatient clinic at 6 weekly intervals to assist with self-management of both conditions. This intervention demonstrated a significantly enhanced likelihood of sinus rhythm, as demonstrated by Holter monitoring, after 12 months of follow up in the intervention group compared to the control group.[148]

6.4.3 Risk factor management post catheter ablation for AF

In the post ablation cohort, aggressive cardiovascular risk factor management has demonstrated a greater likelihood of freedom from AF in those participating in the

intervention. These studies have largely been undertaken in single centre physician led models and have simultaneously targeted numerous cardiovascular risk factors in a dedicated clinic. The first of these studies allocated 149 individuals, who had been referred for catheter ablation for symptomatic AF, to an intervention or control arm based on their decision to participate or decline the risk factor management program.[142] The risk factor management program in this study utilised a comprehensive approach including weight reduction, physical activity, dyslipidaemia, hypertension, OSA, diabetes, smoking cessation and alcohol reduction. The clinic is solely dedicated to management of these risk factors with medical management of the arrhythmia occurring outside of this clinic. Follow up occurred on a three-monthly basis, or more frequently if required, and participants were required to maintain a lifestyle journal outlining all food and drink consumption, exercise undertaken and blood pressure results which was reviewed at each clinic visit. This intervention resulted in a greater likelihood of arrhythmia freedom in the intervention group compared to control after a mean follow up of approximately 3.4 years (HR 4.8, 95% CI 2.04-11.04; $p<0.001$).[141] The effectiveness of this intervention was confirmed at longer term follow up of approximately five years, with the same risk factor management program resulting in an almost six fold increase in the likelihood of freedom from AF in individuals who achieved the greatest degree of weight loss (≥10%) compared to those who lost the least amount or gained weight (HR 5.9; 95% CI 3.4-10.3; $p<0.001$).[142] However, although this strategy has been proven to be cost effective[144], the impact on clinical events including hospitalisations and mortality has not been examined, nor has the impact of this intervention on health related quality of life. Furthermore, there is no randomised data to observe the impact of this intervention in the post AF ablation cohort.

6.4.4 Impact of the NEAT intervention on HRQOL and risk factor status

The NEAT intervention did not significantly impact on either quality of life or cardiovascular risk factor status in this cohort of individuals with AF. These results are largely consistent with numerous other studies in AF populations, delivered by nurses and allied health practitioners, which have not demonstrated any impact on QOL.[146,147,211] To date few interventions have positively impacted on this outcomes. One study, examining the impact of nurse led education in a cohort undertaking AF ablation, demonstrated improvement in two subscales of the SF-36 questionnaire.[222] Recently, the quality of life substudy of RACE 3 demonstrated a greater improvement in the intervention arm for the physical functioning, physical role limitations and general health subscores of the SF-36 at one year follow up compared to usual care.[307] Despite the well-recognised importance of patient reported outcomes such as quality of life, inherent difficulties in choosing between general and disease specific questionnaires has also been acknowledged in addition to the large sample sizes often required to demonstrate statistically significant differences.[308]

The lack of impact on cardiovascular risk factor status is speculated to be in part attributable to the lack of intensity of the risk factor management program in addition to the short follow up duration. In the NEAT intervention there was only one face to face visit with the rest of the intervention delivered by telephone follow up. This may lead to a lack of accountability for participants who were not required to maintain a lifestyle journal nor undertake any further in-clinic visits. Furthermore, there were no pre-specified risk factor targets to work towards with participants instead encouraged to set their own self-defined lifestyle goals. A comprehensive approach targeting numerous risk

factors simultaneously was not undertaken in this study, with individuals instead working on risk factor or behavioural goals of their choice. The Substrate Modification with Aggressive Blood Pressure Control in AF (SMAC-AF) study, highlighted the need for a comprehensive approach to cardiovascular risk factor management. In this study, targeting a single risk factor (blood pressure) did not significantly impact on the risk of atrial arrhythmia recurrence in individuals post catheter ablation for AF.[149]

Several other possibilities must be considered in light of the lack of observed effect in this study. The structure of this intervention, in which education and follow up was provided by a nurse without the construct of a multidisciplinary team, may have been a contributory factor. Whilst other studies have demonstrated improved cardiovascular risk factor status with the intervention undertaken by a single physician provider, this has been in the context of support from an electrophysiologist to re-enforce advice provided in this clinic.[141,142] Furthermore, the impact on cardiovascular risk factor status was evident after longer term follow up of 3.5 and 5 years respectively in these studies.[141,142] It is possible that the short follow up duration in part accounted for the lack of improvement in cardiovascular risk factor status.

6.4.5 Future directions

This study has highlighted several areas for consideration in the design of future studies examining alternative models of care delivery in AF. Building on work undertaken to date several factors are likely to contribute to improved patient outcomes in this population. These include provision of multidisciplinary care with the involvement of a specialised cardiologist[133,212] and nurse[209,212] at its core. Referral to other members of the

multidisciplinary team is likely to further enhance outcomes although the optimal team compositions remains unknown and, given the heterogenous nature of the conditions, is likely to require an individualised approach. Indeed, the impact of a multidisciplinary approach in AF has not been fully explored, although the RACE 3 study involved the use of a specialist nurse, physiotherapist and dietician where required. This study did demonstrate an increased likelihood of sinus rhythm at final follow up, although little clinically significant difference in cardiovascular risk factor status. Interventions that have demonstrated marked improvements in cardiovascular risk factor status in AF have simultaneously addressed multiple factors in a single intervention within a dedicated clinic.[141,142] The impact of a clinic combining AF care and risk factor management in a single intervention has not been tested to date.

6.5 LIMITATIONS

Whilst this study examined the impact of a brief nurse led education and risk factor management program on outcomes in a random sample of individuals with AF, several limitations exist. Firstly, our sample represents a well-treated cohort overall at baseline which is not generally comparable to other reported AF populations. For example, a global anticoagulation registry (GARFIELD) demonstrated the appropriate use of OAC in 63.1% of individuals whilst in our cohort this occurred in 97.2% and 97.1% of individuals for the intervention and control groups respectively.[266] This represents a sample with limited opportunity for improvement and is reflective of the high level of specialist care given to most participants in this cohort.

Secondly, the short-term duration of follow up in this study allows little time to significantly impact on parameters such as cardiovascular risk factors which have only demonstrated improvement in studies with longer follow up duration. Furthermore, although this was a generally overweight and obese cohort, blood pressure was well controlled at baseline and therefore the impact on risk factor outcomes is likely to be minimal, as weight management generally requires longer and more intense follow up management. Health related quality of life has been difficult to impact on in prior studies related to AF interventions and highlights the difficulty associated with impacting on this outcome measure. Finally, as this was a feasibility study, the limitation of the small sample size needs to be acknowledged and could, in part, account for the lack of impact observed, particularly in relation to cardiovascular risk factor status as the study was not powered for this outcome.

6.6 CONCLUSIONS

A brief nurse delivered education and risk factor management program, limited to one single clinic visit and telephone follow up, did not significantly impact on health-related quality of life in individuals with AF after short term follow up. This intervention had no significant impact on cardiovascular risk factor outcomes including blood pressure, smoking status, alcohol consumption, physical activity levels or weight reduction. Future interventions should focus on evaluating the impact of a comprehensive approach to AF management including intense and targeted control of cardiovascular risk factors to improve outcomes in this population.

Table 1: Baseline characteristics of study participants

	Intervention (n=36)	Control (n=36)	P value
Age, mean±SD	63±12	66±10	0.23
Females, n (%)	16 (44.4)	16 (45.7)	1.0
Heart failure, n (%)	5 (13.9)	4 (11.4)	1.0
Hypertension, n (%)	23 (63.9)	26 (74.3)	0.44
Diabetes, n (%)	6 (16.7)	6 (17.1)	1.0
Stroke/TIA, n (%)	4 (11.1)	5 (14.3)	0.74
Vascular disease, n (%)	4 (11.1)	3 (8.6)	1.0
Systolic BP, mean±SD	128 ± 21	130 ± 21	0.65
Diastolic BP, mean±SD	71 ± 11	73 ± 11	0.30
BMI, mean±SD	30.3 ± 6.9	30.1 ± 5.8	0.87
Waist, mean±SD	103 ± 15	105 ± 20	0.67
Current smoker, n (%)	1 (2.8)	1 (2.9)	0.75
Non-smokers, n (%)	35 (97.2)	34 (97.1)	
Any alcohol intake, n (%)	29 (80.6)	25 (71.4)	0.42
Alcohol bingers, n (%)	4 (11.1)	9 (25.7)	0.14
CHA_2DS_2-VASc score, mean±SD	2.4±1.4	2.5±1.4	0.78
CHA_2DS_2-VASc 0, n (%)	3 (8.3)	2 (5.7)	0.91
CHA_2DS_2-VASc 1, n (%)	7 (19.4)	7 (20.0)	
CHA_2DS_2-VASc ≥ 2, n (%)	26 (72.2)	26 (74.3)	
Appropriate OAC, n (%)	35 (97.2)	34 (97.1)	1.0
OAC			0.84
Warfarin, n (%)	5 (13.9)	4 (11.4)	
DOAC, n (%)	21 (58.3)	24 (68.6)	
Other antithrombotic	3 (8.3)	2 (5.7)	
None, n (%)	7 (19.4)	5 (14.3)	
MMAS			.08
Low, n (%)	9 (25.7)	9 (27.3)	
Medium, n (%)	7 (20.0)	14 (42.4)	
High, n (%)	19 (54.3)	10 (30.3)	
GPAC, mean±SD	8.6±1	8.5±1	0.67

(TIA – transient ischaemic attack, BP – blood pressure, OAC – oral anticoagulation, DOAC – direct oral anticoagulant, MMAS – Morisky Medication Adherence Scale, GPAC – General Physical Activity Questionnaire)

Table 2: Participant goal setting by type

	Goal 1 (%)	Goal 2 (%)	Goal 3 (%)	Total (%)
Physical activity	34	50	12	32
Weight loss	46	6	12	22
Dietary interventions not focussing on weight loss	6	3	0	3
Smoking cessation	3	0	0	1
Hypertension management	6	24	42	24
Improved self-monitoring	3	9	18	10
Social interaction	0	0	6	3
Medication adherence	0	3	6	3
Other	3	6	6	3

Table 3: SF-12 summary and subscale scores at baseline and follow up

	Study group	Baseline median (IQR)	3 month follow up median (IQR)	Change over time median (IQR)	Difference between groups at baseline (p value)	Difference between groups at follow up (p value)	Difference between groups over time (p value)	Difference within groups over time (p value)
PCS	I	51 (35-55)	51 (43-57)	1 (-2-4)	0.03	0.03	0.59	0.19
	C	41 (33-48)	45 (37-50)	2 (-4-11)				0.17
MCS	I	52 (44-56)	53 (49-57)	1 (-3-8)	0.42	0.47	0.50	0.23
	C	50 (41-55)	52 (47-56)	3 (-3-11)				0.05
Physical functioning	I	75 (31-100)	75 (50-100)	0 (0-0)	0.04	0.03	0.69	0.40
	C	50 (25-75)	50 (25-88)	0 (-25-25)				0.47
Role Physical	I	75 (50-100)	75 (56-100)	0 (-9-22)	0.01	0.03	0.39	0.39
	C	50 (25-75)	50 (50-83)	0 (-13-31)				0.12
Bodily Pain	I	75 (50-100)	100 (75-100)	0 (0-25)	0.12	0.01	0.83	0.003
	C	50 (25-100)	75 (50-100)	0 (-25-25)				0.16
General Health	I	60 (25-85)	60 (43-85)	0 (-20-25)	0.17	0.63	0.10	0.52
	C	60 (25-60)	60 (25-85)	0 (0-35)				0.01
Vitality	I	50 (25-75)	50 (50-75)	0 (0-25)	0.19	0.12	0.27	0.24
	C	38 (25-50)	50 (25-63)	25 (0-25)				0.32
Social functioning	I	75 (50-100)	100 (75-100)	0 (0-25)	0.44	0.56	0.51	0.06
	C	75 (50-100)	100 (63-100)	0 (0-25)				0.02
Role emotional	I	88 (50-100)	88 (75-100)	0 (0-22)	0.16	0.17	0.25	0.34
	C	75 (38-100)	75 (63-100)	13 (0-25)				0.02
Mental Health	I	75 (53-88)	75 (63-88)	0 (-13-13)	0.19	0.19	0.95	0.30
	C	63 (50-88)	75 (63-88)	0 (-4-13)				0.15

(PCS - physical component summary score, MCS – mental component summary score, I – intervention study group, C- control study group

Table 4: Risk factors and medication adherence measures at baseline and follow up

	Baseline			Follow up		
	Intervention (n=36)	**Control (n=36)**	**P value**	**Intervention (n=33)**	**Control (n=33)**	**P value**
Systolic BP mmHg, mean±SD	128 ± 21	130 ± 21	0.65	125±21	124±15	0.80
Diastolic BP mmHg, mean±SD	71 ± 11	73 ± 11	0.30	71±11	73±11	0.39
BMI kg/m^2, mean±SD	30.3 ± 6.9	30.1 ± 5.8	0.87	30.0±6.7	30.2±5.9	0.90
Waist cms, mean±SD	103 ± 15	105 ± 20	0.67	104±13	104±16	0.97
Current smoker, n (%)	1 (2.8)	1 (2.9)	0.75	2 (6.1)	1 (3.0)	1.0
Non-smokers, n (%)	35 (97.2)	34 (97.1)		31 (93.9)	32 (97.0)	
Any alcohol intake, n (%)	29 (80.6)	25 (71.4)	0.42	28 (84.8)	26 (78.8)	0.75
Alcohol bingers, n (%)	4 (11.1)	9 (25.7)	0.14	6 (18.2)	6 (18.2)	1.0
Appropriate OAC, n (%)	35 (97.2)	34 (97.1)	1.0	31 (93.9)	32 (97.0)	1.0
OAC						
Warfarin, n (%)	5 (13.9)	4 (11.4)	0.84	4 (12.1)	3 (9.1)	0.65
DOAC, n (%)	21 (58.3)	24 (68.6)		18 (54.5)	23 (69.7)	
Other antithrombotic, n (%)	3 (8.3)	2 (5.7)		3 (9.1)	2 (6.1)	
None, n (%)	7 (19.4)	5 (14.3)		8 (24.2)	5 (15.2)	
MMAS						
Low, n (%)	9 (25.7)	9 (27.3)	0.08	6 (18.2)	4 (12.5)	0.81
Medium, n (%)	7 (20.0)	14 (42.4)		14 (42.4)	15 (46.9)	
High, n (%)	19 (54.3)	10 (30.3)		13 (39.4)	13 (40.6)	
GPAC, mean±SD	8.6±1	8.5±1	0.67	8.5±1.1	8.4±1.2	0.60

(BMI – body mass index, OAC – oral anticoagulation, DOAC – direct oral anticoagulant, MMAS – Morisky Medication Adherence Scale, GPAC – General Physical Activity Questionnaire)

Figure 1: CONSORT diagram

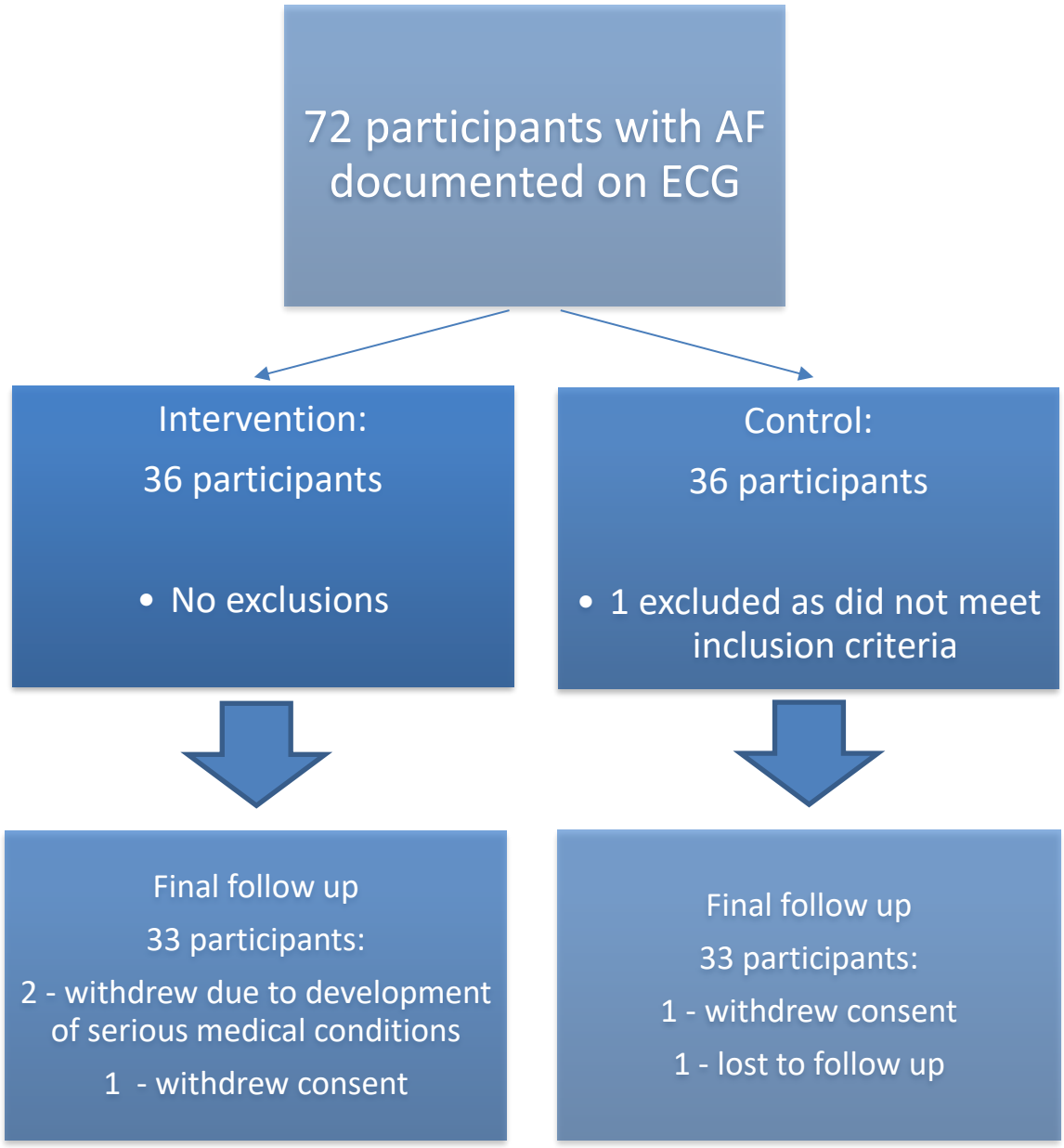


Figure 2: SF-12 summary component scores at final follow up

(PCS – Physical component summary score, MCS – mental component summary score.

Error bars represent interquartile range)

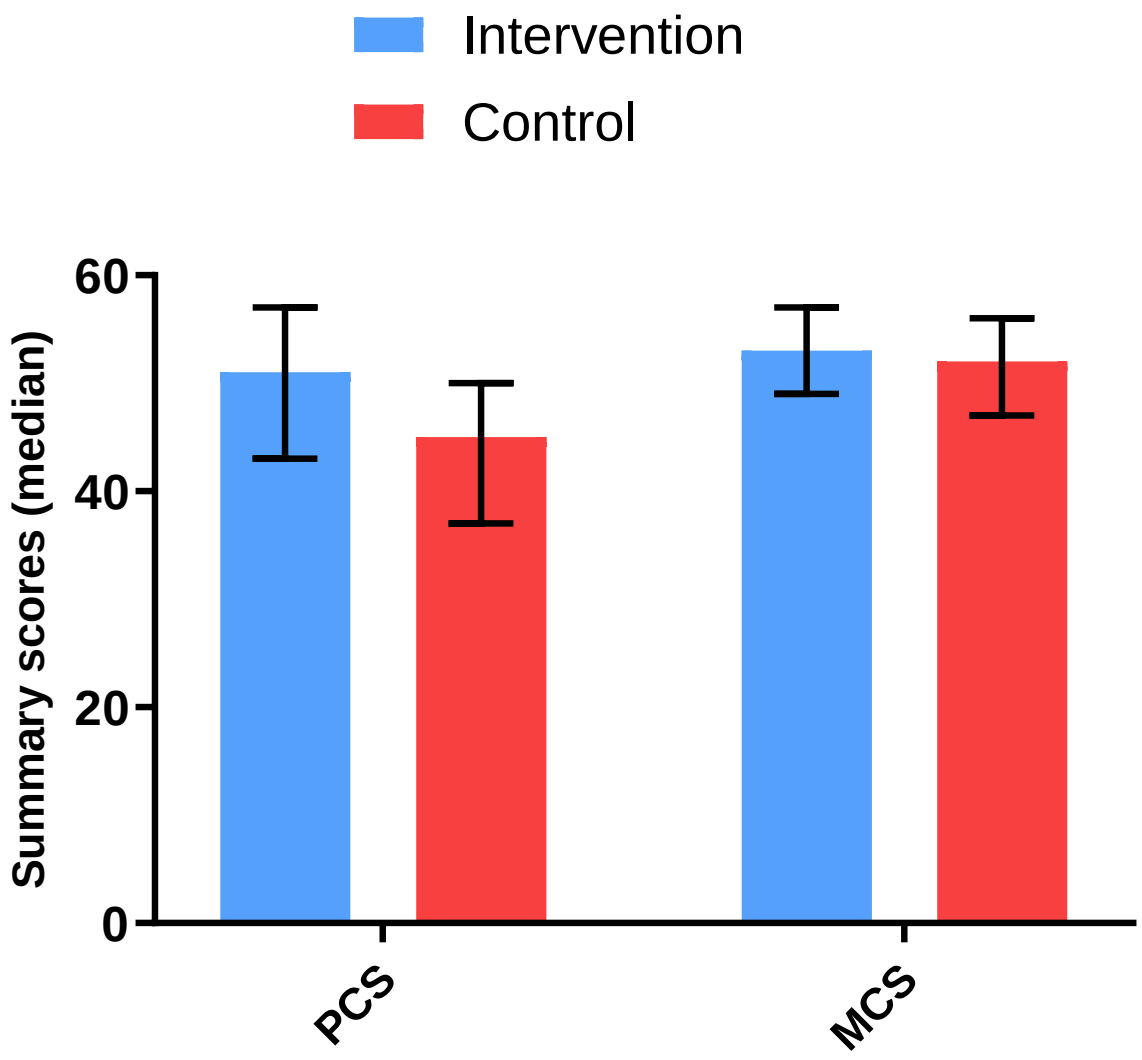
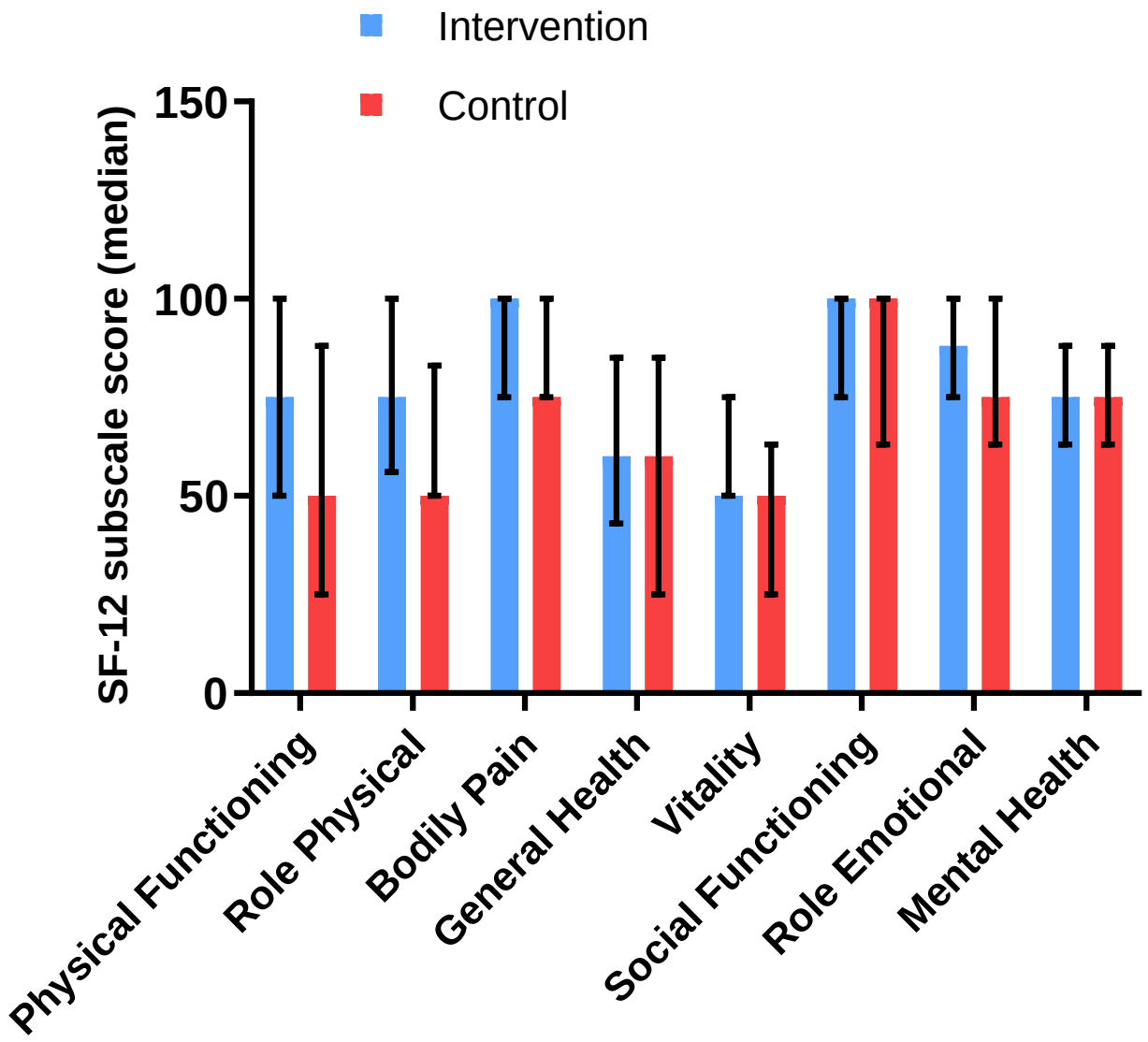


Figure 3: SF-12 subscale outcomes at final follow up

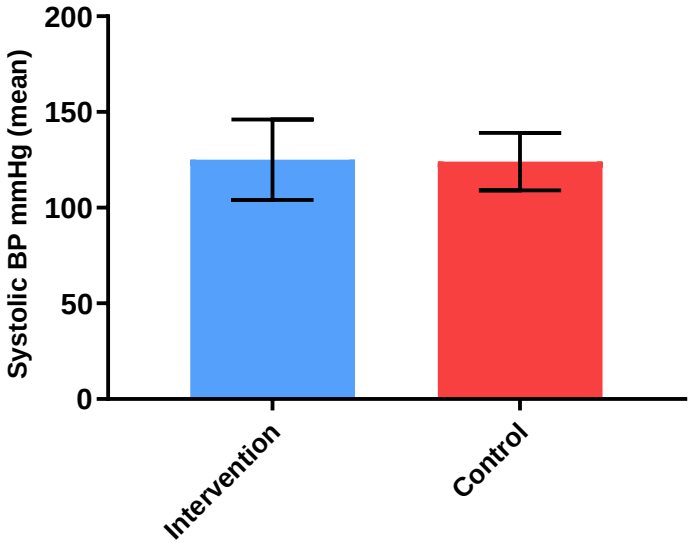
Error bars represent interquartile range



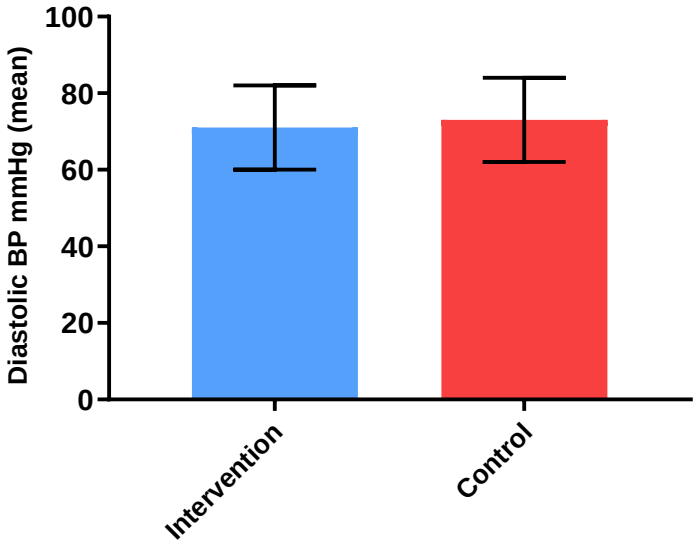
Figures 4a and b: Systolic and diastolic blood pressure at final follow up

Error bars represent standard deviation

a)



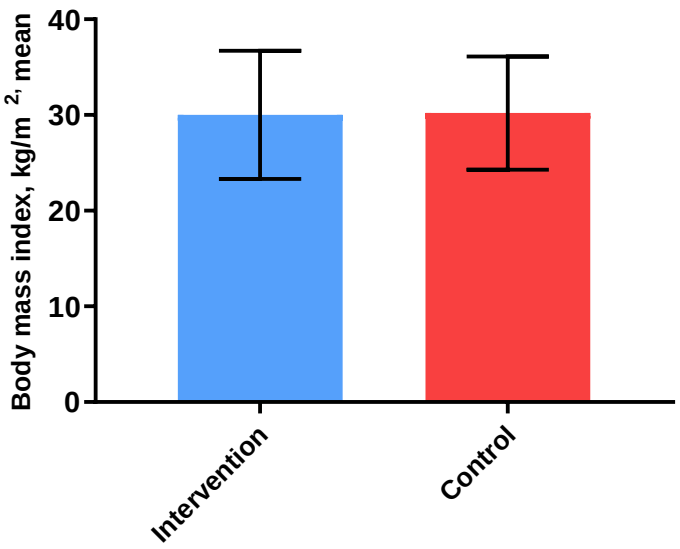
b)



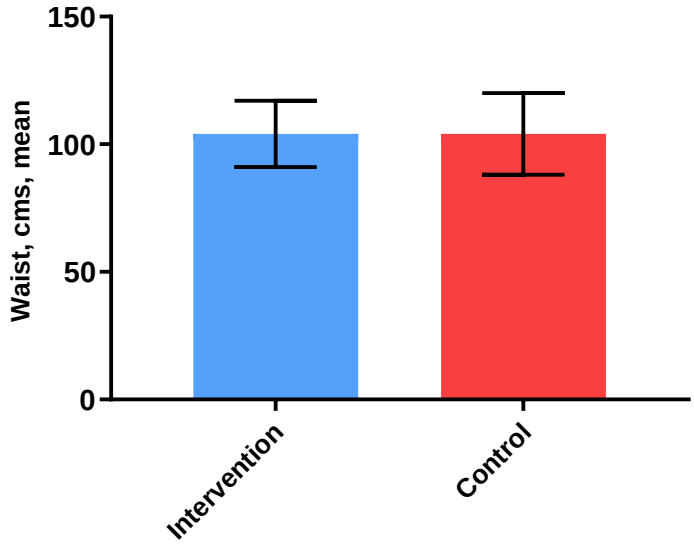
Figures 5a and b: BMI and waist circumference at final follow up

Error bars represent standard deviation

a)



b)



Chapter 7: Polypharmacy and Atrial Fibrillation

7.1 INTRODUCTION

7.1.1 Background

In many countries ageing populations and the rising numbers of concomitant cardiovascular risk factors are contributing to the increasing prevalence of AF and other chronic diseases.[309,310] A Swedish registry study of 272,186 patients with incident AF reported that 69.5% of patients had at least one of seven other long term co-morbid conditions compared to 29.2% in matched controls.[311] A United Kingdome (UK) Biobank study of 3651 patients aged 40-70 years with self-reported AF found the presence of at least one other self-reported long-term co-morbidity in 80.4% of participants, compared to 65.3% of 498,986 controls.[312]

Pharmacotherapy is a cornerstone in the management for AF and many of the co-morbidities common in AF patients, including hypertension, heart failure, coronary artery disease and diabetes. Disease specific treatment guidelines recommend the prescribing of medication for many patients, and combination therapy is common in those with moderate to severe disease.[128,313-317] For patients with multi-morbidity the potential benefit of combining evidence-based therapies needs to be balanced with the risk of adverse health outcomes. Definitions of polypharmacy have varied in research studies, with the most common being the use of five or more medications,[318] although there is evidence suggesting a continuum of risk.[319] The challenge of adjusting for multi-morbidity is well-recognised.[320] Many studies have focused on adverse outcomes in older patients over 65 years. These harms may include increased mortality,[178,321-323] adverse

drug reactions and events,[324,325] falls,[178,321,326,327] increased hospitalisations,[178,321,322,328,329] lower quality of life,[330,331] increased healthcare costs,[332] and medication burden on patients and carers.[333]

7.1.2 Polypharmacy and AF

Comparatively little research has been done on the prevalence of polypharmacy in AF patients, whether this is clinically appropriate or inappropriate, and possible associated adverse health outcomes. Polypharmacy prevalence has ranged from 40% to 95% depending on the setting, study population, ascertainment criteria and methods[334,335] . Some medications commonly used by AF patients, including antihypertensive agents and anticoagulation agents, are leading causes of adverse drug events in the elderly[325]. Many patients also take non-prescription or alternative medicines which carry their own potential for harm and may interact with prescribed medicines[336]. In a cross-sectional study of chronic disease clusters in elderly hospitalised patients, AF with co-morbid heart failure showed the third strongest association with polypharmacy [337]. Post hoc analyses of two direct acting oral anticoagulant trials suggest that polypharmacy may be independently associated with adverse health outcomes[181,182].

As polypharmacy in AF may be an under-appreciated risk factor for harm irrespective of anticoagulation status, we performed a systematic review and meta-analysis to summarise the best available evidence. In addition, we discuss opportunities to identify and minimise inappropriate polypharmacy in patients with AF and explore the potential role of deprescribing to improve health outcomes.

7.2 METHODS

7.2.1 Literature search

This systematic review was registered with PROSPERO (Registration number CRD42018105298) and was undertaken in accordance with the PRISMA guidelines.[338] PubMed and Embase database were searched without date restriction until 31 July, 2018. Keywords used included ‘atrial fibrillation’, ‘polypharmacy’, ‘polypharmacology’, ‘pharmacoepidemiology’, ‘cardiovascular outcomes’, 'health outcomes', 'cerebrovascular accident’, 'bleeding', 'mortality’, ‘death’, ‘hospitalisation’, ‘hospital admission’, ‘quality of life’, ‘transient ischaemic attack’ and ‘falls’. See Table 1 for an outline of the full search strategy in PubMed.

7.2.2 Inclusion and exclusion criteria

Studies were eligible for inclusion if they were prospective randomised controlled trials or of observational design, had a minimum follow up of three months and were published in English. Outcomes eligible for inclusion included all-cause or cardiovascular mortality, all-cause or cardiovascular hospitalisations, stroke and systemic embolism, TIA, major bleeding (according to the International Society of Thrombosis and Haemostasis definition as bleeding associated with: reduction in haemoglobin of 20g/L over a 24 hour period, transfusion of two or more units of red blood cells, fatal bleeding or bleeding at a critical site e.g. retroperitoneal, pericardial[339]), non-major bleeding, intracranial bleeding, quality of life and falls. These outcomes were selected as they are either commonly studied in the AF population, or of significant clinical importance. Studies were excluded if they were of retrospective design, were not published in English or examined other

health outcomes, economic costs or outcomes which were not directly health-related, including drug interactions without clinical sequelae.

7.2.3 Study selection and data extraction

Two study investigators independently reviewed all articles retrieved by the electronic search to determine eligible studies. Any discrepancies were discussed and resolved by consensus decision. Data extracted from relevant studies included: first author, year of publication, total number of participants, gender of included participants, mean age, follow up period, AF ascertainment, polypharmacy definition, types of medicines collected from participants, endpoint adjudication and covariates adjusted for. The risk of bias in each of the included studies was assessed using the Quality in Prognosis Studies tool[243], and subjectively characterised as low, moderate or high.

7.2.4 Statistical analysis

The risk estimate for each outcome was independently extracted by two study investigators according to two levels of polypharmacy (moderate and severe). The most adjusted model in each study was utilised. Heterogeneity across studies was assessed using the I^2 statistic. Publication bias was assessed by visual inspection of funnel plots of effect size against standard error. A two-tailed p value of <0.05 was considered statistically significant. All analyses were performed using a random effects model in RevMan Version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collection, 2014.

7.3 RESULTS

A total of 790 articles were identified from the electronic search, with 64 retrieved for full text review. Of these, 59 did not meet the inclusion criteria, with the remaining 5 studies eligible. (Figure 1). The prevalence of polypharmacy ranged from 40.1% (≥5 cardiovascular medicines) to 76.5% (≥5 medicines).[334] Two of these studies reported on common outcomes, and were able to be utilised for a meta-analysis,[181,182] with the other two studies each looking at unique outcomes including cardiovascular mortality[334] and quality of life.[340] Mean age of the two studies included in the meta-analysis was 71.5±9.63 years with a mean follow up of 682±35.4 days. The total study population of the meta-analysis was 32,825 individuals of which 37.4% were female. In the two studies included in the meta-analysis risk of bias was assessed as low in one study,[182] and moderate in the other (see Table 2 for assessment of risk of bias).[181]

7.3.1 Polypharmacy definition

There was slight variation in the definition of polypharmacy used across the two studies included in the meta-analysis. For the purpose of this study we have classified moderate polypharmacy as the group of 5-9 medications in one study[182] and 6-8 in the other,[181] with severe polypharmacy classified as ≥10 and ≥9 medicines respectively. The reference group was 0-4 medicines and 0-5 medicines respectively. See Table 3 for an outline of studies eligible for inclusion.

7.3.2 All-cause mortality

Both moderate and severe polypharmacy were associated with significant increases in all-cause mortality (HR 1.33; 95% CI 1.18-1.49; p<0.01; HR 1.72; 95% CI 1.23-2.41; p=0.002 respectively; see Figure 1). There was no evidence of statistical heterogeneity with moderate polypharmacy (I^2=33%; p=0.22), however, there was evidence of heterogeneity with severe polypharmacy (I^2=86%; p=0.008).

7.3.3 Stroke or systemic embolism

Neither moderate nor severe polypharmacy was associated with stroke or systemic embolism (HR 1.15; 95% CI 0.98-1.36; p=0.09; HR 1.26; 95% CI 0.84-1.89; p=0.26 respectively; Figure 2). Moderate polypharmacy did not demonstrate any evidence of statistical heterogeneity with this outcome (I^2=27%; p=0.24), with heterogeneity evident at the severe polypharmacy level (I^2=77%; p=0.04).

7.3.4 Major bleeding

Major bleeding was significantly increased with both moderate and severe polypharmacy (HR 1.34; 95% CI 1.15-1.58; p<0.01; HR 1.80; 95% CI 1.55-2.09; p<0.01 respectively; Figure 3). There was no evidence of statistical heterogeneity with either moderate or severe polypharmacy (I^2=38%; p=0.02; I^2=0%; p=0.50 respectively).

7.3.5 Intracranial bleeding

There was no impact of moderate or severe polypharmacy on intracranial bleeding (HR 1.37; 95% CI 0.77-2.44; p=0.29; HR 1.40; 95% CI 0.86-2.28; p=0.18 respectively; see

Figure 5). Whilst there was evidence of statistical heterogeneity at the moderate polypharmacy level (I^2=77%; p=0.04), there was no heterogeneity noted with severe polypharmacy with this outcome (I^2=51%; p=0.15).

7.3.6 Clinically relevant non-major bleeding

Both moderate and severe polypharmacy was associated with an increased risk of clinically relevant non-major bleeding (HR 1.12; 95% CI 1.03-1.22; p<0.01; HR 1.48; 95% CI 1.33-1.64; p<0.01 respectively; see Figure 6). Neither moderate nor severe polypharmacy demonstrated any evidence of statistical heterogeneity for this outcome (I^2=0%; p=0.49; I^2=0%; p=0.39 respectively).

7.3.7 Cardiovascular death

Post hoc analysis of the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) study, which examined the impact of polypharmacy of cardiovascular medicines only (defined as >5 medicines), demonstrated an increase in the risk of cardiovascular death (unadjusted HR 1.47; 95% CI 1.18–1.82; p<0.001) and stroke (unadjusted HR 1.17; 95% CI 0.85–1.60; p=0.34).[334] The adjusted relative risk for cardiovascular death was 1.30 (95 % CI 1.03–1.64; p=0.03).

7.3.8 Quality of life

Post hoc analysis of the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) Study, which examined quality of life in 1762 elderly individuals (>75 years) with AF, demonstrated that >7 medicines, was associated with a significant reduction in quality of

life as assessed by the EQ-5D (parameter estimate -0.06, p=0.03).[340] There was no impact at other polypharmacy levels (1-3 or 4-6 medicines). Both moderate and severe polypharmacy was associated with a reduction in the physical component summary score of the SF-12, but not the mental component summary score.

7.4 DISCUSSION

The increasing complex requirements for the management of patients with AF has involved the use of multiple proven pharmacotherapies. This is compounded further by the need to treat co-existent conditions which often have a determining role on the AF process. Polypharmacy is increasingly recognised to be associated with adverse outcomes in chronic disease. This systematic review and meta-analysis evaluates the impact of polypharmacy on outcomes in a population with AF. In patients with AF, it demonstrates the following:

1. Moderate and severe polypharmacy is associated with a 33% and 72% increase in all-cause mortality respectively;
2. The risk of major bleeding is increased by 34% and 80% for moderate and severe polypharmacy respectively and;
3. Clinically relevant non-major bleeding increased by 12% and 48% respectively with moderate and severe polypharmacy;
4. Polypharmacy is associated with an increased risk of cardiovascular death, reduced quality of life and poorer physical functioning.

To date, there has been a paucity of studies examining the impact of polypharmacy on health outcomes in patients with AF, and few have used outcome data from prospective

studies with independent endpoint adjudication as in the present meta-analysis. Given the increasing prevalence of concomitant risk factors in patients with AF,[309,311] it is likely that, similar to other chronic diseases, the use of multiple medicines is driven by comorbid conditions.[341 342] Adjustment for co-morbidities is a challenge in polypharmacy research and although the studies in our meta-analysis varied in this regard, significant hazard ratios were found in both studies with the exception of stroke or systemic embolism and intracranial bleeding.

7.4.1 Possible reasons for adverse outcomes with polypharmacy

The mechanisms underlying the adverse outcomes associated with polypharmacy are likely to be multifactorial and may vary between outcomes. These could include (i) reduced adherence and persistence to prescribed regimes (ii) drug-drug and drug-disease interactions and (iii) adverse drug reactions.

Adherence and persistence to prescribed regimes has been inversely correlated with number of medicines used.[343] In the heart failure population the number of drug-related negative outcomes, including inadequately treated health issues, inadequate doses or duration of treatment and non-adherence, has demonstrated a significant correlation with increasing number of medicines prescribed.[344] In one of the studies included in our meta-analysis 42.4% of patients taking ≥10 medications discontinued their anticoagulant, compared to 35.4% taking 5-9 medications and 31.8% taking 0-4 medications. Polypharmacy may similarly have affected persistence with other medications. Non-adherence to Dabigatran in patients with AF, defined as less than 20% adherence, has been shown to be associated with an increase in all-cause mortality and stroke in an observational registry (HR 1.54; 95% CI 1.20 to 1.97; $p<0.01$).[345]

Drug-drug and drug-disease interactions may be a contributing factor to polypharmacy associated harm. It is possible that the observed increase in bleeding risk may reflect an increased likelihood of combining certain high-risk medications with anticoagulants.[346] Many commonly used agents have potential interactions with anticoagulants including non-steroidal anti-inflammatory agents (NSAIDs), antiplatelet agents, or others with antiplatelet effects including selective serotonin reuptake inhibitors. In the ARISTOTLE post hoc analysis, Aspirin, NSAIDs or Prednisone were used by 13.8% in those taking 0-5 medications, 31.7% taking 6-8, and 49.7% taking ≥9 medications. The risk of drug-drug interactions likely increases with growing numbers of medicines prescribed, with the risk identified to be as high as 82% in individuals prescribed seven or more medicines.[347] Many of these interactions may be under-recognised by clinicians and possibly result in further use of medicines to treat adverse drug reactions. Compounding this situation, current guidelines are often single disease focussed, with little insight for clinicians concerning management of the comorbid individual, and the potential for interactions with drug therapy for other conditions[348]. The use of over-the-counter medicines is also under-recognised, with the risk of potentially unknown adverse interactions. A study of 250 individuals attending an anticoagulation clinic in Denmark demonstrated that almost 50% of individuals were taking alternative medicines including fish oil, and some with potential for interactions with warfarin. More research is needed to investigate whether adverse bleeding outcomes in AF patients using polypharmacy are associated with certain drug-disease interactions or combinations of pharmacotherapy.

Adverse drug reactions (ADRs) are associated with significant morbidity and mortality and in elderly patients may account for 1 in 10 hospitalisations.[325] As more medicines are taken the risk of adverse drug reactions increases. Anticoagulants and

cardiovascular agents, commonly used in the AF population, are associated with bleeding and falls which may contribute to increased all-cause mortality either as a direct effect or secondary to discontinuation of therapy.

7.4.2 Other possible polypharmacy related adverse health outcomes

Our systematic review did not identify any prospective studies examining the relationship between polypharmacy and hospitalisation or falls. A longitudinal study has shown an increase in age, multi-morbidity and polypharmacy in heart failure patients over the years 1998 to 2008.[342] The question of whether a similar trend may be contributing to observed increased AF hospitalisations deserves further investigation.[349,350] Many studies in older patient populations have found polypharmacy to be associated with falls, and an unadjusted association was found in a small retrospective study of AF patients ($p=0.027$).[351] Multivariate analysis revealed three independent fall predictors; benzodiazepine use, paroxysmal AF and history of hypertension. Falls in older people are typically multifactorial in nature. In a retrospective study of 211 older patients presenting to an emergency department due to falls, AF, neurological disorders and age ≤81 years were found to be independent predictors of non-accidental falls, with a history of AF increasing the risk 2.5 fold.[352] This was after multivariate adjustment for polypharmacy and other predictors of non-accidental falls. Other data has demonstrated an independent association between AF and hip fracture,[353] and raises the possibility that polypharmacy may be a contributing factor to this observation. 8.8% of patients with severe polypharmacy in the ARISTOTLE study had a history of falls during the year prior to enrolment, compared to 2.3% in those taking 0-5 medications ($p<0.001$).[181] A separate post hoc analysis of the ARISTOTLE study found that patients with a history of falls had an increased adjusted risk of major bleeding and all-cause mortality, and a more than

three-fold increased risk of falling during the trial.[354] Larger prospective studies are needed to determine the mechanisms contributing to falls in AF patients and the possible role of polypharmacy.

Other outcomes from our systematic review were identified from single studies and warrant future research to confirm their findings. In the secondary analysis of the BAFTA study, gender, number of medications and disability were found to be independently associated with quality of life in elderly AF patients. Those taking >3 medications reported poorer quality of life, which was observed more consistently in those taking >7 medications. Possible confounders in this study include disease severity and multi-morbidity, and further research is needed to confirm these findings.

7.4.3 Opportunities to improve outcomes

Strategies to reduce inappropriate use of pharmacotherapy might improve outcomes. De-prescribing has been defined as 'the process of withdrawal of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes.[355] Various methods for identifying inappropriate medication use have been described including the Medication Appropriateness Index, the Beers criteria and STOPP/START criteria.[356] Guidelines for safe dose reduction, tapering and cessation of various drug classes, including statins, antiplatelet agents, proton pump inhibitors, sulfonylureas and benzodiazepines are available.[357,358] Clinical knowledge and judgement is needed when applying these in practice, with a consideration of the patient's views, prognosis and treatment goals. Recently, de-prescribing has been shown to be safe in a small study examining the use of de-prescription of non-evidence based medicines in the heart failure population.[359] A cluster randomised trial demonstrated that the de-prescription of antihypertensive and/or lipid lowering medications in those at low

cardiovascular risk can be safely undertaken, provided that appropriate monitoring is instituted, without any significant increase in short term cardiovascular risk.[360] Other studies in older adult populations have suggested that this strategy is associated with clinically significant benefit with minimal risk of harm.[361,362]

7.4.4 Deprescribing in AF

We are unaware of any studies of deprescribing outcomes specific to patients with AF. Current AF treatment guidelines recommend avoidance of certain medications depending on the clinical context, for example antiarrhythmic drugs for rate control in those with permanent AF and aspirin monotherapy for stroke prevention.[363] The adoption of these evidence-based recommendations into practice may be improved by including a separate guideline discussion and summary of deprescribing advice. Recommendations for managing the pharmacotherapy of AF patients in the context of other common co-morbidities including hypertension, heart failure and diabetes may also help to minimise adverse outcomes.[364,365] In all healthcare settings regular reconciliation and review of a patient's medicines is a pre-requisite for identifying inappropriate pharmacotherapy, non-adherence and treatment discontinuation. New models of integrated primary healthcare including patient-centred health care homes and sharing of patient data through electronic health records may help to optimise medication use in patients with multi-morbidity.[366] Multidisciplinary integrated care provided in AF clinics also has the potential to improve outcomes by preventing, identifying and managing inappropriate polypharmacy, and improving communication with other prescribers.[367] Intervention studies of comprehensive medication review and deprescription of inappropriate pharmacotherapy are needed to evaluate whether polypharmacy is a modifiable risk factor in AF patients or represents a risk marker for adverse outcomes.

7.5 LIMITATIONS

Our study has several limitations worthy of consideration. Whilst one of the included studies in our meta-analysis adjusted for multiple confounders,[182] the other only adjusted for age, sex and geographical location.[181] Even extensive adjustment however may not account for all variables which influence prescribing and health outcomes, including frailty, falls history and other unmeasured health markers. Despite heterogeneity in adjustment, the magnitude of effect of polypharmacy on statistically significant outcomes was similar, lending strength to the conclusion of polypharmacy associated harm. Furthermore, the associated risk demonstrated a dose dependent increase, with more 'severe' levels of polypharmacy resulting in incrementally greater risk of adverse events. Other unreported factors may also impact on adverse outcomes, including the number of prescribers caring for individuals. This has been shown to be an independent predictor of adverse drug events,[324,368] with each additional specialist conferring a 19% increase in risk in a multi-centre observational study.[324] The observed increase in all-cause mortality may also be due to underuse of potentially beneficial medications. An Australian observational study of 4260 community-dwelling older men reported that both potential under-utilisation of indicated cardiovascular medicines and polypharmacy were independent predictors of cardiovascular events[178].

Both studies included in our meta-analysis are based on polypharmacy at the time of study enrolment, and the duration of polypharmacy during the study is uncertain. However, patients with multiple chronic diseases usually have a long term need for pharmacotherapy and it is likely that polypharmacy was sustained during the studies. In the ARISTOTLE post hoc analysis use of aspirin, NSAIDs and prednisone increased significantly as polypharmacy increased. It is therefore possible that polypharmacy associated harm may reflect use of high risk medications in combination with

anticoagulants, rather than the total number of medications used. Neither study defined the eligibility of non-prescription medications in their profiling, formulations such as inhalers and topical preparations or medications used only when needed. However, a sensitivity analysis which omitted herbal supplements, topical and eye medications in the ROCKET AF post hoc study also showed a dose-response association between remaining polypharmacy and efficacy and safety outcomes. The completeness and reliability of medication data used in our meta-analysis is likely strengthened by industry sponsorship of the original trials, in which the risk of adverse sequelae from potential drug interactions with new Factor Xa inhibitors in comparison to warfarin was of major interest to the sponsors.

Finally, although only two studies were available for meta-analysis, the total number of patients was 32 825 from two studies with independently adjudicated outcomes, which strengthens the evidence for polypharmacy associated harm. Our systematic review identified four studies examining this area, which demonstrates the need for future research to further confirm our findings, in addition to interventions designed to reduce the risk of polypharmacy related adverse events in AF.

7.6 CONCLUSIONS

The growing burden of AF has led to a pressing need to identify ways in which outcomes can be improved in this population. Polypharmacy is common amongst individuals with AF, and our results demonstrate that, in an anticoagulated population, it is associated with numerous adverse outcomes including increased all-cause mortality, major bleeding and clinically relevant non-major bleeding. Mechanisms underlying this risk are unclear and may be multifactorial, including the use of concomitant high-risk medications, poor

adherence or persistence to prescribed regimens, or poor communication between numerous prescribers. Further studies examining deprescription of inappropriate pharmacotherapy in patients with AF are warranted to evaluate whether polypharmacy is a modifiable risk factor.

Table 1 – Search strategy for PubMed

"atrial fibrillation"	Polypharmacy [mh] OR Pharmacoepidemiology OR prescribing pattern* [all] OR Prescription pattern* [all] OR Practice pattern, Physicians' [mh]	Stroke [all] OR Cerebrovascular accident OR Cerebro vascular accident OR CVA OR Hemorrhage [mh] OR Haemorrhag* [all] OR Haemorrhag* [all] OR Bleeding [all] OR Death* OR mortalit* OR Fatal* OR ((cardiac OR cardiovascular OR heart) AND (outcome* OR event*)) OR Hospitalisation [mh] OR Hospitalisation [all] OR "hospital admission" OR "hospital admissions" OR Health status [mh] OR "quality of life" OR HRQL OR "life quality" OR "quality adjusted life year" OR qaly OR "quality adjusted life years" OR "short form 12" OR SF-12 OR SF12 OR "short form 20" OR SF-20 OR SF20 OR "short form 36" OR SF-36 OR SF36 OR "short form 8" OR SF-8 OR SF8 OR "symptom burden" OR "Cost of illness" OR "transient ischemic attack" OR "transient ischaemic attack" OR "TIA"

Table 2 – Assessment of risk of bias in studies included in meta-analysis

	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis/ reporting
Overall rating ROCKET-AF post hoc analysis	Low	Low	Low	Low	Moderate	Low
Overall rating ARISTOTLE post hoc analysis	Low	Low	Low	Low	Moderate-high	Low

Table 3: Characteristics of studies included in the meta-analysis

Study	Year of publication	Total no. of participants	Median age	% female	Reported medication categories	Median follow up	Outcome measures	Covariates adjusted for
ROCKET - AF[182]	2016	14264	73	39.7	Reference group: 0-4 medicines, 5-9 medicines, ≥10 medicines	1.9 years	All-cause mortality, stroke, non CNS embolism, vascular death, MI, intracranial bleeding, major bleeding, non-major clinically relevant bleeding	Age, sex, BMI, region, DM, previous stroke/TIA, vascular disease, CHF, hypertension, COPD, PAF, DBP, creatinine clearance (Cockcroft-Gault), heart rate, alcohol use, and randomised treatment*
ARISTOTLE[181]	2016	18201	70	35.3	Reference group 0-5 medicines, 6-8 medicines, ≥9 medicines	1.8 years	Stroke, systemic embolism, all-cause mortality, major bleeding, intracranial bleeding, GI bleeding, clinically relevant non-major bleeding	Age, sex, country

(CNS – central nervous system, MI – myocardial infarction, BMI – body mass index, DM – diabetes mellitus, TIA – transient ischaemic attack, CHF – congestive heart failure, COPD – chronic obstructive pulmonary disease, PAF – paroxysmal AF, DBP – diastolic blood pressure)

*Safety end points adjusted for age, sex, region, previous stroke/TIA, anaemia, previous GI bleed, COPD, DBP, creatinine clearance (Cockroft-Gault), platelets, albumin, previous Aspirin, Vitamin K antagonist, thienopyridine and randomised treatment.

Figure 1: Study flow chart

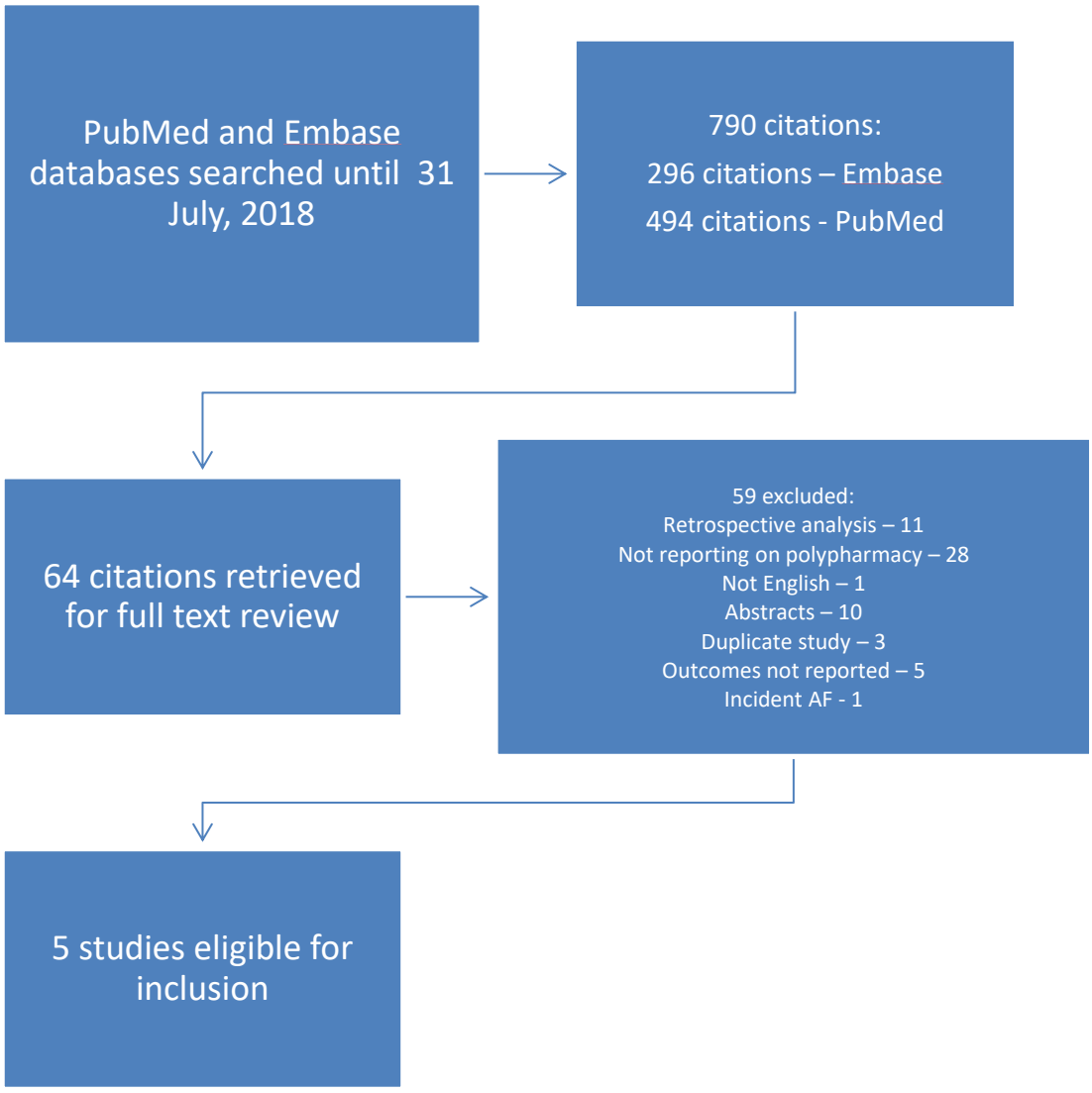
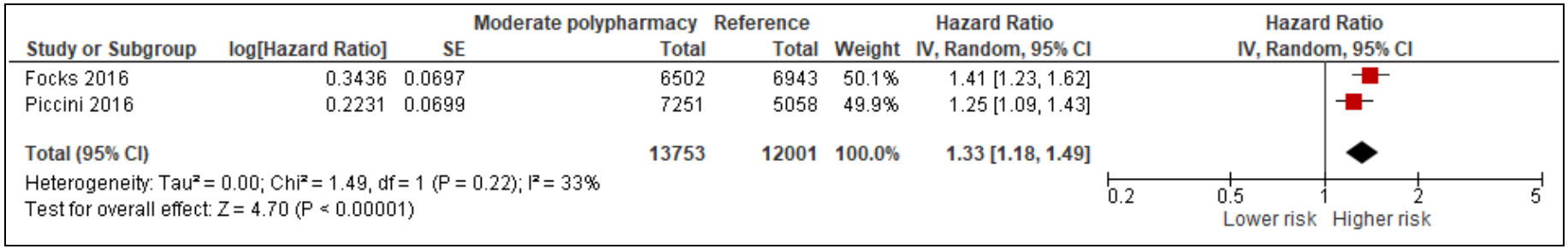


Figure 2 – Impact of moderate (a) and severe (b) polypharmacy on all-cause mortality

a)



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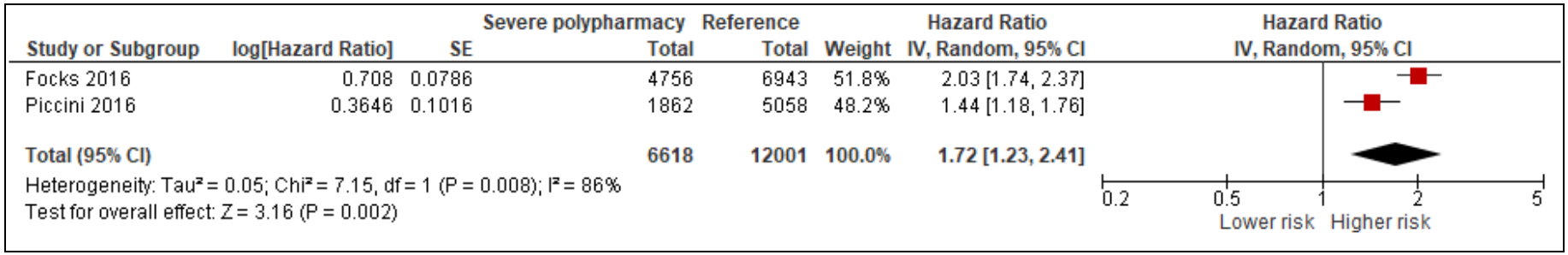
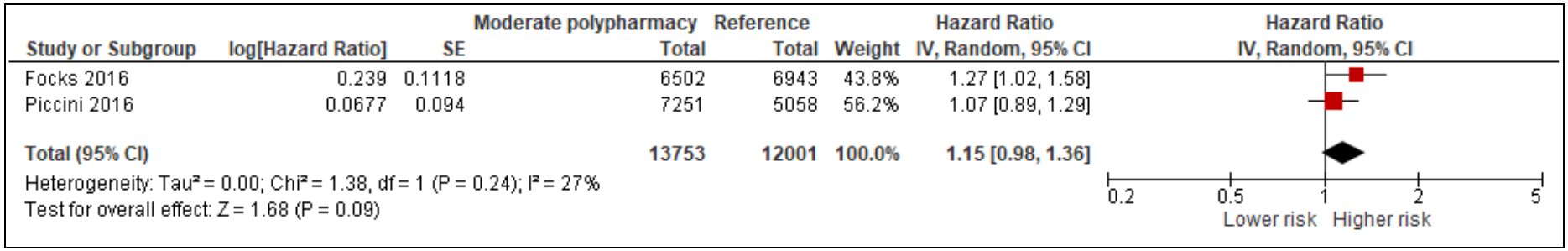


Figure 3: Impact of moderate (a) and severe (b) polypharmacy on stroke or systemic embolism

a)



b)

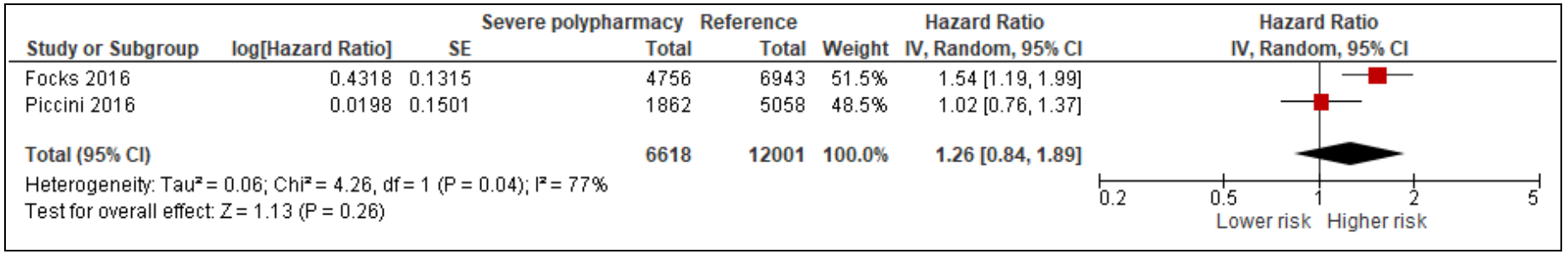
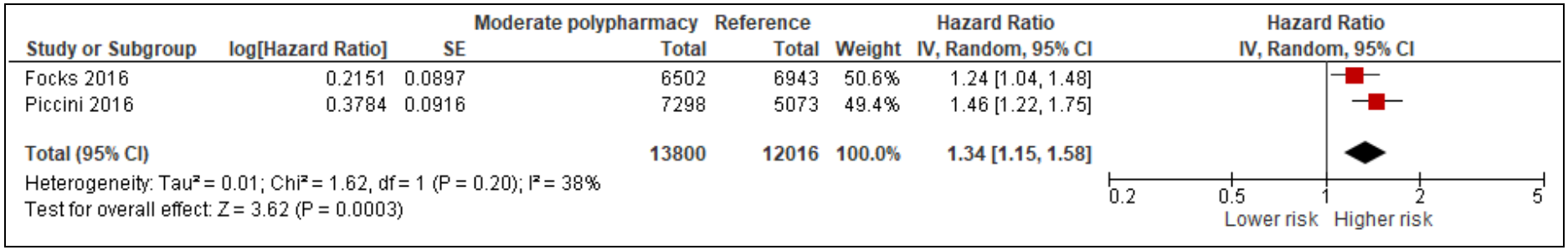


Figure 4: Impact of moderate (a) and severe (b) polypharmacy on major bleeding

a)



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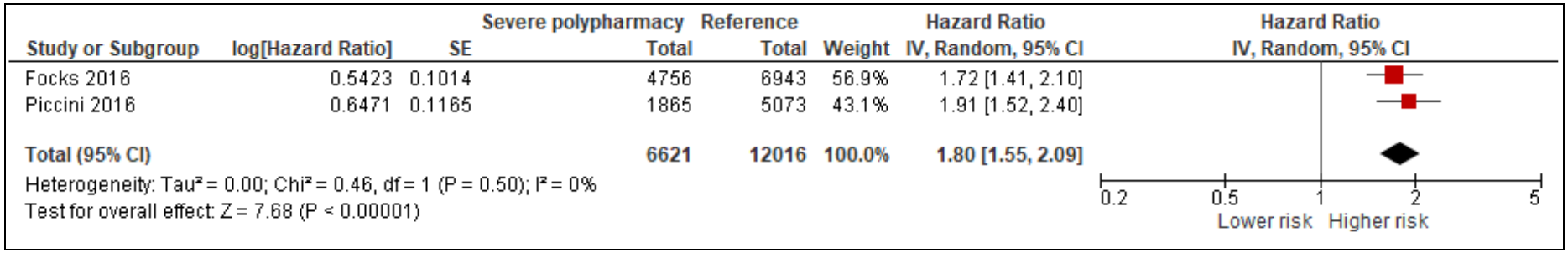
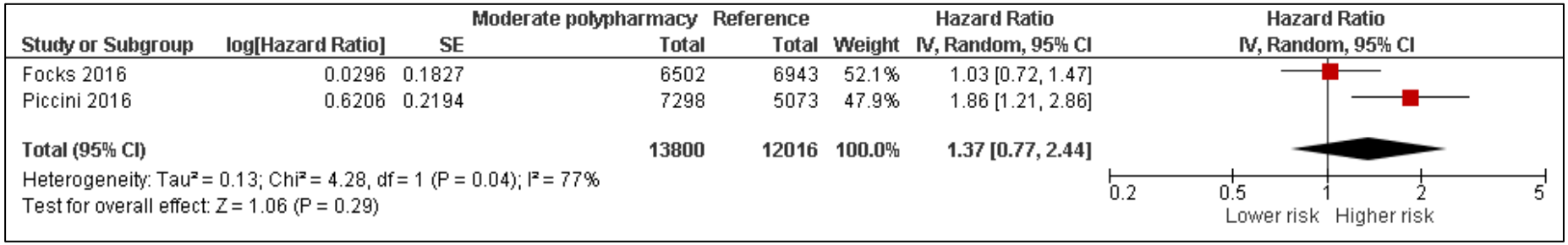


Figure 5: Impact of (a) moderate and (b) severe polypharmacy on intracranial bleeding

a)



b)

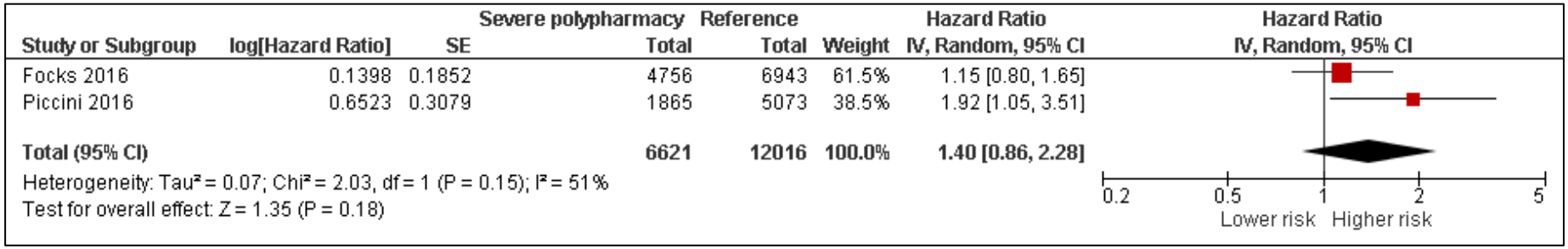
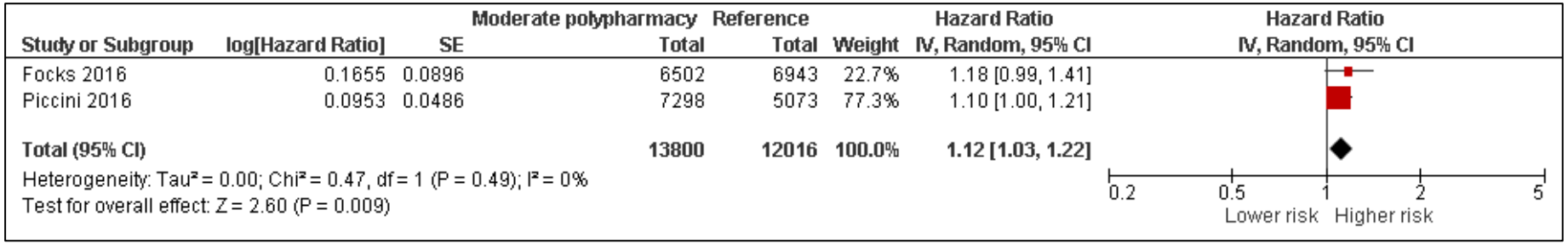
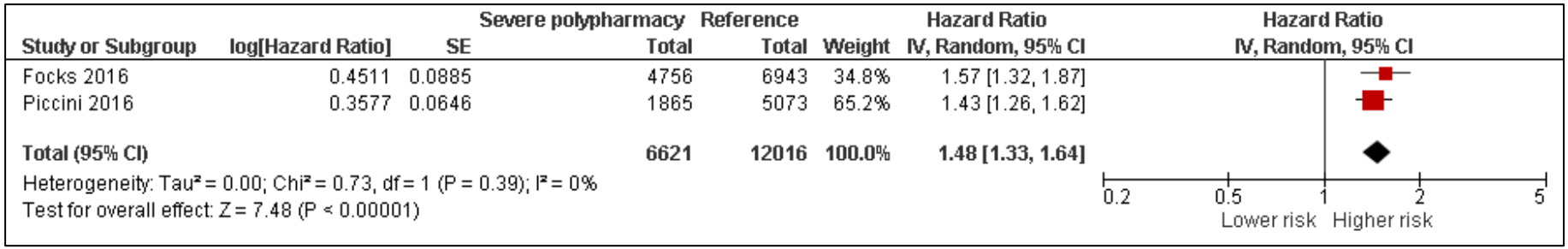


Figure 6: Impact of moderate (a) and severe (b) polypharmacy on clinically relevant non-major bleeding

a)



b)



Chapter 8: Final Discussion

There is a pressing need to stem the growing tide of AF related health care resource utilisation and to improve outcomes in this condition. This thesis has demonstrated that hospitalisations due to AF now outnumber those for both MI and HF in Australia and highlights the urgent need to develop strategies to curtail this growing epidemic. The rising tide of AF related hospitalisations, as discussed in Chapter 2, has occurred across all age groups and both genders and is not accounted for by the increasing use of AF related procedures such as catheter ablation. The costs associated with AF hospitalisations have grown such that the growth over the sixteen-year period leading up to 2013, was more than double that of both MI and HF. The current trajectory of AF in Australia is not sustainable and urgent steps must be taken to address this epidemic.

Steps taken must address the spectrum of AF from prevention to optimal management and possible cure. Globally the incidence of AF continues to rise and therefore strategies to prevent the onset of the condition are of significant interest. Numerous cardiovascular risk factors have demonstrated consistent associations with incident AF, however this has been poorly defined in the case of alcohol consumption. Whilst high levels of alcohol intake are known to be associated with development of the condition, Chapter 3 demonstrated that low levels of alcohol intake, of up to one SD per day, does not heighten AF risk. Furthermore, gender differences were apparent with males exhibiting a higher risk at lower levels of intake. Much remains unknown in this field including variations in AF risk across alcohol types and patterns of intake and subsequent risk.

Enhanced outpatient management using an integrated care approach in AF represents another avenue to improve outcomes in this population. The systematic review and meta-analysis undertaken in Chapter 4, which is the first to systematically evaluate the evidence for integrated care in AF, demonstrates that whilst only a small number of studies have evaluated this approach in AF, it is associated with a significant reduction in all-cause mortality and cardiovascular hospitalisations. No impact on cerebrovascular events or AF hospitalisations were observed and further research in this field is warranted to explore optimal modes and components of care delivery.

The REVIEW AF study in Chapter 5 highlighted the need for improved strategies to reduce AF hospitalisations. This local data, abstracted through both coding and individual patient electronic health record review for each event and encompassing almost four years of follow up, demonstrated that health care resource utilisation in the AF population is significant. Males and younger ages were associated with higher rates of AF re-presentations and identify target populations to direct future strategies towards. The only factor predictive of both AF related ED presentations and hospitalisations was the presence of an AF action plan for management of AF episodes. Whilst this was a surprising finding, it provides important insights in to the possible role of health literacy and ensuring patient understanding and involvement in their care management.

Whilst cardiovascular risk factor management in AF and the use of comprehensive AF care have demonstrated enhanced patient outcomes, Chapter 6 demonstrated that a brief educational intervention which incorporated the use of motivational interviewing techniques and goal setting, did not result in an improved quality of life or cardiovascular risk factor status at short term follow up. This further supports the need for more comprehensive and integrated approaches to AF management to improve outcomes in this condition.

Finally, in Chapter 7, the results of the first systematic review and meta-analysis examining the impact of polypharmacy on health outcomes in AF demonstrated that both moderate and severe levels of polypharmacy were associated with increased risks of all-cause mortality, major bleeding and clinically relevant non-major bleeding. Whilst the use of additional medications in many other cardiovascular conditions including HF and MI is generally thought to be an important component of improved prognosis, this study demonstrates that this may not be the case in AF. The need to assess the appropriateness of each individual's medication regime as well as their adherence and persistence are strategies that could be immediately implemented and may provide an avenue for reducing polypharmacy associated harm.

Chapter 9: Future Directions

Many unanswered questions remain in the field of AF related research. From prevention to cure there is much to be achieved in endeavours to improve patient outcomes and reduce health care burden in the burgeoning AF population. In the prevention sphere, the identification of new risk factors will assist in strategies to prevent disease onset. A greater understanding of how modification of existing risk factors may impact on disease development and appropriate targets for these in AF prevention would contribute to stemming the growing incidence of this condition.

Further down the disease trajectory, optimal ways of managing the condition need to be explored. The in-hospital management of AF and ways in which admissions related to the condition can be prevented are a research priority, as AF admissions continue to grow exponentially and remain the costliest component of AF care. Whilst alternative models of care delivery have shown early promise in improving patient outcomes, further research in to optimal methods and components of service delivery need to be elucidated to better understand and develop translatable models. The evidence to date suggests that comprehensive models of care, targeting all aspects of AF management are associated with better patient outcomes, with less intense or fragmented models not associated with the same magnitude of effect. This approach would benefit from large multi-centre RCTs, to examine appropriate and relevant outcomes, and to ensure the widespread applicability of such models. Multiple opportunities exist to improve AF outcomes and there has never been a more pressing need to stem the ever-rising tide of AF related burden.

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