CHARACTERISATION OF ATRIAL FIBRILLATION PATIENTS: RISK FACTORS, PROGRESSION, GENDER AND THROMBOGENIC RISK

By

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In Loving Memory of

my Oma

7/11/1926 – 12/5/2017

This thesis is not a conclusion of an achievement but simply the ending of one chapter and the beginning of another

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Abstract

Atrial fibrillation (AF) is the most common cardiac arrhythmia which is fast reaching epidemic measures. This thesis evaluates several aspects of AF: the role of AF screening, risk factor management in reversal of the AF substrate, impact of socio-economic background and risk-factor management, gender and ablation outcomes, thrombogenic risk following ablation and anticoagulation treatments.

Screening to detect AF prevalence and asymptomatic AF is increasingly being evaluated to reduce complications. Chapter 2 evaluates the results of a nationwide screening event. This study provides insight into detection rates around Australia and New Zealand. Additionally, due to the information collected we were able to establish the risk of AF development in individuals based on their risk factor profile. Screening enabled raised awareness of the AF and an opportunity to educate individuals on their individual risk factors.

AF is well demonstrated to be a progressive disease. Many patients present with short paroxysmal episodes which over time become long-lasting and eventually persistent in nature. Chapter 3 presents the REVERSE-AF study which demonstrated that with increasing weight-loss there is an increase likelihood of AF reversal. Patients who were able to achieve >10% weight-loss were more likely to have AF reversal with 88% of patients reversing from persistent to paroxysmal or no AF at follow-up.

The role of socioeconomic determinants on risk factor management in AF is not well studied. Chapter 4 investigates the socioeconomic influence on patients undergoing risk factor management and AF outcomes. Despite evaluating many

factors of socioeconomic background, no specific factor demonstrated an association with AF freedom. Interestingly, we did note that married individuals were able to achieve greater weight-loss. This has important implications suggesting that socio-economic boundaries are not determinants of the success of risk-factor management in AF. Socioeconomic status in not a barrier to successful risk-factor management in AF.

Ablation has been shown to be successful in treating patients with AF. The difference between outcomes of genders is very varied in the current literature, with women often having worse outcomes. In chapter 5 we present the long-term follow-up data, assessing ablation outcomes. This study found women present with more paroxysmal AF and a smaller atrium. Despite this, women are more likely to have AF recurrence over long-term follow-up. This data adds further weight for biological differences between genders in the outcomes of AF management.

Stroke is one of the most devastating outcomes of AF; however, it has a complex pathophysiological basis. As such chapter 6 evaluates a large cohort of patients undergoing AF ablation to shed light on the impact of eliminating AF. Interestingly despite eliminating arrhythmia, a small group of individuals had a stroke during follow-up. This demonstrates that AF itself remains only one component of the risk of stroke in patients with AF; highlighting ongoing vigilance is needed in managing all stroke risk factors. Additionally, further caution and evaluation is required to cease anticoagulation after successful catheter ablation of AF.

Finally, Non-vitamin K antagonists (NOAC) have become a popular method of anticoagulation for AF patients in the prevention of stroke. It has been suggested there is a significant discontinuation rate warranting the evaluation of non-pharmacological strategies for stroke prevention. Chapter 7 evaluates cessation rates in a single-centre

when prescription is undertaken in an integrated care setting. Interestingly, despite suggestions in the literature, we found with appropriate education and individual participation in decision making, the rate of cessation was low. Age and gender were independent predictors of NOAC cessation. This data highlights the need for improved care pathways and delivery to improve compliance with proven therapies.

Declaration

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.

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Table of Contents

List of Abbreviations

AF – Atrial fibrillation

AFSS – Atrial fibrillation symptom severity

AHI – Apnoea hypopnea index

AV – Atrioventricular

BMI – Body mass index

BP – Blood pressure

CI – Confidence interval

CPAP – Continuous positive airway pressure

CT – Computed tomography

CVA – Cerebrovascular accident

DM – Diabetes mellitus

GI – Glycaemic index

HDL – High density lipoprotein

HR – Hazard ratio

IGT – Impaired glucose tolerance

IQR – Interquartile range

IVsd – Intraventricular septum diameter

LA – Left atria

LDL – Low density lipoprotein

LV – Left ventricular

LVEF – Left ventricular ejection fraction

METs – Metabolic equivalent

MI – Myocardial infarction

MRI – Magnetic resonance imaging

NOAC – Non-vitamin K antagonist

NS – Not significant

OAC – Oral anticoagulation

OR – Odds ratio

OSA – Obstructive sleep apnoea

QoL – Quality of life

PPM – Permanent pacemaker

RDI – Respiratory disturbance index

RFM – Risk factor management

RR – Relative risk

SD – Standard deviation

SHR – Spontaneously hypertensive rats

SVT – Supraventricular tachycardia

TE – Thromboembolism

TEE – Transesophageal echocardiogram

TG – Triglycerides

TIA – Transient ischaemic attack

VKA – Vitamin K antagonist

Publications and Presentations

Chapter 1: Literature Review

i. **Manuscript:** Gallagher C, **MIDDELDORP ME**, Sanders P. Weight and risk of incident AF – body mass index variability or body mass gain. *Mayo Clinic Proceedings 2018; 94: 186-188.*

ii. **Manuscript:** Hendriks JM, Gallagher C, **MIDDELDORP ME**, Sanders P. New approaches to detection of atrial fibrillation. *Heart 2018: 104: 1898-1899.*

iii. **Manuscript:** Gallagher C, Elliott A, Wong XC Rangnekar G, **MIDDELDORP ME**, Mahajan R, Lau DH, Sanders P, Hendriks JM. Integrated care in atrial fibrillation – a systematic review and meta-analysis. *Heart 2017; 10: 1-7.*

iv. **Manuscript:** Gallagher C, Elliott A, Wong CX, Rangnekar G, **MIDDELDORP ME**, Mahajan R, Lau DH, Sanders P, Hendriks JM. Alcohol and atrial fibrillation – a systematic review and meta-analysis. *International Journal of Cardiology 2017; 246: 46-52.*

v. **Manuscript:** Lau DH, **MIDDELDORP ME**, Sanders P. Obesity paradox in atrial fibrillation: A distracting reality or fictitious finding? *European Heart Journal 2016: 2879-2881*.

vi. **Manuscript:** Gallagher, C Hendriks JM, Mahajan R, **MIDDELDORP M,** Elliott A, Pathak R, Sanders P, Lau DH. Lifestyle management to prevent and treat atrial fibrillation. *Expert Review in Cardiovascular therapy 2016: 1-11.*

Chapter 2: Screening Australia Wide for overAll pREvalence of Atrial Fibrillation: AWARE-AF

i. **Presentation from Abstract:** Outcomes of AF awareness week: A population screening strategy: AF frequency and risk. **MIDDELDORP ME**, Elliott AD, Hall T, Munawar DA, Kumar S, Khokhar K, Gallagher C, Hendriks JM, Thiyagarajah A, Mahajan R, Lau D, Sanders P. Asia Pacific Heart Rhythm Society, Yokohama, Japan; September 2017. Journal of Arrhythmia 2016: 32; AB40975, O49-54.

ii. **Award: First Prize -** HRS Afib Awareness Funding Award; September 2016.

Chapter 3: Evaluating the reversal of the AF Substrate - pREVEntion and regReSsive Effect of weight-loss and risk factor modification on AF: The REVERSE-AF Study

i. **Manuscript: MIDDELDORP ME,** Pathak RK, Lau DH, Sanders PS. Response to the editor: PREVEntion and regReSsive Effect of weight-loss and risk factor modification on Atrial Fibrillation: The REVERSE-AF study. (*Europace– In Press)*

ii. **Manuscript: MIDDELDORP ME,** Pathak RK, Meredith M, Mehta A, Elliott AD, Mahajan R, Twomey D, Hendriks JM, Abhayaratna WP, Kalman JK, Lau DH, Sanders PS. PREVEntion and regReSsive Effect of weight-loss and risk factor modification on Atrial Fibrillation: The REVERSE-AF study. *Europace 2018; 20: 1929-1935.*

iii. **Manuscript:** Pathak RK, Evans M, **MIDDELDORP ME**, Mahajan R, Mehta AB, Meredith M, Twomey D, Wong CX, Hendriks JML, Abhayaratna WP, Kalman JM, Lau DH, Sanders P. Cost-effectiveness and clinical effectiveness of the risk factor management clinic in atrial fibrillation: the CENT study. *Journal of the American College of Cardiology: Clinical Electrophysiology 2017; 3: 436-447*.

iv. **Presentation from Abstract:** PREVEntion and regReSsive Effect of weight loss and risk factor modification on Atrial Fibrillation (REVERSE-AF). **MIDDELDORP ME**, Pathak RK, Meredith M, Mehta A, Mahajan R, Elliott AD, Lau DH, Sanders P. Royal Adelaide Hospital Medical Staff Society Research Sessions, Adelaide, Australia; May 2018.

v. **Presentation from Abstract:** PREVEntion and regReSsive Effect of weight loss and risk factor modification on Atrial Fibrillation (REVERSE-AF). **MIDDELDORP ME**, Pathak RK, Meredith M, Mehta A, Mahajan R, Elliott AD, Lau DH, Sanders P. Heart Rhythm Society, San Francisco, California, USA; May 2016. Heart Rhythm Journal 2016:13: S49.

vi. **Presentation from Abstract:** Impact of Weight Reduction on the Progression of AF: The PROGRESS-AF Study. **MIDDELDORP ME**, Pathak RK, Meredith M, Mehta A, Mahajan R, Elliott AD, Lau DH, Sanders P. Asia Pacific Heart Rhythm Society, Melbourne, Australia; November 2015. Journal of Arrhythmia 2016: AB01-PO1.

vii. **Award: Finalist -** Royal Adelaide Hospital Medical Staff Society Research Prize; May 2018.

Chapter 4: SoCio-EcoNomic StatUS Impact on Risk Factor Management in Atrial Fibrillation: CENSUS-AF Study

i. **Presentation from Abstract:** Does socioeconomic factors influence the outcomes of risk factor management and freedom of patients with atrial fibrillation. **MIDDELDORP ME**, Elliott AD, Gupta A, Gallagher C, Hendriks JM, Munawar DA, Khokhar K, Thiyagarajah A, Mahajan R, Lau DH, Sanders P. European Heart Rhythm Society, Barcelona, Spain; March 2018. Europace 2018:20 S1; i236-i237.

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iii. **Presentation from Abstract:** The influence of socioeconomic status and risk factor management in patients with atrial fibrillation. **MIDDELDORP ME**, Elliott AD, Pathak RK, Gupta A, Gallagher C, Hendriks JM, Munawar DA, Khokhar K, Thiyagarajah A, Mahajan R, Lau DH, Sanders P. Asia Pacific Heart Rhythm Society, Yokohama, Japan; September 2017. Journal of Arrhythmia 2017: 32; AB41216, RF14-2.

Chapter 5: Role of Gender in Long-term Outcomes of Atrial Fibrillation Ablation: GENDER-AF

i. **Presentation from Abstract:** Gender differences in atrial fibrillation recurrence after ablation: Long-term outcomes. **MIDDELDORP ME**, Elliott AD, Linz D, Kadhim K, Gallagher C, Hendriks JM, Lau DH, Sanders P. Heart Rhythm Society, San Francisco, California; May 2019.

ii. **Presentation from Abstract:** Differences in ablation outcomes between genders: Long-term outcomes. **MIDDELDORP ME**, Elliott AD, Kadhim K, Linz D, Thiyagarajah A, Gallagher C, Hendriks JM, Lau DH, Sanders P. European Heart Rhythm Association, Lisbon, Portugal; PO4175, March 2019.

iii. **Presentation from Abstract:** Gender differences in 1-year outcomes of first-time AF ablation. **MIDDELDORP ME**, Elliott AD, Gallagher C, Hendriks JM, Thiyagarajah A, Mahajan R, Lau DH, Sanders P. SAHMRI Annual Scientific Meeting, Australia; November 2018.

iv. **Presentation from Abstract:** Gender differences in 1-year outcomes of first-time AF ablation. **MIDDELDORP ME**, Elliott AD, Gallagher C, Hendriks JM, Thiyagarajah A, Mahajan R, Lau DH, Sanders P. 12th Annual SA Cardiovascular Research Showcase, Australia; November 2018.

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vii. **Presentation from Abstract:** The influence of gender on 1-year outcomes of patients undergoing primary AF ablation. **MIDDELDORP ME**, Elliott AD, Gallagher C, Hendriks JM, Munawar DA, Kumar S, Khokhar K, Thiyagarajah A, Mahajan R, Lau D, Sanders P. European Society of Cardiology Congress, Barcelona, Spain; August 2017. European Heart Journal 2017: 38, 51; P201.

viii. **Presentation from Abstract:** Gender differences in 1-year outcomes of first-time AF ablation. **MIDDELDORP ME**, Elliott AD, Gallagher C, Hendriks JM, Munawar DA, Kumar S, Khokhar K, Thiyagarajah A, Mahajan R, Lau D, Sanders P. Asia Pacific Heart Rhythm Society, Yokohama, Japan; September 2017. Journal of Arrhythmia 2017: 32; AB40966, RF2-5.

ix. **Award: First Prize –** Northern Communities Health Foundation Prize, University of Adelaide, 12th Annual Florey Postgraduate Research Conference, Adelaide Australia; October 2018.

x. **Award: First Prize –** Florey Medical Research Foundation Prize, University of Adelaide, 12th Annual Florey Postgraduate Research Conference, Adelaide Australia; October 2018.

xi. **Award: Finalist –** 2018 SA Cardiovascular Research Showcase, Adelaide, Australia; November 2018.

xii. **Award: Best Moderated Poster Award –** AF Ablation outcomes and predictors session, European Society of Cardiology, Barcelona, Spain; August 2017.

Chapter 6: ThrombogeneSIs Risk LatE FollowiNg AF AblaTion – SILENT Study

i. **Presentation from Abstract:** Thromboembolic Events Following Clinically Successful Catheter Ablation of Atrial Fibrillation: Implication for Long-term Anticoagulation. **MIDDELDORP ME**, Mahajan R, Pathak R, Lau DH, Sanders P. Heart Rhythm Society, Boston, Massachusetts, USA; May 2015. Heart Rhythm Journal 2015: 12; S317, PO 03-27.

Chapter 7: Cessation of Non-vitamin K Antagonist Oral Anticoagulants in Atrial Fibrillation Patients

i. **Manuscript: MIDDELDORP ME**, Gupta AK, Elliott AD, Thiyagarajah A, Gallagher C, Hendriks JML, Linz D, Kadhim K, Emami M, Mahajan R, Lau DH, Sanders P. Cessation of non-vitamin K antagonist oral anticoagulants in atrial fibrillation patients. (In Submission)

ii. **Presentation from Abstract:** What and how many reactions caused by novel oral anticoagulation use? **MIDDELDORP ME**, Elliott AD, Gupta A, Gallagher C, Hendriks JM, Munawar DA, Khokhar K, Thiyagarajah A, Mahajan R, Lau DH, Sanders P. European Heart Rhythm Society, Barcelona, Spain; March 2018. Europace: S1; i69-i70.

iii. **Presentation from Abstract:** Cessation of novel oral anticoagulants: Who and why? **MIDDELDORP ME**, Elliott AD, Gupta A, Gallagher C, Hendriks JM, Munawar DA, Khokhar K, Thiyagarajah A, Mahajan R, Lau DH, Sanders P. Heart Rhythm Society, Boston, Massachusetts, USA; May 2018. Heart Rhythm Journal 2018: 15; S504, PO04-25.

iv. **Presentation from Abstract:** Are novel oral anticoagulants associated with a significant number of reactions? **MIDDELDORP ME**, Elliott AD, Gupta A, Gallagher C, Hendriks JM, Munawar DA, Khokhar K, Thiyagarajah A, Mahajan R, Lau DH, Sanders P. Asia Pacific Heart Rhythm Society, Yokohama, Japan; September 2017. Journal of Arrhythmia 2017: 32; AB41235, RF2-1.

Invited Faculty Presentations

2019

i. **INVITED PLENARY SPEAKER:** PREVEntion and regReSsive Effect of weight-loss and risk factor modification on Atrial Fibrillation: The REVERSE-AF study. (Top publications impacting AF management for 2019 Session) Heart Rhythm Society, San Francisco, California, USA; May 2019.

ii. **INVITED PLENARY SPEAKER:** Risk factor modification: Can it really prevent or reverse AF? Heart Rhythm Society, San Francisco, California, USA; May 2019.

iii. **INVITED SPEAKER:** Reversing AF disease by lifestyle management: Current role and potential implications for timing and recommendation of AF ablation. Heart Rhythm Society, San Francisco, California, USA; May 2019.

2018

iv. **INVITED SPEAKER:** Weight loss and Atrial Fibrillation. SA Cardiovascular Research Showcase. Adelaide, South Australia; November 2018.

v. **INVITED SPEAKER:** Gender disparities in AF ablation outcomes. Asia Pacific Heart Rhythm Society, Taipei, Taiwan; October 2018.

vi. **INVITED CHAIR:** Non-Cardiovascular Risk Factors: Beyond Your Understanding. Asia Pacific Heart Rhythm Society, Taipei, Taiwan; October 2018.

vii. **INVITED CHAIR:** Special Session: Gender in Heart Rhythm Disorders. Asia Pacific Heart Rhythm Society, Taipei, Taiwan; October 2018.

viii. **INVITED SPEAKER:** Role of Lifestyle Management in AF Reduction. Heart Rhythm Society, Boston, Massachusetts, USA; May 2018.

2017

ix. **INVITED SPEAKER:** Risk Reduction/Lifestyle Modifications – What is the Science? How can we incorporate this evidence into an AF program. Heart Rhythm Society, Chicago, Illinois, USA; May 2017.

2016

x. **INVITED OPENING PLENARY SPEAKER: Allied Health Professional Forum –** Risk Factor Modification to Improve AF Ablation Outcomes and Reduce Complications. Heart Rhythm Society, San Francisco, California, USA; May 2016.

xi. **INVITED SPEAKER:** Risk Factor Modification to Improve Outcome-Weight Reduction, Sleep Apnea, and Hypertension. Heart Rhythm Society, San Francisco, California, USA; May 2016.

xii. **INVITED SPEAKER:** PREVEntion and regReSsive Effect of weight loss and risk factor modification on AF: The REVERSE-AF Study. SA Health and Medical Research Showcase. Adelaide, South Australia; November 2016.

2015

xiii. **INVITED PLENARY SPEAKER: Allied Health Professional Forum –** Research Concepts in AF: Markers, Risk Factors and What's Coming. Heart Rhythm Society, Boston, Massachusetts, USA; May 2015.

Chapter 1: Review of the Literature

1.1 ATRIAL FIBRILLATION – GLOBAL BURDEN

Atrial fibrillation (AF) has emerged as a global epidemic, affecting 33.5 million individuals worldwide, however this figure is likely to be an underestimate of the true burden of AF due to 70% of the data coming from the developed world.[1] In addition, due to the nature of AF many individuals are unaccounted for due to the intermittent and variable nature of the symptoms associated with the disease. This high incidence is only predicted to increase over the years. The Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study estimated that the United States alone accounts for 2.3 million adults with AF and this is projected to rise to 5.6 million by 2050, with 50% of these being 80 years or older.[2] More recent projections suggest the US prevalence to rise to 15.9 million by 2050.[3] Similarly, in Asia the prevalence is on the rise also, over an 11 year time period the prevalence increased 20 fold with an estimated on in five Chinese adults likely to have AF in their lifetime.[4] In Australia the prevalence is estimated to be between 1.4 and 5%.[5-7] The Busselton Study of 1770 participants found the prevalence to be 4.9% in those aged over 60 years. A recent study of 8,272 individuals in the AusDiab study reported 1.4% of baseline ECG's were in AF.[7] Additionally prevalence data has been obtained using the seven international epidemiological studies and collated the statistics to estimate AF prevalence based on what would be most applicable to the Australian population. To do this they applied the international AF prevalence statistics to predict prevalence of over 600,000 individuals by 2034.[5]

With this growing burden of AF comes a rise in AF-related morbidity, mortality and healthcare costs, which will consequently place a huge demand on the already overburdened healthcare systems. Studies from the United States highlights an increase of AF related hospitalisations by 23% over a 10-year duration.[8] In Australia, we see similar trends with the number of hospital admissions due to AF is rising exponentially such that it is now a more common cause of hospitalisations than other cardiovascular causes including heart failure and acute coronary syndromes.[9] The economic cost of this burden is staggering with millions of dollars being absorbed by this condition, related to a range of therapies from procedures, hospitalisations, medication use and complications such as stroke. In the United Kingdom the cost of AF in 1995 was between 244 and 531 million pounds and additionally it demonstrated this cost was set to increase.[10] Indeed, it has also been shown that in the United States the cost is estimated to be between $6 and $26 billion annually.[11] The cost of AF to our healthcare system in Australia, was approximately $873.8m between 2008-2009, with an annual cost of $5,200 per person.[12] These alarming figures highlight the need for intervention and prevention to stem the rising incidence of AF, reduce AF morbidity and subsequently alleviate healthcare demands.

1.1.1 Screening for AF

In 2015 AF-Screen was established as an international collaboration in order to promote discussion and further research into screening for AF.[13] This initiative includes multidisciplinary teams of electrophysiologists, cardiologist, general physicians, neurologist, nurses, allied professionals, epidemiologists, health economists and patient advocates from 31 countries. The consensus from this team of experts is that singe-timepoint screening is warranted and cost-effective. Additional

benefits may be obtained in screening those who are considered at higher risk of AF or >75 years of age.

A recent method used to establish the prevalence of AF is systematic, community, high risk populations screening as well as opportunistic screening for AF. As per the European Heart Rhythm Association Consensus Statement in 2017[14] types of screening are defined as community screening this is done via the same method as systematic screening but involves screening of subjects living in a specific area. Systematic screening is single time point methodical pulse or ECG check as part of a routine consultation. High risk population screening is methodical screening of subjects presenting with critical characteristics such as screening within medical clinics and pharmacies with opportunistic screening is done to target large populations undertaken in various locations taking advantage of the circumstances. A large percentage of the population have asymptomatic AF with ill-defined or no symptoms, this is estimated at being approximately one-third of patients. Screening enables the ability to detect AF in these patients.[15,16] Unfortunately, due to the nature of paroxysmal AF, screening precludes from detecting paroxysmal episodes, which are usually limited to clinical diagnosis and symptoms. In addition, there is a lack of randomised data in this area to show benefit in hard endpoints such as stroke or mortality. In 2016 the European Society of Cardiology (ESC) AF guidelines[17] included screening for AF with a class 1 level B recommendation for opportunistic screening for patients >65 by use of pulse or ECG rhythm strip, and additionally a IIb level B recommendation for systematic ECG screening in those >75 years old or those who are at high risk of stroke.

There have been many screening studies over the last two decades given the advances in technology over this time. The prevalence of detected AF has varied from

0.5% to over 5%; when these twenty-three prospective, cross sectional studies are combined the weighted average for newly detected AF was around 0.9% (95% CI; 0.7-1.1).[14] Additionally, given the aging population it is prudent to note that the prevalence of detected AF increases with age. This was demonstrated in a large cohort of over 65,700 subjects from Belgium undertaken as part of 'Belgian Heart Rhythm Week' where the prevalence detected using handheld ECG found AF was 1.4%, this was further broken down by age. AF was detected in 1% of participants aged <65 compared to 6.5% in individuals aged 85-89, with AF being more prevalent in males.[18] To date there has only been three studies from Australia which have been pilot studies assessing feasibility opportunistic screening.[19-21] One was performed across 10 pharmacies of 1000 participants who were aged ≥65 has been undertaken using handheld ECG, the prevalence of AF detected in this study was 1.5%.[22] No systematic screening has been performed in Australia to date.

It has been demonstrated that it is beneficial to screen at-risk populations, with studies having demonstrated that this will yield diagnosis of AF this would seem reasonable. It does appear to be less futile in the general public, particularly the younger population. It is perhaps with new technology such as the Apple watch that large scale mass screening may prove beneficial.

1.1.2 Tools and Technology Used for Screening

Although AF can be detected by regular pulse checks other irregularities can be mistaken for AF. It has been shown that the use of blood pressure monitors, ECG, and smartphone applications are superior forms of detection when compared with pulse palpation.[23] To date the primary methods of AF detection has been ECG and Holter monitoring. ECG while useful clinically is too intrusive to undertake in mass screening

events. Holter monitoring requires fitting, programming then analysing, while this is suitable in a clinical setting this is not suitable for screening. Similarly, there has been patches that have been developed, these are less cumbersome than a standard Holter monitoring as they don't require leads. The Zio Patch developed by iRhythm technologies is a waterproof, single use, continuous monitor that can be worn for up to 14 days. Once the recording is finished this is returned to the manufacturer who then return a report with results to the referring physician. There was an early study of comparing 24-hour Holter monitoring to the Zio Patch. This found that the Zio detected 57% more clinical events compared to the traditional Holter.[24] More recently the mSToPs randomised clinical trial used the Zio Patch to detect asymptomatic AF after a duration of 4 months.[25] The participants were randomised to either immediate monitoring or delayed monitoring. The study design was those in the immediate group wore the patch for 2 weeks then a second device after 3 months before reaching the primary endpoint. The delayed group had no monitor until the 4-month mark where they then underwent the same protocol of 2 weeks monitoring followed by a further 2 weeks at 3 months. This demonstrated a detection of new incident AF cases in 3.9% of the immediate group compared to 0.9% in the delayed group. This device is not inexpensive which therefore makes it difficult to use for large scale screening event.

Given the advances in technology we now have new easy and often inexpensive tools available to undertake single point screening. The common tools used for screening include the Zenicor EKG® (Zenicor Medical Systems) which is a small device that requires the patient placing their thumbs on two electrodes for 30 second and obtains a single lead ECG which has been shown to correctly diagnose AF with a sensitivity in 96% and specificity in 92%.[26] The MyDiagnostik (Applied Biomedical Systems BV, Maastricht, The Netherlands) tool is used commonly in

Europe. This is a simple tool shaped like a wand which is held between an individuals hands and it has the ability to obtain a single lead ECG over 1 minute with a sensitivity of 94% and specificity of 93%.[27] The Omeron HCG (Model HCG-801, Omeron Healthcare Europe, the Netherlands) monitor, which provides a single change 20 second ECG by placing the device on the patient's chest with a sensitivity of 99% and specificity of 76%.[28] However due to the slightly invasive nature of this device it is not often used for opportunistic screening. One of the most common tools is the AliveCor (AliveCor Inc., USA) device which can be used with an app on any smartphone. This is used by placing fingers on the electrode and recording either 30 or 60 second single lead ECGs. The sensitivity of has been found to be 98% and specificity 96%.[29] The recent release of the Apple Watch with the ability to take a single lead ECG has prompted possibilities for large scale monitoring; also comes with the issue of people self-diagnosing or increasing appointments to primary care physicians due to lack of knowledge as to normal and abnormal readings. We will await the results of the Apple Heart Study being run with Stanford University, which is due for completion in early 2019. This study uses and Apple watch-based App and will look for irregularities in rhythm. If an abnormality is detected the participant is notified and they may be asked to wear an ePatch for 7-day monitoring. Due to the fact so many individuals have these devices this study has managed to recruit a staggering 400,000 plus participants. This will be the largest mass screening ever undertaken and will lead the way for future studies. In time it is likely studies will be undertaken to better evaluate the use of this as a tool for screening and diagnosis of AF.

1.2 RISK FACTORS FOR THE DEVELOPMENT OF AF

Cardiovascular disease is estimated to be the cause of every 1 in 3 deaths in the United States.[30] A recent study of almost 45,000 individuals showed the importance of seven lifestyle-based health metrics taken from the American Heart Association (AHA) recommendations; physical activity, healthy diet, glucose and cholesterol levels, smoking status, normal blood pressure and weight.[31] This study showed that 99% of the population had at least one cardiovascular risk factor. A third were hypertensive, a third were overweight and 50% were inactive. This study demonstrates the penetrance of cardiovascular risk factors in the general population.

Although it was believed that the increasing epidemic of AF was due to an aging population, there are many other comorbidities that potentially contribute to the growing burden of AF. AF results from a rather complex interplay between triggers and substrate. The major pathophysiological mechanisms which underly AF can be broadly categorised into: electrical, ionic, structural and autonomic remodelling. This can be due to various cardiac conditions and risk factors such as hypertension, heart failure, diabetes, dyslipidaemia, smoking, valvular heart disease and alcohol. More recently we have seen the emergence of other important risk factors, obesity, physical inactivity, obstructive sleep apnea, pre-hypertension, aortic stiffness and genetic profiles as potential triggers for AF. These mechanisms contribute to imitation and maintenance of AF by means of ectopic firing or drivers and re-entry substrate which is due to the abnormal atrial conduction. Certainly, AF itself can contribute to further remodelling this is a concept well known to us as 'AF begets AF'.[32] These risk factors are significant contributors to the development of AF and more likely to be the cause of the recent upsurge in AF incidence. The Atherosclerosis Risk in Communities (ARIC) study demonstrated that the risk of AF, dependent on co-existing risk factors

is additive with each additional component of the metabolic syndrome (waist circumference, elevated blood pressure, elevated triglycerides, low HDL cholesterol, impaired fasting glucose). This study demonstrated that there was an 67% increase in the risk of developing AF for individuals with metabolic syndrome.[33] Notably, this study demonstrated that 56.5% of new AF presentations had ≥1 risk factor, with hypertension being the most prevalent.[34] Additionally, it is shown that concomitant risk factors affect the type of AF that individuals present with. The German registry of over 9,500 patients demonstrated that predisposing risk factors were present in 88% of patients.[35] They were able to show that with an incremental rise in risk factors there is a subsequently increased risk of developing persistent and eventually permanent AF. This highlights the dynamic impact that multiple risk factors play in the development and progression of AF disease.

1.2.1 HYPERTENSION

1.2.1.1 Hypertension and the Relationship with AF

Hypertension is the most prevalent risk factor for AF, with an estimated prevalence of 39% in the ARIC cohort [34] and 31% and 40% of males and females in the Framingham cohort, respectively.[36] Additionally, the Framingham study highlighted the for each decade after the age of 50 the incidence of AF doubles with it reaching around 10% at the age of 80.[37] Hypertension in the developed countries is the most prevalent cardiovascular disease and is known to affect 20-50% of adults.[38]

Even with pre-hypertension, it has been demonstrated that there is a 28% increased risk of AF. In a large study of male participants, a baseline blood pressure (BP) of >140 mmHG had a 1.60-fold incident risk of AF compared to those in the

normotensive range. [39] Similar results were presented in the Women's Health Study where women with a pre-hypertensive BP of 130-139 systolic and 85-89 diastolic had a 28% and 53% increased risk of incident AF when compared to women with a normal BP of <120 mmHG systolic and <65 mmHG diastolic.[40] While these studies have shown that even pre-hypertension has an increased risk of AF, there is still no clarity on what is considered the optimal blood pressure for individuals with AF; it does seem that aiming for targets and management of pre-hypertension is imperative given it is shown that a target of 120 mmHG systolic BP reduces all-cause mortality and cardiovascular events,[41] additionally by reducing the systolic blood pressure by 10 mmHG this was also shown to reduces cardiovascular events and reduce all-cause mortality by 13% [42] thus highlighting the need for tighter monitoring and treatment of hypertension.

Hypertension has been shown to be responsible for progression of atrial remodelling and the substrate therefore leading to AF.[43,44] An early ovine study assessing a chronic hypertension model of 5 years found this resulted in significant conduction slowing, increase atrial fibrosis and evidence of cellular myolysis which in turn resulted in increase of AF.[45] Surprisingly, even short durations of hypertension in an animal model was associated with significant effects on the atrium. This was done using the "one-kidney, one clip" induced hypertension technique.[43] When compared to controls those in the hypertensive group demonstrated significantly higher blood pressure ($p<0.0001$). This short-term hypertension resulted in significant atrial remodelling. Electrophysiology studies showed an increase in effective refractory periods and conduction slowing in addition to atrial enlargement and dysfunction, interstitial fibrosis and inflammation. Another study using the same technique showed that over 5 weeks of induced hypertension there was significant atrial remodelling.

This was associated with increased arterial pressure and biatrial hypertrophy increase refractoriness additionally there was greater AF inducibility, significant conduction slowing and increase heterogeneity.[46] In a rat model using spontaneously hypertensive rats (SHR), demonstrated the first evidence that hypertension was indeed associated with the substrate for atrial arrhythmias including left atrial fibrosis.[47] This study provided the evidence that SHR were suitable for further studies assessing atrial remodelling due to hypertension. An additional study in SHR rats assessed the impact on the atria due to hypertension and aging the atria demonstrated significant atrial structural and electrical remodelling.[44]

Mapping studies in humans have shown similar outcomes. Patients who were free from AF with chronic hypertension and left ventricular hypertrophy were compared to a control normotensive cohort.[48] Patients underwent EP study, this demonstrated those with hypertension had atrial remodelling characterised by conduction slowing, regional conduction delay and increased inducibility of AF. It has been demonstrated however that this substrate may indeed be reversible. This was shown in the SHR rat model with the use of angiotensin II receptor blockade.[49] Hypertension is also responsible for left ventricular hypertrophy, left atrial enlargement and aortic stiffness all of which are causative factors of AF.[50] Therefore studies indicate that therapies to target the substrate promote tight blood pressure control is imperative in managing patients with AF.

1.2.1.2 Management of Hypertension

The management of hypertension has developed over the years. Due to the nature of the condition we know that BP is a dynamic measurement and can vary significantly based on how, when and where the measurement is taken. Initially in 2014 the

American College of Cardiology (ACC) and American Heart Association (AHA) developed guidelines for the management, detection, evaluation and prevention of hypertension.[51] The recommendations for management of hypertension was largely based on age. In individuals aged >60 the treatment for hypertension should be initiated if a BP was >150/>90 mmHg. For those <60 years of age treatment should be initiated to achieve a BP of <140/<90 mmHg. Pharmacological treatment should be based on the race and risk factors that individuals present with. In 2017, the American College of Cardiology and American Heart Association released guidelines whereby they reduced the hypertension target BP from 140/90 to 130/80 mmHg.[52] This created some controversy on what the optimal level is. This definition was potentially based on the SPRINT trial whereby concerns were raised over the method of measurement, so they therefore set the target systolic BP as <130.[41] To date there is very inconsistent data surrounding the optimal targets with inconsistent literature available.[42,53-55]

Additionally, these guidelines suggest the optimal way to take a blood pressure is a 6-step process which if performed in the optimal setting would take around 15-20mins. This is not feasible in a clinic setting and is not representative of daily BP. As such 24 ambulatory monitoring is suggested for those with suspected hypertension.[52] The current European Society of Cardiology/European Society of Hypertension (ESC/ESH) guidelines in hypertension released less than a year after the ACC/AHA guidelines suggest that optimal blood pressure is <120 mmHG systolic and <80 mmHG diastolic, with normal being 120-129 and/or 80-84 mmHG, high normal is classified as 130-139 and/or 85-89. Grade 1 hypertension is 140-159 and/or 90-99 mmHG, grade 2 is 160-179 and/or 100-109 mmHG and grade 3 hypertension is ≥180 and/or ≥110 mmHG.[56] The recommendations suggest that hypertension should not be based solely on the BP reading but rather that other additional cardiovascular risk

factors including age, smoking, sex, dyslipidaemia, diabetes, obesity, renal disease, family history, prior myocardial infarction, or transient ischaemic attack should be taken into consideration such that treatment of the cause is also addressed. Based on these a scoring system was established in the guidelines, this demonstrates for example a patient with symptomatic cardiovascular (CV) disease, renal disease or diabetes would present as a very high-risk patient with blood pressures in the high normal range. The guidelines suggest for the treatment of hypertension should include lifestyle changes and pharmacotherapy for those with diagnosed hypertension and who are at high risk by use of antihypertensive agents.

1.2.1.3 Aortic Stiffness

Recently the concept of arterial and aortic stiffness has been correlated with the development AF. This technique is a non-invasive and clinically validated reproducible method to assess aortic stiffness through central pulse wave analysis.[57,58] This technique allows for important measure of potential sub-clinical organ damage, allowing for enhanced patho-physiological relevance, which can't be assess by peripherally derived blood pressures.[57,59,60] It has been shown that increased arterial stiffness in hypertensive patients is a strong independent predictor of AF even after adjusting for age, 24-hour pulse pressure and left atrial diameter.[61] The Framingham study demonstrated that increase augmentation index, brachial artery diameter and lower flow-mediated dilatation was associated with higher risk of incident AF. Additionally, arterial stiffness when adjusted for age, sex and hypertension (HR 0.79; 95% CI; 1.02-1.28, p 0.02) was associated with increased incident AF.[62] In lone atrial fibrillation patients undergoing AF ablation evidence of increased peripheral, central pulse pressures and augmentation index was significantly associated with higher rates

of AF recurrence.[63] Additional benefits of central blood pressure is the potential it provides to diagnose pre-hypertension, therefore enabling early management. While this is a new area of interest there is still a strong need for more larger studies to provide further insight into the implications this has on patients with AF.

1.2.2 OBESITY

1.2.2.1 Overall Prevalence

Obesity is a global epidemic that in turn contributes to hypertension, hyperlipidaemia, and diabetes. Early studies of data taken from 199 countries and territories showed obesity doubled from 6.4% up to 12% between 1980 and 2008.[64] More current data demonstrates the global prevalence have seen these numbers continuing to increase with 2015 worldwide data estimating 107.7 million children and 603.7 million adults being obese.[65] A large pooled analysis of 1.8 million participants from cohort studies across the world highlighted the impact that obesity has on coronary heart disease and stroke.[66] This demonstrated a 50% and 44% increase risk for coronary heart disease for overweight and obese individuals respectively. Additionally, stroke rates were substantially higher 98% for the overweight and 69% for obese patients. Worldwide data assessing the rates of obesity in children and adolescents found that the mean BMI for girls in 1975 was 17.2 this rose to 18.6 in 2016, and for boys it was 16.8 in 1975 rising to 18.5 in 2016.[67] These figures suggest that obesity is now starting at a younger age, therefore this may influence the incidence of AF in younger populations. These staggering numbers will place a huge burden on our healthcare system given the causal relationship this has with other cardiovascular comorbidities, with an estimated annual

cost of $873.8 million between 2008-2009 in Australia[12] and $66 billion annually to the United States healthcare system.[68]

1.2.2.2 Relationship to AF

The similarity in temporal trends of obesity and AF, suggest a potential cause and effect relationship. It is perhaps not surprising that with an increase in the prevalence of obesity we have seen a similar rise in the prevalence of AF, as many of the associated risk factors for obesity are the same as those of AF. A large study in 2004 of 5282 patients over a follow up of 13.7 years, showed there was a 52% increase risk of new onset AF as a result of obesity.[69] A recent meta-analysis risk of AF associated with obesity, in which there was a 29% increase in incident AF for every 5-unit increase in body mass index.[70] The recent HUNT3 study undertaken in Norway found that overweight and obesity not surprisingly were associated with an 18% and 59% higher risk of AF respectively when compared to those with a BMI range between 18-25.[71] Obesity is associated with numerous co-morbidities. These include hypertension, diabetes, sleep apnea, cancers, and cardiovascular disease. Obesity has been demonstrated to be an independent risk factor for cardiovascular disease.[72,73] Despite the corresponding risk factors between obesity and AF, obesity in itself remains an independent risk factor for AF.[69,74-76]

Experimental studies in the ovine model have demonstrated short term weight gain results in progressive remodelling of the atria, this was show with a greater deposition of fibrous tissue, a greater expression of endothelin receptors and abnormalities in atrial conduction which in turn resulted in greater inducibility of AF.[77] A subsequent chronic ovine model of obesity extended these findings and describes a unique component of the substrate for AF. This study demonstrated a marked increase

in the pericardial fat volumes. Interestingly histological samples of the atrial myocardium from regions adjacent to the pericardial fat depots showed epicardial fat infiltrating the myocardium, potentially resulting in voltage abnormalities which disrupt normal conduction and promote AF.[78]

Clinical data also demonstrates the relationship the role of obesity and epicardial fat in the promotion of AF. Early studies demonstrated that when compared to normal weight patients with obesity undergoing electrophysiological studies were significantly more likely to have increased LA pressure and volumes.[79] Additionally, obese individuals had significant LA remodelling and impaired contractility. These variances were significant following adjustment for common risk factors such as hypertension, sleep apnoea and diabetes. More recently a larger cohort who were undergoing AF ablation were studied using cardiac magnetic resonance imaging and electroanatomic mapping of the LA prior to undergoing ablation.[80] This study demonstrated that there was significantly more atrial remodelling, with areas of low voltage, conduction slowing and increased fractionation of electrograms. Interestingly in regions of epicardial fat depots there were more distinct changes noted, highlighting the role of epicardial fat in the promotion of AF.

Not only does obesity result in the substrate for AF but it may have an important impact on the clinical management of obese individuals with AF. A recent study of 3333 patients who were undergoing AF ablation demonstrated that patients with a BMI ≥30 had a significantly higher recurrence rate of AF, highlighting indeed that it is crucial to target obesity as a first-line treatment prior to undergoing AF ablation.[81]

1.2.2.3 Obesity Paradox

Previously there have been studies that suggest obese patients with heart failure, hypertension and coronary heart disease paradoxically do have better long-term outcomes when compared with non-obese patients.[82-84] While the strong relationship between obesity and AF has been shown there is also on the other hand data suggesting an obesity paradox and AF. In 2016 the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) study presented data from their large cohort of 17, 913 AF patients with at least 1 risk factor for stroke, these were randomized to either Apixaban or Warfarin anticoagulation. They concluded that both higher BMI (>25kg/m^2) and waist circumference (>102cm for men and >88cm) for women was associated with a lower all-cause mortality and stroke.[85] The obese cohort had many other comorbidities for AF such as hypertension, hyperlipidaemia and diabetes, and this may have resulted in early intervention therefore treating the risk factors and subsequently contributing to the paradox. Similarly, other studies have suggested the obesity paradox, with the AFFIRM (The Atrial Fibrillation Follow-up Investigation of Rhythm Management) study suggesting that overweight and obese patients (HR 0.40, 95% CI; 0.26-0.60; p <0.001 and HR 0.77, 95% CI; 0.62-0.95; p=0.01 respectively) had a lower cardiovascular mortality compared to normal weight patients.[86] Of note both these studies had younger cohorts in the obese categories. Given age is a factor for AF, this factor could have also contributed to the outcomes being greater in the obese cohorts. Additionally, as AF is a progressive disease previous data has demonstrated that with each added cardiometabolic risk factor the risk of a more progressive disease increase proportionately,[87] it is therefore hard to ignore that the short term follow-up in both these studies, 1.8 years for ARISTOTLE and 3 years for AFFIRM, may be erroneous

due to the progressive nature of this disease and the relationship of obesity to AF has been demonstrated in studies greater than 13 years.[69,88]

With this contradicting data on obesity and its benefit for AF all-cause mortality and stroke, more research is required to understand if the "obesity paradox in AF" is indeed a factor to consider in the management of AF.

1.2.3 PHYSICAL ACTIVITY

It has been shown that the US sedentary rates have increased from 19%-52% in women and 11%-44% in men from 1988-2010.[89] Exercise and physical activity have been widely reported to reduce cardiovascular disease incidence. Compared to sedentary, runners had a significantly reduced risk 30% and 45% of all-cause and cardiovascular mortality respectively.[90] Interestingly, this reduction in risk was achieved by running as low as 5 to 10 minutes a day and slow speeds. Sedentary lifestyle has been shown to promote all risk factors for metabolic syndrome.[91] Physical inactivity is known to promote obesity. It has been shown that early inactivity leads to subsequent obesity. Adolescents with decreased physical activity were a significantly higher risk of obesity (OR 3.9), there was a stronger risk of abdominal obesity (OR 4.8).[92] Independent of obesity, physical activity predicts a lower risk of cardiovascular disease.[93] A large randomised trial of obese >65 years of age, found that physical activity in this group combined assisted with significant reduction in BMI over the duration of the study.[94] Specifically for AF, greater levels of physical activity result in lowered incidence of AF.[95,96] Similarly, poor cardiorespiratory fitness has been reported to increase the incidence of AF, even after adjustment for other risk factors.[97]

Importantly, physical activity has also been reported to diminish the risk associated with other notable risk factors such as obesity.[98,99] The HUNT3 study

interestingly showed that active obese individuals had a 22% lower risk of AF than those who were obese and sedentary, therefore suggesting physical activity seems to offset some of the risks associated with that of obesity and AF.[71] A recent study has shown that physical inactivity was significantly independently associated with worsened AF severity.[100] The Women's Health Study found that women who engaged in strenuous physical activity up to 3 times a week had a 16% reduction in AF, however when corrected for BMI this was not so significant.[101] The large Swedish Mammograph Cohort study which assessed 36,513 women at baseline found the incidence of AF over a long follow-up of 12 years was 15% lower in those who exercised >4 hours weekly.[96] Likewise the Women's Health Initiative study looking at 81,317 women demonstrated over a follow-up of 11.5 years a 10% lower incidence of AF in those who exercised over those who did not.[99] The Cardiovascular Health Study highlighted that moderate-intense physical activity was associated with a 28% lower incidence of AF.[95]

Interestingly, the risk of AF paradoxically increases in those who engage in high volumes of exercise, such as endurance sports participants.[102,103] High-intensity or elite athletes seem to present with similar risks of AF as those who demonstrate physical inactivity. Nordic skiers who participated in 5 high endurance events were 29 more likely to develop AF compared to those who only undertook 1 race.[104] Males who exercised vigorously 7 days a week presented with a 20% higher risk of AF than a no-exercise group.[105]

There are limited studies which have researched the underlying mechanism which impact exercise on AF.[106] Reduction in weight interesting even at modest levels demonstrated improvements in LA and LV function. The CARDIO-FIT study demonstrated that with improvements in exercise capacity as small as >2 MET gain

resulted in improvement of atrial remodelling.[107] Additional benefits were seen in ablation outcome, with individuals who were able to achieve weight reduction >10% and improvement of >2 MET gains having a 13% higher AF freedom. It has been suggested that 3 potential mediators; ectopic triggers, modulators and altered atrial substrate may be responsible for promotion of AF with endurance sport.[108] An increase in vagal tone subsequently could result in pulmonary vein triggers. Similarly, atrial stretch due to biatrial dilation play a role in the promotion of arrhythmogenesis.[106] Mechanisms that promote AF freedom also comes from the benefits of exercise training. Exercise results in a decrease in oxidative and inflammatory stress which results in improved autonomic balance, blood pressure control, glycaemic control, diastolic function and a decrease in visceral fat.[106]

It would seem there is a U-curve association between exercise and AF with too little and too much increasing the risk of AF. The guidelines suggest moderate regular physical activity is recommended in the prevention of AF.[109]

1.2.4 DIABETES MELLITUS

In 2014 the International Diabetes Federation has estimated that by 2035 around 592 million individuals will be affected by this disease. Studies have shown that there is a 40% increase risk of AF in individuals who have type II diabetes mellitus.[110] In a observational cohort, over a follow-up of just over 7 years, diabetes was associated with a 26% increase risk of AF in women.[111]

A large study of almost 300,000 patients it was demonstrated that AF occurred in 15% of diabetes patients compared to only 10% in the control group this was significant even following multi-variable analysis suggesting a strong link between diabetes and AF.[112] The Framingham study showed that in patients with diabetes there

was a 1.4 increased risk of AF in males and 1.6 fold increased risk in women following multivariate analysis.[113] More recently a meta-analysis of the literature including both cohort and case-control studies demonstrated that there was 40% (RR 1.39, 95% CI; 1.10-1.75, p<0.001) greater risk of AF in diabetes patients, following correction for publication bias the RR was 1.34 (CI; 1.07 to 1.68).[114]

The role of type 1 diabetes in promoting the development of AF is not well studied. This is perhaps due to the population with Type 1 being a younger population. An interesting study out of Sweden, has for the first time shown an increased risk of AF in type 1 diabetes.[115] Over 36,000 patients were studies in comparison to control patients and were followed for almost 10 years. The incidence of AF was higher in females than males (HR: 1.50, 95% CI; 1.30-1.72; p<0.0001) versus (HR: 1.13, 95% CI: 1.0.1-1.25; p=0.029), overall p=0.0019.

There are several mechanisms that are believed to correlate diabetes and AF. Inflammation along with autonomic remodelling by impaired nerve blood perfusion and vagal activation, structural abnormalities with atrial dilatation, myocardial hypertrophy and interstitial fibrosis, electromechanical remodelling due to atrial fibrosis and interatrial electrical conduction delay and atrial electrical remodelling due to conduction abnormalities have all been associated as possible mechanisms.[116-119] However not only is there is a lack of human data in the area but additionally there are no large randomised control studies in this area. Early detection and improved diet are important in addressing glucose intolerance.

1.2.5 OBSTUCTIVE SLEEP APNOEA

Obstructive sleep apnoea (OSA) is becoming increasingly recognised as a causative risk factor for AF. Sleep disordered breathing is a highly prevalent issue in cardiovascular disease with 45% of patient with hypertension, 50% with heart failure, 60% with AF and 30% coronary disease all having OSA.[120] Several studies have demonstrated a greater prevalence of OSA in patients with AF. Gami et al, showed that in patients with persistent AF who were referred for cardioversion, <10% had undergone a sleep study compared to the general cardiology control population 49% versus 29% (p=0.0004) had OSA.[121] A more recent study found similar findings, suggesting the apnoea hypopnea index predicts the recurrence of AF. With patients who had an apnoea hypopnea index (AHI) >15 significantly more likely to have recurrent AF following cardioversion (p=0.003).[122]

This work has been demonstrated in a rat model. In a study by Iwasaki et al who were able to show that repeated obstructive episodes of the airway was associated with repeated bursts of AF with ongoing repetitive episodes there was the eventual changes resulting in chronic cardiac remodelling in atrial substrate similar to what we observe in the clinical scenario, increase atrial size, AF induction, conduction slowing and atrial fibrosis.[123] A study of pigs showed that by applying negative tracheal pressure during tracheal occlusion not only reversibly shortened atrial refractory periods but also promoted inducibility of AF.[124-126] In a sheep model hypercapnia transitioning to normal blood-gas levels was found to be associated with atrial refractory and conduction recovery, which may explain the prevalence of AF in OSA and pulmonary disease.[127]

In the human model, OSA has been shown to result in chronic atrial remodelling which could explain the relationship between OSA and AF. This has been shown in a

group of patients undergoing paroxysmal AF ablation, with a significant AHI compared to a reference-patient's undergoing SVT ablation.[128] This study demonstrated large areas of low voltage in patients with OSA along with atrial structural changes and abnormal conduction, this was significantly worse than seen in the control patients. The progressive atrial structural substrate may be a result of chronic comorbidities and risk factors such as obesity and hypertension.[129] A recent study of patients with paroxysmal AF assessed the role of OSA in a cohort of patients undergoing ablation.[130] Patients with OSA had an increase incidence of extra-PV triggers associated with structural and functional atrial remodelling. Successful ablation of these triggers improved outcomes and freedom from AF. Further studies demonstrated the relationship of OSA and obesity as independent risk factors for AF, highlighting that with an increase in BMI and apnoea-hypopnoea index there was a relative increase in AF frequency.[131] In this study of over 3500 individuals, incident AF occurred in 14% of the patients over the follow-up of almost 5 years. Stevenson et al showed that 62% of patients in the AF group compared to 38% of reference patients had moderate to severe sleep disordered breathing.[132] This study compared patients with no past or current AF and demonstrated a significantly higher number of patients with OSA and AF than no AF 49% versus 32%, (p=0,0004). Additionally, with adjustment for common risk factors such as age, BMI, hypertension and heart failure, patients with AF doubled the risk of OSA (OR: 2.19; 95% CI 1.40-3.42). These studies demonstrate chronic risk factors such as hypertension, obesity and metabolic syndrome results in progression of the atrial substrate. This progression is due to the complex and dynamic arrhythmogenic atrial substrate promoted by obstructive apnoea's and the frequency of nocturnal premature atrial contractions.[133]

A recent study examining the sleep apnoea monitoring algorithm in pacemaker patients has shown patients who had higher RDI had a 1.6-fold increased risk of an AF episode that corresponding day.[134] By assessing the RDI from the pacemakers it was clear there was significant night-to-night variability in sleep disordered breathing. This raises the question as to the impact this may have on individuals who undergo single overnight polysomnography to diagnose sleep disordered breathing.

1.2.5.1 Management of Sleep Apnoea

Treatment for OSA is usually achieved with continuous positive airway pressure (CPAP) therapy. The large Outcomes Registry for Better Informed Treatment of AF (ORBIT-AF) trial of over 10,000 patients found for patients with AF 18% more hospitalisations were required.[135] Similarly, they demonstrated that those with OSA who were using CPAP were less likely to have progression of AF disease to more permanent AF (HR 0.66%; 95% CI 0.46-0.94; p=0.02).

There have now been several studies which have demonstrated that treatment of OSA reduces the risk of AF recurrence following catheter ablation. An early study assessing the role of OSA on ablation outcomes, showed that those with OSA were more likely to have recurrent arrhythmia.[136] Among patients with paroxysmal AF 69% without OSA compared to 48% with OSA were free from AF at follow-up. Among chronic AF, 47% without OSA compared to 22% with OSA remained free from AF. In a recent study among patients who underwent pulmonary vein isolation, Fein et al identified 62 patients had a confirmed diagnosis of OSA.[137] While 32 patients were "CPAP users" the remaining 30 patients were "CPAP non-users". These were matched with patients without a history of OSA undergoing AF ablation and a group of AF

patients with OSA who were managed on CPAP but no AF ablation. This study showed AF free survival for patients with some interesting results. In the patient who doesn't undergo AF ablation and has no OSA has a 66% AF free survival whereas if the patient with OSA and AF is treated with AF ablation and CPAP therapy their results are the same as an individual who has no OSA with a 72% AF free survival. Remarkably, patients who do not undergo AF ablation but having their OSA treated with CPAP was 33%; if one has an AF ablation without treatment of their OSA, they have the same AF free survival 37%, as the patient who had not had an AF ablation. These results while observational have been reproduced repeatedly in the literature and argues in favour of treating OSA to improve the outcomes of AF ablation. Similarly, another study assessing outcomes of ablation in patients using CPAP found comparable findings.[138] In individuals undergoing AF ablation, those treated with CPAP therapy had significantly greater AF free survival this was almost comparable to those with no OSA (p=0.33). For those who had OSA but were not being treated with CPAP there was more AF recurrence following AF ablation (p=0.009). This study found that concomitant OSA was an independent predictor of AF recurrence HR: 2.61 (95% CI: 1.12-6.09; $p<0.05$).

An early meta-analysis of 6 studies, demonstrated that patients with OSA had a 25% increase risk of AF recurrence following ablation (RR 1.25, 85% CI: 1.08-1.45; p=0.003).[139] While more recently another meta-analysis assessing the use of CPAP and AF recurrence confirmed the above studies. Those who used CPAP experienced less AF recurrence 24.9% versus 42.5%; RR 0.60, 95% CI: 0.51-0.70; p=0.000.[140] These meta-analysis highlight the role that OSA plays in AF recurrence and that appropriate treatment is imperative when managing patients with these conditions.

Despite these compelling results there has been no large randomised control study in this area which would be needed to further evaluate the role CPAP plays in ablation outcomes.

1.2.6 SMOKING

The literature demonstrates that smoking results in an increase in sympathetic tone, inflammation, thrombus, endothelial dysfunction, atrial fibrosis and oxidative stress which are potential mechanisms for the development of AF.[141-144] The Framingham study demonstrated the risk of AF for males smokers was 1.0 (95% CI; 0.8-1.4) and for females 1.4 (95% CI; 1.0-2.0).[36] The ARIC Study has shown more than a 2-fold (2.05; 95% CI, 1.71-2.47) increase in the incidence of AF for current smokers. The risk of AF reduced for those who were former smokers and similarly the risk of AF decreased in those who ceased smoking (HR, 0.88; 95% CI, 0.65-1.17)[145]. The Rotterdam Study looked at a large cohort of individuals who were followed for a median of 7.2 years and had no AF at baseline to assess for the incidence of AF, following multivariate analysis there was an increased risk of AF in current smokers (RR 1.51, 95% CI; 1.07-2.12) and the same was seen for former smokers (RR 1.49, 95% CI; 1.14-1.97), suggesting that cigarette smoking is related to an increased risk of AF development.[146] More recently the REGARDS study, of over 11,000 participants from the US over a 10.5 year follow up demonstrated quite a high incidence of AF 9.5% in smokers compared to 7.8% in non-smokers ($p<0.001$), this was associated with a 15% increased risk of AF. Following adjustment for cardiovascular risk factors this was no longer significant. There was a strong association between smoking and AF in subgroups such as young compared to old and those with and without prior cardiovascular disease, and blacks compared to whites,

suggesting that the relationship between smoking and AF is possibly arbitrated by these risk factors.[147]

A recent meta-analysis demonstrated that there was a higher prevalence of AF in current smokers was RR 1.23 (95% CI; 1.08-1.39) additionally they estimated a 6.7% and 1.4% increased risk of AF in men and women respectively based on the studies included in their analysis. This study also recognised that smoking cessation reduced the risk of AF but did not eliminate it.[148] Interestingly, was another meta-analysis which was aimed to assess the risk of AF in males compare to females. This highlighted that smoking is a significant risk factor for AF (RR 1.24; 95% CI: 1.12-1.36, p<0.001). This demonstrated that men RR 1.38 (95 CI; 1.21-1.57, p<0.001) were more likely to develop AF than women 1.28 (95% CI; 0.93-1.76, p=0.1356).[149]

1.2.7 ALCOHOL

The mechanisms by which alcohol is attributed to the initiation of AF can be associated with the direct cellular effects on atrial myocytes with acute oxidative stress and autonomic function by sympathetic activation and change in heart rate variability, with long term alcohol consumption together with cardiovascular risk factors responsible for LA remodelling and dilation, with an increase in LA pressure and fibrosis.[150] There have been varied findings relating to the proarrhythmogenic influence of alcohol intake, likely due to significant heterogeneity in the method for measuring and reporting alcohol intake. The Malmo Diet and Cancer study reported an association of incident AF in men who consumed high levels but this was not seen in women.[151] The Framingham data showed similar findings with an increased risk of AF in men but not women.[152]

Mechanisms for this relationship are not clearly defined. One study outlined the 'holiday heart syndrome' suggesting that the prolongation of the PR, QRS and QTc intervals may promote re-entry.[153] A meta-analysis of the literature showed that based on the intake of alcohol those with high consumption had an increased risk of AF (HR 1.34, 95% CI; 1.20-1.49, p<0.001) for moderate intake the risk of AF was increased for males but not females (HR 1.26, 95% CI; 1.04-1.54, p=0.02 and HR 1.03, 95% CI; 0.86-1.25, p=0.37) respectively. For low alcohol intake there was no associated risk of AF (HR 0.95, 95% CI; 0.85-1.06, p=0.37).[154] More recently the Norwegian Hunt Study of over 47,000 participants showed a curvilinear association between alcohol and the risk of AF, there was almost no increase risk with up to 7 drinks per week but this increase significantly with more than 14 drinks per week (1.28 95% CI; 1.07-1.73). They demonstrated that if alcohol was consumed at up to 1 drink per day for women and 2 per day for men there was essentially no risk of AF 0.07% (95% CI; -0.01-0.13). The overall AF incidence with alcohol intake compared to non-drinkers was 1.6% (95% CI; 0.6%-2.7%).[155] A recent publication has demonstrated that in 75 patients with regular moderate alcohol consumption there was associated lower atrial voltage and conduction slowing suggesting these electrical and structural changes may explain AF in patients with moderate regular alcohol intake.[156] These studies while heterogeneous do demonstrate a direct influence of alcohol as a risk factor for the development of AF.

1.2.8 CAFFIENE

The association between caffeine and atrial fibrillation requires further studies. Early studies have varied results. The Multifactor Primary Prevention Study found consumption of 1-4 cups of coffee daily was associated with a risk of AF (OR 1.24,

95% CI: 1.00-1.54).[157] There was no association though when drinking >4 cups daily. The large Danish Diet, Cancer and Health Study found that regardless of the amount of caffeine consumed there was no increased risk of AF or atrial flutter.[158]

A very early study undertaken in mice was able to demonstrate that with administering extremely high doses, 15mg/kg of caffeine,[159] there was subsequent sympathetic overdrive resulting in tachycardia, ventricular ectopy and consequently ventricular fibrillation. There has been one study undertaken in dogs where caffeine was intravenously injected at a dose of 1-5 mg/kg, this surprisingly resulted in reduced inducibility of AF.[160] In a similar model undertaken in humans who were received oral caffeine at a dose of 5mg/kg prior to undergoing electrophysiology study for supraventricular tachycardia this also demonstrated inability to induce arrhythmia.[161]

Given caffeine is a stimulant it is perhaps not surprising that the assumption is made that it would therefore be pro-arrhythmic. Caffeine effects the sympathetic activation, intracellular calcium trafficking, adenosine receptors and is and antioxidant.[162] The increase of intracellular calcium potentially results in enhancing the automaticity of atrial pacemaker cells therefore potential resulting in atrial arrhythmia.

Systematic review and meta-analysis of 7 observation studies with 115,993 individuals found no associated with an increased risk of AF (OF 0.92, 95% CI; 0.82-1.04).[163] There was a slight significance suggesting that caffeine may have a protective effect. Another meta-analysis pooled together 6 large studies with a cohort of 228,465.[164] The primary results found that there was a weak association with reduced risk of AF (RR 0.90, 95% CI; 0.81-1.01, p=0.07). Habitual caffeine intake showed an inverse relationship with a 6% decrease risk of AF for every 300 mg/d increment in habitual intake.

More recent data has suggested that a higher intake of caffeine is associated with a lower incidence of AF.[165] This was a long study of 12-year incidence, high intake was defined as >320 mg/day. There was stepwise new incident cases of AF based on intake: 10.2% for low intake and 2.2% for high intake ($p<0.001$).

Despite significantly lacking data and evidence many clinicians advise on caffeine avoidance. Based on the literature it is suggested that caffeine intake of up to 300 mg/day seems safe and indeed may be protective rather than harmful against AF.[162]

1.2.9 HYPERLIPIDAEMIA

Hyperlipidaemia also has been demonstrated to show an association with AF, to date the data has been varied and inconsistent.[166-168] Similarly studies have also suggested there is a cholesterol paradox with low levels of cholesterol associated to an increased risk of AF.[169,170] The Japan the Niigata Preventive Medicine Study was a large study which demonstrated following multivariate adjustment low HDL was associated with a risk of AF in women but not men (HR 2.86, 95% CI; 1.49-5.50 and HR 1.35, 95% CI; 0.77-2.38) respectively.[166] In addition with every 10 % decrease in HDL women had a 28% higher risk of AF. Neither triglycerides or other lipid rations were associated with a risk of AF. The ARIC Study which had a long follow up of up to 18.5 years showed a 20% increase risk of AF associated with low high-density lipoprotein (HDL), although elevated triglycerides were not associated with AF.[33] Similarly a subsequent analysis of this cohort demonstrated lower incidence of AF in those with higher low-density lipoprotein (LDL) and total cholesterol, although HDL and triglycerides were not independently associated with AF following multivariate analysis.[168] In a

combination of two large community based cohorts, the Framingham Heart Study and Multi-Ethnic Study of Atherosclerosis cohorts it was observed that following multivariate adjustment HDL was associated with a lower risk of AF (HR 0.64, 95% CI; 0.48-0.87) in higher levels of HDL compared to lower levels of HDL. However, triglycerides were associated with a higher risk of AF based on increased levels (HR 1.60, 95% CI; 1.23-2.05) but total cholesterol and LDL were not associated with a risk of AF.[167] Adding to the heterogeneous literature, the Women's Health Study demonstrated a paradoxical association between AF and lipoprotein measures. Following adjustment for risk factors there was an inverse relationship for several measures namely, LDL (0.72, 95% CI; 0.56-0.92, p 0.009, total LDL particles (HR 0.77, 95% CI; 0.60-0.99, p 0.045) and small LDL particles (HR 0.78, 95% CI; 0.61-1.00, p 0.05) with an overall p <0.05.[171] More recently a large study of over 88,500 participants in the Kailuan Study found and inverse association with TC and LDL and incident AF.[172] This was a long-term study of over 7 years, which found higher TC (HR: 0.60, 95% CI; 0.43-0.84) and LDL (HR: 0.60, 95% CI; 0.43-0.83) were following multivariate adjustment inversely associated with incident AF. While HDL and TG were not shown to be associated with incident AF. Given the vast differences and gaps in the data, there is a need for further studies are required to determine the role of blood lipids on AF risk.

1.2.10 FAMILIAL AF

The genetic or hereditary impact on AF has been one of ongoing research and largely remains unknown. In 1997 a study undertaken in families with AF to assess the potential genes, highlighted they were not able to conclude definitively the genes

responsible but were able to show that screening was a rapid process and could be used to find the potential link.[173] A recent study of Europeans looking at genetic risk score based on ancestry using 5 large prospective studies.[174] They were able to determine that genetic risk scores were associated with incident AF after adjusting for clinical risk factors for those in the highest quartile of scoring having up to 67 higher risk of new-onset AF. This was also associated with around a two-fold increased risk of cardioembolic stroke.

The first gene that was directly linked to hereditary AF was the mutation of the KCNQ1 gene.[175] From here there has a multitude of genes that have been associated with AF, this area is continuing to evolve and new genes seem to be found, there is not always the ability to replicate findings.[176-179] The recent PREVEND study found 3 known-AF gene variants (rs6666258, rs6817105 and rs10821415) were associated with AF that was self-terminating, this was not the case for persistent non-terminating AF.[180]

A very recent large trans-ancestry meta-analyses assessing common and rare variant was able to identify 12 new loci which are seen to implicate genes which affect cardiac structural and electrical remodelling.[181]

A recent overview of genetics and AF by Fatkin et al, eloquently looks at the current knowledge available regarding genetics and AF. This demonstrates 25 ion channel related genes, 13 transcription factors, 9 associated with myocardial structural components, 8 signalling or protein genes, and 6 gene loci with no particular gene identified.[182] The effect these genes have on AF are genetic, pathophysiological and mechanistic through ion channels, transcription factors and myocardial structural components which lead to repolarisation, refractoriness, cell identity differentiation

and proliferation as well as cell-cell coupling, conduction heterogeneity all of which lead to automaticity and re-entry followed by AF.[182]

While the genetic factor is a somewhat complex relationship, studies have shown there is a relationship between genetics and AF, albeit still not overly conclusive. This remains an area of ongoing investigation which is largely uncharted and requires a significant amount more research and studies to fully understand the genetic link.

1.3 MECHANISMS AND PROGRESSION OF ATRIAL FIBRILLATION

1.3.1 Mechanisms of AF

While AF is a complex disease there is several key mechanisms that are believed to be associated with atrial structural remodelling. This begins at a cellular level, with the downregulation of calcium and upregulation of potassium, this results in shortening of the atrial refractory period and AF cycle length.[183,184] Electrical remodelling is a result of this given that the electrophysiological properties of the atria are administered by ion channels, pumps, and exchanges.[32] These instabilities may mediate AF and in effect alter autonomic tone to propagate AF.[185,186] Structural remodelling in many patients will begin before the onset of AF.[187] This process can be due to many factors including fatty infiltration,[80,188,189] amyloid deposition,[190,191] inflammation,[192] and fibrosis[32,187,193-195]. Electrical dissociation between the muscle bundles and local conduction heterogeneity are a result of structural remodelling.[196] These changes can be associated with various cardiac conditions and risk factors.

1.3.2 Mechanisms Promoted by Risk Factors

Age one of the most common risk factors for AF. It has been shown that age is associated with electrical and structural remodelling which resulted in a greater propensity for AF.[197] Hypertension has been well described to result in an abnormal atrial substrate. Atrial fibrosis, atrial enlargement, atrial fibrosis, increase in AF duration, conduction slowing, increase conduction heterogeneity, and cellular changes has been shown in many models.[43-45,48,198-200] Several animal studies have shown the correlation between obesity and AF. Obesity results in many of the modifiable risk factors. Studies in the ovine model have shown that by increasing the weight of the animals there is a great increase in fibrous tissue which is associated with increase inducibility and abnormal conduction.[77] Further studies have shown, also in a sheep model, obesity resulting in epicardial fat infiltration, which promoted in significant atrial remodelling and fibrosis which resulted in propensity for AF.[78] A recent human study has demonstrated through MRI and EP study obesity was associated with electroanatomical remodelling of the atria, this was more distinct in areas adjacent to epicardial fat depots.[80] During sleep, obstructive apnoea's cause the upper airway to collapse, this results in swings in intrathoracic pressure which has been attributed to myocardial stretch in the heart, therefore promoting AF.[129,201] Atrial remodelling has been shown in a human model whereby patients with OSA had significant atrial enlargement, reduction in voltage and widespread conduction abnormalities, which lead to the propagation of AF.[128] Exercise has positive influences on the heart by a decrease in inflammatory and oxidative stress, this in turn leads to improvement in blood pressure and glycaemic control, improvement in autonomic balance and diastolic function and decrease in visceral fat.[106] There is an increase in arrhythmogenesis as a result of atrial stretch and an increase in vagal tone as a potential

mechanism for pulmonary vein triggers.[106] Several other risk factors have shown to promote AF due to structural and electrical atrial remodelling.[202]

1.3.3 Progression of the AF Substrate

Atrial fibrillation is known to be a progressive disease. While initially many patients present with paroxysmal episodes over the course of time these episodes become more persistent and eventually transpire into more sustained forms of AF.[87,203] It was initially considered that this progression was due to the arrhythmic process whereby "AF begets AF";[203] recent data has also implicated risk factors in the progression of the disease. Progression of the atrial substrate therefore may be more related to the underlying risk factors of the individual. Several studies have demonstrated the correlation between fibrosis and risk factors, along with aging, congestive heart failure, obstructive sleep apnoea, hypertension, and obesity has been known to promote fibrosis and progress the atrial substrate.[48,77,78,123,128,197,204]

Indeed, it would seem that the more concomitant risk factors an individual has the more likely they are to have more persistent episodes of AF.[35,205] In a large cohort of patients demonstrated that 17% of patients progressed from paroxysmal to permanent AF over a 5 year follow up.[205] This study found that a BMI $\geq$ 30 was associated with a 1.5-fold increase risk of progression from paroxysmal to permanent AF. The large German registry found that only 18.7% of patients had permanent AF in the absence of risk factors.[35] This increased based on the number of risk factors a patient had. With 54.8% of patients who had five or more concomitant risk factors presenting with permanent AF. A systematic review of AF progression found that at 1 year there was a 10-20% progression of AF disease in patients with AF.[206] For longer-

term studies this increase with progression rate from 50-55% after 12 years. For patients who underwent ablation the rate of progression was lower at 5 years of follow up 2.4-2.7%.

A recent study demonstrated that even following successful ablation of AF.[207] In this study patients undergoing AF ablation were compared to control patients undergoing SVT ablation. At baseline the AF patients had significantly great areas of low voltage ($p<0.001$), conduction slowing ($p=0.005$), increased fractionation ($p<0.05$) and left atrial dilation ($p=0.01$). Following a successful AF ablation and in the absence of any arrhythmia the patients underwent further EP study to assess progression. This demonstrated that despite no AF, the AF patients had greater areas of low voltage associated with persistent conduction slowing ($P=0.005$) and an increase in fractionation ($p<0.001$). This suggests there is progression of the atrial substrate suggesting progressive injury to the atrial myocardium despite the cessation of arrhythmia.

While there is much data to support the progression of AF disease the ability to reverse the AF substrate is still in its infancy and we await the results of several studies in this area.

1.4 SOCIOECONOMIC STATUS AND ATRIAL FIBRILLATION

Socioeconomic status (SES) is commonly used to assess an individual's social position in and according to the World Health Organisation is defined as circumstances in which people are born, grow, live, work, and age, along with the systems put in place to deal with the illness.[208] It is known that poorer health is the results of poorer socioeconomic circumstances, however this can vary dependent on the medical

condition.[209] The impact of wealth has been associated with mortality outcomes, with less wealth associated with a 62% increased risk of deaths among the least wealthy.[210]

1.4.1 Cardiovascular Health

The key factors used to assess the social determinants in patients with cardiovascular disease include, socioeconomic position, race and ethnicity, social support, culture and language, access to care, residential environment.[211] The markers of socioeconomic position include material condition based on income and wealth, health, education, access to valued personal activities such as work, political voice, social connections, environment, physical insecurity such as crime or violence.[211]

While SES has previously been associated with cardiovascular health. Low SES status has been linked to greater mortality. Previous studies have shown the correlation between SES and stroke rates, a significantly higher stroke rate among elderly women in a low socioeconomic stratum. Similarly, large cohort study individuals between 40 - 50 years, ischemic stroke was more prevalent in low SES neighbourhoods compared to high SES neighbourhoods.[212]

The National Heart Foundation in Australia has recently released the Australian Heart Maps, which provides statistics from around the nation on various cardiovascular diseases.[213] The data available, was collated in conjunction with Australian census data which enables correlation with socioeconomic status. The maps enable a breakdown by state or region and provides detailed statistics on admission, and a breakdown of heart disease risk factors of that area. An example of what is available is if one wanted data on Sydney, the maps demonstrate that 3.9% left school prior to completion of year 9, this compares to 11.3% the Australian national average. Sydney has a lower rate of admission 35 per 10,000 persons compared to the national

average of 48 per 10,000. The mortality heart disease mortality rate is 60 per 100,000 compared to the national average of 68 per 100,000 persons. In terms of heart disease risk factors, there is a high prevalence of hypertension 43% much higher than the national average of 23%. Physical inactivity is significantly lower 57% compared to the national average of 66%. Obesity prevalence is 17% which is significantly lower than the national average of 28%. These maps contain in-depth and useful information of the cardiovascular impact of regions around Australia.

1.4.2 Atrial Fibrillation

There is limited data surrounding the association between AF and SES. While there have been several studies that have assessed the differences in race and AF development[214-217], many of these did not look at social determinants such as income and education. The Atherosclerosis Risk in Communities (ARIC) Study prospectively followed over 14,000 patients who at baseline were free from AF.[218] This study was a long study of 20.6 years follow-up, over this duration there was 12.5% incident AF diagnosed. This study demonstrated that low income was associated with a higher risk of AF with low education also a risk for women although this was not the case for men (HR: 1.88, 95% CI 1.55-2.28 and HR: 1.15, 95% CI 0.97-1.36, respectively). Interestingly, the risk of AF was higher for Caucasians compared to blacks for which socioeconomic status did not seem to be able to account for.

Patients with AF and low SES has also been seen to have a higher mortality following adjustment for other co-morbidities.[219] Another relatively large cohort from Sweden showed that in males with AF who were living in a low SES neighbourhood there was a higher relative risk of all-cause mortality (HR 1.49, 95% CI; 1.13-1.96)

compared to those who were in a middleclass neighbourhood. Additionally, there was a shorter time to death for those in the middle compared to low SES neighbourhood.

1.4.3 Obesity and the Link to Socioeconomic Status

The World Health organization has demonstrated that obesity rates in high income countries has not risen as quickly as those in middle- and low-income countries. Within Australian and indeed internationally there has been shown to be a significant relationship between obesity and SES.[220-222] Given the established link between obesity and AF, taking into account SES may enable more targeted management of patients who present to our clinics with AF.

1.5 GENDER DIFFERENCES IN ATRIAL FIBRILLATION

1.5.1 Incidence and Prevalence of AF by Gender

Although the prevalence of AF in males over a 20-year period rose 28%, females over the same period rose 35%.[1] Several large studies have evaluated the specific sex prevalence and incidence of AF. There have been many studies using different methods of detection which show varying rates of AF incidence, these have been predominately from the US and Europe.[3,223-228] When assessing this within the US, the two major studies, the Framingham Heart Study and the Olmstead County, Minnesota studies report the incidence of AF in women is 1.6 and 2.7 respectively compared to 3.8 and 4.7 in men, per 1,000 person-years.[3,229] The most familiar study the Global Burden Worldwide study[1] which combined all published studies, found the incidence of AF in women to be 0.9 and 0.4 per 1,000 person years for the developed and

developing countries respectively. For men this was 1.23 and 0.54 per 1,000-person years for the developed and developing countries respectively. There is a significant lack of AF incidence data from the Asia-Pacific, Middle East, South American and African populations.

As with the incidence of AF, Chugh et al once again showed in the Global Burden Worldwide study[1] demonstrated the global prevalence of AF to 373.1 (per 100,0000 population) for women, for males this 596.2 (per 100,000 population). Various studies have demonstrated country-based prevalence as with the above mentioned these are mostly from the developed countries and there are limited studies outside of the US and Europe.

The age adjusted prevalence of AF in the Framingham study was 49.4 in women and 96.2 in men per 1,000 person-years.[229] Due to the life expectancy of females being longer this results in the number of women with AF greater than men based on US Medicare data. This data suggests that in 2007 the prevalence of AF was 10.3% in males and 7.4% in females.[223]

In Europe there is data from various countries. There are two Rotterdam Studies in the Netherlands which found prevalence of 7.1% and 5.1% in females and 8.6% and 6.0% in males.[228,230] In Spain the overall prevalence was also slightly higher for women 4.5% compared to 4.4%.[231] A couple of studies have been done in Germany with the results showing a prevalence of 1.9% in both for female and 2.4 - 4.6% in male.[226,232] Sweden has several studies with varying prevalence from 0.06% to 9.2% in females compared to 1.3% to 16% in males, the large variation in prevalence could be due to the method in which the prevalence was obtained.[224,233,234] The United Kingdom have several prevalence studies which has fairly consistent reports of between 0.3-1.29% in females and 0.27% to 1.49% in males.[235-238] Other countries

have minimal data. Portugal doesn't demonstrate any difference with a prevalence of 2.5% for both males and females.[239] Switzerland has a low prevalence in females 0.54% compared to 1.23% in males.[240] Denmark has a prevalence of 1.1% in females and 3.3% in males. Iceland demonstrated 1.5% for females and 2.3% for males.[241] There is one study from Northern Italy which found a high prevalence of 7.3% in females and 7.5% in males.[242] Ireland had a significant difference in prevalence between sexes finding 4.8% in males compared to 1.4% in females.[243] Scotland has quite extreme differences in prevalence rates from 0.56% up to 7.9% in females and 0.75% up to 9.4% in males.[10,244] The higher rates however were obtained by using hospital coding versus the lower rate which was obtained by ECG diagnosis.

From the Asia Pacific region there is much less data. Two studies from China demonstrate similar prevalence from 0.63% to 0.63% in females and 0.66% to 0.78% in males.[245,246] From Japan, three studies have prevalence at relatively the same ranging from 0.43% to 1.2% in females and 1% to 2.4% in males.[111,247,248] Additionally, there is a study from Korea with females prevalence at 0.4% and males at 1.2%,[249] and Taiwan 0.7% and 1.4% for females and males respectively.[250]

The prevalence of AF within Australia has been estimated at 6% in males and 4.8% in females, with a projected increase of 1.25% in males and 0.85% in females by 2034, suggesting fairly similar rates of increase exclusive of gender.[5]

A recent review has shown the Asia Pacific projected prevalence is estimated to reach 49 million males and 23 million females by 2050, this is 12-fold higher than the equivalent predictors for men and women in the US.[2,251,252]

To date there is minimal data from South American, Africa and the Middle East, with more studies needed to better understand the true prevalence of AF in these countries. It is also of course reasonable to surmise that based on the variety of

prevalence rates in the current data there is significant work that needs to be undertaken in the area of screening for AF prevalence and incidence.

1.5.2 Gender specific risk factors

1.5.2.1 Age

Age is well known as a leading cause of AF, it has been associated with a two-fold increase in AF for every 10-year increase in age.[36] There are many studies that demonstrate that women present with AF at an older age.[229,253-256] This has been shown particularly when presenting for AF ablation women present later and are often significantly older than men.[257-259] In 2 large European registry cohorts women were shown to not only be older but present with more heart failure with persevered ejection fraction, hypertension and valvular heart disease.[255,260]

1.5.2.2 Obesity

The Women's Health Study demonstrated over 12 years of follow-up increase in BMI >30 resulted with an 18.3% attributable risk of AF.[74] Interestingly this study also demonstrated that women who were able to reduce their weight to a BMI <30 they also reduced their risk of AF. The Framingham study demonstrated a 4% increase risk of AF per 1-unit increase in BMI for men (95% CI, 1-7%, p=0.02) and women (95% CI, 1-7%, p=0.009).[69] Following adjustment HR: 1.52 (95% CI, 1.09-2.13, p=0.02) for men and 1.46 (95% CI, 1.03-2.07, p=0.03) for women. A similar result was seen in the Danish Diet, Cancer, and Health study where 1 unit increase in BMI conferred a HR 1.08 (95% CI, 1.05-1.11) in men and 1.06 (95% CI, 1.03-1.09) in women.[76] This data

all from large cohort studies highlights the importance of obesity as a major risk factor for AF in both sexes.

1.5.2.3 Hypertension

Hypertension is one of the key modifiable risk factors and this has been demonstrated to be higher in women. The European Observational Research Programme Pilot survey on AF of 3119 patients, examined the sex differences in presentation, treatment and outcomes. This demonstrated that females were older at presentations 71.7 ± 10.6 versus 66.9 ± 11.7 ($p<0.0001$), more likely to have hypertension 74.7% versus 68% ($p<0.0001$).[260] Similarly a large Health Claims and Medicare database study also demonstrated a significantly higher rate of hypertension for females 66.2% versus 61.8% ($p<0.001$).[258] The Women's Health study was able to demonstrate that in a cohort of healthy women, systolic BP was shown to be a better predictor than diastolic BP with systolic blood pressure, following adjustment, strongly associated with incident AF 1.17 [95%CI, 1.08-1.27, $p<0.0001$].[40]

1.5.2.4 Hormones

There is limited data surrounding the relationship between sex hormones, it has been suggested that women may develop AF later in life due to the impact of progesterone, this has been demonstrated to shorten action potential therefore providing a protective mechanism against AF.[261,262] The Multi-Ethnic Study of Atherosclerosis found that higher levels of testosterone was associated with the development of AF in men.[263] While lower testosterone has been demonstrated in the Framingham Heart Study to be associated with an increased risk of AF in males aged over 80 years old.[264] In new-

onset AF the use of hormone replacement demonstrated a decreased risk of myocardial infarction in a large cohort of women.[265] While the Women's Health Initiative Study found no difference in postmenopausal women who were randomised to placebo or oestrogen replacement.[266] The Framingham Heart Study of women over 60 years old did not identify a particular age related to menopause which would contribute to a significantly increase risk of AF.[267] There is a substantial gap in the knowledge of hormones and AF, to date no consistent data has suggest this to be a significant contributor to the time of onset or development of AF.

1.5.2.5 Atrial Fibrosis

Atrial fibrosis has been shown in animal data adverse remodelling of that atria both structure and function has resulted from persistent AF.[268] Human data has shown higher levels of fibrosis associated with the presence of AF.[269,270] Emerging data has suggested left atrial fibrosis as a marker for outcomes in AF ablation.[271,272] There is limited data in this area given it is still an evolving area, to date in patients with long-standing persistent AF demonstrated that women presented with more worsening of remodelling due to fibrosis in women compared to men, thus potentially mediating recurrence of AF following ablation.[273] A recent study has found that women have more advance fibrosis, furthermore women who had prior history of stroke when compared to both men and women with no prior history were found to have higher fibrosis.[274]

1.5.3 Stroke and Mortality

Women with AF tend to present more highly symptomatic and carry a significantly stronger risk of stroke, cardiovascular and all-cause mortality.[273,275-277] Early data demonstrates that women with AF have been shown to have a 5-fold higher increase risk of ischemic stroke when compared to males.[2,37] This is reflective of the fact that women score an extra point in the CHA_2DS_2-VASc score given the increased risk for women who have AF.[278]

A recent large observational study demonstrated a 19% risk of stroke in females with AF, this also remained significant following adjustment for risk factors.[279] Conversely, another study found that after multivariate analysis female sex was not significantly associated with stroke.[280] It is potentially not just related to sex but rather the risk of AF and stroke is more age related. There are several studies which show an independent relationship of female sex and stroke for those age ≥65 [281,282] years to 75 years.[279,283-285] While stroke is often associated with severe complications, it has been shown that women who experience stroke often present with more severity than males,[286] with poorer long-term outcomes.[287]

Recent data suggests that female sex may not in fact confer a significant risk in the absence of additional risk factors.[288-290] A study of 3 nationwide registries found that sex was a prognostic factor for stroke in AF patients.[284] It did reveal the risk for females was significant in those who had additional non sex-related risk factors for stroke. The recommendation as such was that for women in the absence of additional risk factors, female sex would not score 1. As such the recent Heart Foundation Guidelines in Australia has simplified the score by removing female sex from the CHA_2DS_2-VASc score – changing it to CHADS-VA.[291] Similar changes have also been made to the scoring used in the European Society of Cardiology (ESC)

guidelines.[17] The ESC guidelines have shown evidence to suggest that female sex in the absence of other risk factors does not appear to increase the risk of stroke. Therefore, it is recommended that should a female score 1 due to sex and without other risk factors, anticoagulation should only be considered on an individualised bases following co-decision with the patients.

The Framingham Heart Study reported AF being associated with a 1.9-fold increase in mortality for women compared to 1.5-fold for men. 15 The Olmsted County, Minnesota study reported double the risk of mortality for new onset AF.[292] Similar results were reported in the Copenhagen City Heart Study with the risk of mortality double for women compared to men.[293] However, there is heterogenous data surrounding mortality given studies also report that the risk of mortality is higher for men not women.[86,294-296] This data suggests perhaps that further studies may be required to tease out the role of female sex and stroke as well as the risk of mortality between genders and possible confounding factors.

1.5.4 Symptomatic Differences

There is a lot of literature to demonstrate that women not only present older and often with more comorbidities they also present with more atypical symptoms. A review reporting on symptomatic and asymptomatic AF has shown that the RR 0.57 of asymptomatic AF was less common in women compared to men.[297] The European Observational Research Program demonstrated that women presented with more palpitations (08.2% versus 68.5%, $p<0.0001$), more fear and anxiety (14.6% versus 10.5%, $p=0.0007$) and they had a higher proportion in European Heart Rhythm Association class III and IV ($p=0.0012$).[260] The RACE study which assessed difference

in symptoms of patients with persistent AF demonstrated by using the SF-36 quality of life questionnaire assessing symptoms such as general health, physical functioning, pain, mental health, vitality, social functioning and emotional state. Women with AF had worse QoL compared to both healthy female subjects and males who had AF ($p<0.05$).[298] The ORBIT-AF registry similarly found women to be older and have a higher CHA_2DS_2-VASc score, but yet they were more likely to be less asymptomatic 32% versus 42.5% ($p<0.001$), with more palpitations, dyspnoea, light-headedness, fatigue and chest discomfort compared to males ($p<0.001$).[257] Despite more comorbidities and symptoms, the management and treatment of women differs significantly.

1.5.5 Treatment Differences

The European Observational Research Program (EORP) study demonstrated that when compared to males females are more likely to be treated with rate control as opposed to rhythm control ($p=0.002$)[298]. The ORBIT-AF registry also demonstrated that women were less likely to undergo cardioversion (<0.001), AF ablation ($p=0.04$), receive β-blockers ($p<0.001$) but more likely to receive AV Node ablation for rate control (<0.001).[257] Similarly, a short-term study of only 1 year of a large cohort also demonstrated that women were less likely than men to receive electrical cardioversion (14.9%versus 20.6%) and ablation (3.3% versus 6.3% ($p<0.001$))[275]. It would seem women present with more commonly with fatigue and weakness which are fairly atypical symptoms this may impact on diagnosis time.[299,300] A review of the Health Claims and Medicare database of over 21,000 patients undergoing index AF ablation (29% female) demonstrated that women were more likely to be re-hospitalised for AF

but less likely to undergo cardioversion or repeat ablation.[258] With ablation emerging as a frontline treatment for AF, we can see that the rates of ablation have risen significantly over the years. Despite this fact, while the percentage of females undergoing ablation has risen 560% over 12 years, this is still significantly lower than that of males who tend to undergo more AF ablation than females.[216] Conservative treatment tends to be undertaken in women with AF. More often women are treated with rate control measures in comparison to men who are provided rhythm control. Further larger studies may be required to better understand this and the impact it may play on outcomes of women.

1.5.6 Ablation Outcomes

One of the striking things in gender and AF is the disparity and heterogenous data surrounding that of ablation outcomes. While many studies have looked at outcomes of ablation there is limited data on gender differences, despite them all reporting older presentation and more comorbidities. Of the studies which do report this the is low numbers of females in the cohorts, varying blanking periods and follow-up and in many cases a lack of clinical data.

One of the earliest studies which addressed outcome differences found that despite the baseline differences there was no difference in the need to undergo repeat ablation, success rates of ablation or AF recurrence between males and females.[301] Of note this was a small study with 221 patients of which only 71 were female. Since this the reports have been different. Results from the German Ablation Registry, which has one of the largest cohorts of females found that women presented with more paroxysmal AF 72% versus 61% ($p<0.001$) but yet less freedom from AF and/or antiarrhythmic drugs ($p<0.001$), and overall freedom from AF ($p<0.05$) following

ablation.[259] Additionally, they found that there were more moderate complications ($p<0.05$) and persistence of symptoms ($p<0.001$) for women compared to men following ablation. Being a registry, they lack significant clinical and follow-up data. Another study of ablation outcome demonstrated the 1- and 4-year AF free rates following initial ablation were comparable between men (79.1% and 70.9%) and women (71.6% and 64.7%) however the final outcome did show worse outcomes for females ($p=0.02$).[302] When assessing patients with long-standing persistent AF only a study with once again a small cohort, 73 females following both initial ablation ($p=0.004$) and overall freedom ($p=0.087$) females fared worse than males.[303] In individuals with paroxysmal AF, despite once again more comorbidities there was no major difference following primary ablation with similar maintenance of sinus rhythm ($p=0.24$), following final procedure there was a significant change in women more likely to have failed ablation and have recurrence of AF ($p=0.007$).[304] One of the largest cohorts of females with 518 females, found that there were 5 times more males than females that underwent AF ablation, despite this women were less likely to be free from AF at follow-up ($p=0.001$) and have more complications post operatively ($p<0.001$), of note they did have a short blanking period of 8 weeks.[305] The recent Fire and Ice trial following multivariate analysis found female sex to be the strongest predictor of outcomes following ablation with almost 40% increased risk of ablation failure and a 36% increased likelihood of rehospitalisation at final follow-up regardless of ablation modality.[306] Vallikati et al undertook a meta-analysis of 20 pooled studies looking at ablation outcomes.[307] Despite significant heterogeneity in the studies included such as follow-up durations, blanking periods, and studies not primarily aimed at gender outcomes, this demonstrated women were more likely to have AF recurrence following AF ablation. What is striking in the meta-analysis is that 65% of

the studies included has less than 100 females in their cohorts. Additionally, 25% had sort follow-up of approximately 12 months, this highlights the paucity of data, lack of female inclusion (possibly due to lower numbers undergoing ablation) and lack of gender driven ablation outcome studies, suggesting more is needed to better understand the disparities in outcomes.

1.6 LIFESTYLE MANAGEMENT

1.6.1 Initial Randomised Pilot Study

In 2013, a randomized clinical trial demonstrated that weight loss and risk factor management in overweight or obese individuals with AF, resulted in a dramatic reduction in patient symptoms and AF burden determined by ambulatory monitoring. In the group who underwent intervention with weight loss and lifestyle changes, there were also significant improvements in patient well-being, blood pressure, glycaemic control and cholesterol.[308]

1.6.2 Method of Lifestyle and Risk Factor Management Delivery

Several approaches could be used to achieve lifestyle and risk factor management in patients with AF. In the management of AF, to date, a dedicated risk factor clinic has been shown to yield the most impressive results.[107,308,309] The program used to achieve these results focuses on all the primary modifiable risk factor targeting lifestyle and diet changes to achieve outcomes based on each individual patient's particular risk factors. This begins with personalised assessment with patients maintaining a lifestyle journal recording food intake and exercise undertaking. This is reviewed, and

recommendations based on current diet to of diet and promotes high protein, low Glycaemic Index (GI) diet with calorie restriction, with portion control. Sodium restriction is encouraged particularly in patients with hypertension. Individuals are encouraged to exercise up to 30 minutes 3-4 times a week with an aim to increase this up to 250 minutes a week. Patients are screened for hyperlipidaemia which is initially managed by lifestyle and dietary changes if this is not achieved then statins or fibrates are introduced. It is important that all patients with AF undergo sleep studies to evaluate if this risk factor is a causative factor of AF, with CPAP initiated if the AHI is >30. Hypertension is managed aggressively with patients recording this 2-3 times a day with an aim of <130/80 mmHg 80% of the time on home monitoring readings. In addition, patients undergo a clinical stress test to ensure there is no exercise induced hypertension with BP remaining <200/100 mmHg. As with hyperlipidaemia, diabetes is also initially managed with dietary and lifestyle changes with Metformin introduced if HbA1c is >6.5%, patients are also referred to endocrinologist for management. Smoking cessation is encouraged as well as reduce alcohol intake to 3 standard drinks a week.[107] Not only was there a reduction in overall AF burden but there was also marked improvement in other risk factors, patients with hypertension, were able to significantly reduce the use of or cease antihypertensive medications, their cholesterol improved, as did glucose intolerance.

1.6.3 Impact of Risk Factor Management on Ablation Outcomes

The Aggressive Risk factor Reduction Study for Atrial Fibrillation and implications for the outcome of ablation (ARREST-AF cohort study) showed the benefits of risk factor management (RFM) on the outcomes of AF ablation.[309] This study showed that

not only did AF frequency, symptoms and duration improve in the group undergoing risk factor management compared to the controls but there was also more favourable ablation outcomes with 62% AF freedom in the RFM group compared to 26% in the control group following single procedure. This was also replicated in multiple procedural outcomes with 87% in the RFM group and 48% in the control group free from AF at final follow-up. This study also looked at AF freedom at follow up with a step-wise improvement based on the degree of weight loss, with ≥10% weight loss associated with 46% AF freedom, compared to 13% in those who lost <3% weight without the use of anti-arrhythmic drugs or ablation.[309]

1.6.4 Long-term Outcomes of Risk Factor Management

In an ongoing cohort study analysis, the Long-term Effect of Goal-directed weight management in AF Cohort: A Long-Term Follow-up studY (LEGACY) highlighted the importance of long-term weight loss, and management of risk factors such as hypertension.[107] It was shown that with a step wise reduction in weight there was a relative reduction in patient symptoms and overall AF burden. Importantly, in the group who lost ≥10% of their initial body mass, 46% patients remained free from AF without the use of rhythm control strategies over long term follow-up of 5 years. Interestingly, weight fluctuation was shown to offset, but not eliminate the benefits of weight loss on AF freedom.

1.6.5 Role of Exercise and Risk Factor Management

Several studies have attempted to address the benefits of exercise and cardiorespiratory fitness in the management of AF. The Impact of CARDIOrespiratory FITness on

Arrhythmia Recurrence in Obese Individuals with Atrial Fibrillation (CARDIO-FIT) study demonstrated the benefits of exercise by showing that patients who achieved a cardiorespiratory fitness gain ≥2 METs, significantly improved freedom from AF and alleviated AF specific symptoms, when compared to those with <2 METs.[107] A recent randomized trial also demonstrated reduced AF burden with aerobic interval training, alongside fewer hospital admission and cardioversions.[310] Although this was only a short exercise intervention study, those randomised to exercise training reported reduced AF symptoms, improved quality of life, and peak oxygen uptake.[310] These studies support the prescription of exercise in the management of AF.

1.6.6 Further Studies Addressing Risk Factors for AF

In comparison to the benefits shown in these studies to improve blood pressure, the SMAC-AF study looked at the impact treatment in aggressive management of blood pressure would have in the reduction of AF symptom burden and prevent recurrence following ablation. Following ablation and the aggressive treatment of BP, there was no reduction in AF in patients with a BP >130/80 mmHg, and they found that the aggressive treatment consequently resulted in more hypotension.[311] While this study demonstrated no real reduction in recurrence of AF, potentially due to only addressing one risk factors rather than all concomitant risks in the patient, it didn't manage to assess if other substrates may have been the reason for this. Another study has suggested that undertaking renal artery denervation to manage severe drug resistant hypertension in patients undergoing AF ablation results in a significant improved control of blood pressure but also a significantly better control of AF.[312] Therefore, it is feasible that in such extreme states, treatment of a single risk factor may have a role.

In terms of other risk factor clinics, the RACE 3 trial assessed cardiac rehabilitation in patients with AF focusing on pharmacotherapy.[313] While not strictly a clinic which focused solely on risk factors, patients were provided general dietary and physical activity advice. This study demonstrated that patients who were randomised to targeted therapy in the intervention group were more likely to be in sinus rhythm at final follow-up. The also did note a small number of patients reversed their AF type from persistent to paroxysmal over the course of the study.

In long-standing persistent AF patients, a study has demonstrated that in 90 patients who underwent weight reduction management outcomes were not so significant.[314] While there was significant weight loss over 12 months, they were unable to demonstrate improvement in symptoms, AF burden and ablation outcomes. An important limitation is that this is in longstanding persistent population, and therefore the question needs to be asked if it is 'too little too late'. Additionally, the outcome was only assessed at 12 months, given the significant remodelling the atria would have undergone due to longstanding persistent AF, more time may be required to see the full benefit.

In late 2016, the European Society of Cardiology Guidelines have included in the management of AF, risk factor modification and weight reduction as a Class II recommendation.[17] These recommendations are based on recent studies, which have assessed the impact of weight and risk factor management on AF outcomes.

While to date there is compelling data to support risk factor management there is a lack of studies from differing sites. These findings highlight the importance of weight and risk factor management in the first instance when treating patients with atrial fibrillation. Treatment of obesity, hypertension and associated risk factors not only assists with reduction in symptoms, AF burden, ablation outcomes, but may be

used to prevent the occurrence of AF, whilst likely contributing to improved general cardiovascular health.

1.7 DELIVERY OF ATRIAL FIBRILLATION MANAGEMENT

While Australian data shows that admissions for AF have over a 15-year period demonstrated a relative increase of 203%, compared to admissions for other common cardiovascular conditions, acute coronary syndromes 79% and heart failure 17%, nothing seems to have changed in managing these patients.[9] Data taken from the Royal Adelaide Hospital assessing presentations demonstrated 55% of patients who presented had known AF, but yet were on inadequate anticoagulation. Additionally, at discharge 37% were still not adequately anticoagulated, over the subsequent year 26% of all cause readmission were for AF and there was a 10% mortality rate.[315] In comparison heart failure has established clinics where by patients are able to be largely managed outside the hospital, this model has been demonstrated to be highly effective.[316,317] This has been shown for some time, despite the relentless rise in AF prevalence and admissions no such management has been implemented.

Current management is based on the AF guidelines which recommend anticoagulation based on CHA_2DS_2-VASc risk, rate and rhythm control, management of risk factors such as hypertension, diabetes mellitus, obesity and for those who remain symptomatic despite pharmacotherapy.[17]

1.7.1 Key Elements in AF Management

The European Society of Cardiology have provided five domains of management for AF.[17] 1. Haemodynamic instability or limiting, severe symptoms; 2. Presences of precipitating factors and underlying conditions; 3. Stroke risk and need for anticoagulation; 4. Heart rate and need for rate control; 5. Symptom assessment and decision for rhythm control. Together these aim to improved haemodynamic stability, reduce cardiovascular risk, provide stroke prevention, improve symptoms and preserve LV function. Consequently, this provides patient benefit with improved life expectancy, quality of life, autonomy and social functioning.

1.7.1.1 Anticoagulation

The use of oral anticoagulation can assist in preventing ischemic strokes as well as prolonging life.[318-320] Warfarin or vitamin K antagonists (VKA) the traditional form of anticoagulation, have been demonstrated to reduce stroke risk by two thirds and a quarter of patients have reduced mortality.[318] Additionally, a large study of over 94,000 patients found 84% of stroke patients who had a prior history of AF were not on therapeutic anticoagulation prior to stroke.[321] However more recently the non-vitamin K antagonists NOACs have emerged and increase in popularity as a preference for anticoagulation due to the lack of regular blood testing required and reduced interactions. Warfarin is a Vitamin K antagonist, in comparison all the NOACs are Factor Xa inhibitor except for Dabigatran with is a direct thrombin inhibitor. These drugs not only have a shorter time to effect compared to Warfarin but also have a shorter half-life. The NOACs are hepatically metabolised and predominately renally cleared.[322] Supporting the preference for NOACs amongst recent guidelines with a Class I, level A recommendation for stroke prevention over VKA,[109] several studies

have demonstrated superior efficacy with NOACs versus VKA.[323,324] A meta-analysis performed in 2012 by Dentali et al demonstrated that when comparing NOACs to Warfarin, there was a 23% relative risk reduction for stroke and systemic embolism, 14% relative risk reduction for major bleeds, and 11% relative risk reduction in total and cardiovascular mortality.[325] Likewise a meta-analysis of the large randomised trials which assessed 42,411 individuals on NOACs, found similar results with a significant reduction in stroke by (19%), intracranial haemorrhage rates were halved and mortality reduced (10%), this demonstrated similar major bleeds but interestingly demonstrated an increase in gastrointestinal bleeding.[319] Despite this we see that the NOACs have provided an alternative therapy for stroke prevention for patients with AF.

A recent meta-analysis of integrated care has demonstrated that it is a highly effective method of management in the AF population.[326] The method of care is that of the patient being the central focus, being provided education and tools to enable self-empowerment and management of their condition.[17] The care of the patient is done with the assistance of their treating cardiologist/electrophysiologist, AF nurse and the use of decision support technology to assist with guideline adherence. Together this team utilises a multidisciplinary team were required including the primary care physician, exercise physiologist, sleep physician, dietician, pharmacist, endocrinologist, and psychologist.[326]

1.7.1.2 Rate Control

Rate control is recommended in the guidelines although they do also state that there is little robust data to support the best type and the intensity of rate control therapy.[17] This is due to much of the data coming from observational studies as well as short term

cross over trials.[327-330] In the acute setting, particularly that of rapid new-onset AF, rate control is important. This is often delivered in the form of beta-blockers and diltiazem or verapamil as these have rapid effectiveness at high sympathetic tone.[330-334] It is also important to firstly evaluate the cause of the rapid rates, by investigating if due to an infection, anaemia, endocrine imbalance or pulmonary embolism. The guidelines suggest in the setting of acute heart rate, left ventricular function should be evaluated, if there is signs of a decreased function or heart failure then low dose of beta-blocker is recommended, with the use of digoxin if required.[17] For those with stable function, beta-blocker, diltiazem or verapamil is suggested with the addition of digoxin if required. Amiodarone is suggested as useful as a last resort therapy. Ongoing maintenance such as avoiding bradycardia and repeat echocardiography to further manage or determine choice of long-term maintenance is recommended. Urgent cardioversion should be considered for patients in rapid AF who are unstable.[17]

It is unclear what the optima heart rate for AF patients is. The Rate Control Efficacy In the Permanent Atrial Fibrillation (RACE) II study randomised a large group of permanent AF patients to different heart rates.[335,336] Despite this there was no statistical difference in the outcomes of clinical events in between the two groups. The Rate-control versus rhythm-control in atrial fibrillation (AFFIRM) study was designed to assess the two common factors in AF management.[337] The outcomes of this suggested that rate control should be the primary approach to managing AF patients. Compared to rhythm-control it was associated with a decrease incidence of adverse events but did not have any difference in morality. When combined the RACE and AFFIRM studies demonstrated a similar outcome with no association in clinical events.[338]

In patients where medications fail, and the patients remains symptomatic an alternative therapy is that of atrioventricular node ablation and implantation of a pacemaker. Based on recent data from randomised trials rate control may have a limited role in patients with AF and heart failure.[339-341] This procedure is considered to have minimal complications and the risk of long-term mortality is low.[342,343] This procedure does remove the hearts natural pacemaker therefore the patient becomes entirely pacemaker-dependent for the remainder of their life as this is irreversible.

1.7.1.3 Rhythm Control

While it is often the consensus amongst clinicians is by maintaining sinus rhythm the outcomes of AF patients are improved, the data in fact all the clinical trials to date comparing rate and rhythm control have remained neutral.[337,344-350] Despite this there is evidence to also demonstrate that antiarrhythmic drugs when compared to placebo double the rate of sinus rhythm.[346,351-354] Pharmacological restoration by use of antiarrhythmic drugs is a useful method of reversion to sinus rhythm.[355-357] In terms of the drugs of choice, flecainide along with highly potent amiodarone, have been shown to be more effective than sotalol.[358-360] Aside from drugs, electrical cardioversion by the use of direct electrical current is a quick and effect method of sinus rhythm restoration.[361,362] This is best performed when the electrodes are positioned anterior-posterior as this generates a stronger shock field to the left atrium and has been shown to be more effective.[363,364]

It is important to consider carefully the drug of choice as there can be significant side effect associated with anti-arrhythmic drugs. Amiodarone while highly effective can results in a myriad of potential organ damage including the liver, lung, cornea, skin, and thyroid gland. Flecainide is also effective,[353,365] but should be

avoided in those with ischaemic heart disease or heart failure as it can promote ventricular arrhythmias.[366] Sotalol is also very common but does come with the risk of torsades de pointes,[367] so caution needs to be taken when introducing this drug. Other drugs that are commonly used outside of Australia are: dronedarone, propafenone, quinidine and dofetilide.

For highly symptomatic patients and those who are resistant to anti-arrhythmic therapy catheter ablation is also used as a treatment for AF.[368,369] Several studies have shown that compared to antiarrhythmic therapy catheter ablation is more effective in the maintenance of sinus rhythm.[370-375] A recent review of the literature assessed the outcomes of AF ablation on persistent and long-standing persistent patients. This demonstrated that the single procedure efficacy was 43%, this increase to 69% following multiple procedure with and without antiarrhythmic drugs.[376] However the procedure does come with risk of complications due to the invasiveness and length of the procedure. It has been shown in a systematic review comprised of over 83,000 patients the overall complication rate was 2.9% with procedure related mortality 0.005%.[377] However, there are emerging signals in the literature that suggest that there may be greater benefits in some subsets of patients. The recent Catheter Ablation for Atrial Fibrillation with Heart Failure (CASTLE-AF) study has provided interesting results. Patients with heart failure had a significantly lower rate of the composite end point of death from any cause or hospitalisation for heart failure compared to standard medical therapy (HR: 0.62, 95% CI: 0.43-0.87, p=0.007).[339] Similarly the Catheter ablation versus medical rate control in atrial fibrillation and systolic dysfunction (CAMERA-MRI) study in patients with idiopathic cardiomyopathy comparing ablation to rate control in persistent AF patients using loop recorders to assess

recurrence demonstrated an improvement in heart failure in the ablation arm assessed using CMR.[340]

1.7.2 Integrated Care Approach

To date the management of atrial fibrillation has been suboptimal, recently evidence has demonstrated that these strategies have been inadequate in the care of patients with AF. The Euro heart Survey has shown that despite the provided guidelines we are seeing poor adherence to these resulting in an increase in morbidity and mortality.[294] Recent data has shown the same outcomes, the Global Anticoagulation Registry in the field (GARFIELD) highlighted significant inadequacies.[378] At diagnosis of AF 61% of patients were not prescribed anticoagulation. While anticoagulation was associated with a 35% lower risk of death, it was not prescribed in 37% patients who had a higher risk of AF due to CHA_2DS_2-VASc $\geq$2. Perhaps some of the reasons for the non-adherence to guidelines is complex. There is a growing number of patients with multiple problems, healthcare systems are at capacity, there is an inability for a single professional to adequately perform management of AF, resultant in fragmented care.

The chronic care model originally developed some time ago, found the need to develop alternative models of care than what was traditionally being undertaken.[379] This has provided the grounding for the integrated care approach. There have been several effective examples of chronic care models particularly that of heart failure[380] and acute coronary syndromes.[381] To date, AF has not been managed as a chronic condition with recent studies highlighting the need for chronic care. Recent data suggests integrated care for patients with AF may be a solution to improve adherence and reduce hospitalisations.

A randomised controlled trial demonstrated that a multi-disciplinary integrated care clinic which is nurse-led, protocol driven, guideline-based clinic may provide better outcomes. Patients who were in the integrated care group showed a relative risk reduction of 35% of the primary composite endpoint of cardiovascular hospitalisation and mortality.[382] A meta-analysis of integrated care in AF demonstrated that while there was a reduction in all-cause mortality and cardiovascular hospitalisations, there was no significant impact on AF-related hospitalisations or cerebrovascular events.[326]

A pilot study, the Before and After study recruited patients from the emergency department.[383] Those who presented due to AF were provided an appointment in a dedicated AF clinic within seven days of their presentation. This clinic was run by a nurse practitioner and electrophysiologist. Management was systematically undertaken to assess causative factors, symptoms, quality of life and stroke risk. Patients were provided a treatment plan, inclusive of rate, rhythm control and anticoagulation based on guidelines. Patients were then contacted by phone at three months and completed questionnaires. These patients were compared with a propensity matched cohort with a primary composite endpoint of all-cause death, cardiovascular hospitalisations and ED visits due to AF. The primary composite endpoints in this study were statistically significant (OR: 0.71, 95% CI; 0.50-1.0, p=0.049).

An Australian study, the Standard versus Atrial Fibrillation specific strategy (SAFETY) study was a multicentre, randomised controlled study of patients admitted with chronic, non-valvular AF.[384] The integrated care approach was that of a home visit by a cardiac nurse within two weeks of discharge, educational information package if required, referral to other healthcare providers where required and then the treating medical team were provided with recommendations of optimal treatment. The

primary endpoints were all-cause death or unplanned readmission. Interestingly the findings of this study were negative with no significant difference in the primary outcome of all-cause hospitalisations and mortality (HR: 0.97, 95% CI: 0.76-1.23). Despite this there were proportionately more days alive and out of hospital for those in the intervention group this did not result in prolonged event-free survival.

1.8 THROMBOGENIC RISK FOLLOWING ABLATION

1.8.1 Stroke and the Relationship with AF

It is well documented that stroke is the most devastating complication of patients with AF with approximately one third of ischemic strokes attributed to atrial fibrillation.[385] It has been well established that AF is a risk factor for systemic thromboembolism, ischemic stroke, and transient ischaemic attack, with an almost five-fold increased associated risk.[37] The mechanisms behind this is believed to be the formation of thrombus in the left atrium due to a decreased blood flow in the left atrial appendage.[386] While thrombus formation occurs primarily in the left atrium, the mechanisms are complex and somewhat poorly understood, with factors such as mechanical dysfunction, clotting, endothelial dysfunction, inflammation and platelet activation as potential contributors.[387]

Vichow's triad has described the three factors that are responsible for the development of thrombus being abnormal blood flow and stasis, endothelial dysfunction and hypercoagulability.[388] The Vichow's triad perhaps suggest that it is not only the abnormal blood flow but perhaps the role of the thrombus formation as a results of the fibrillation left atrium. As such the use of anticoagulation as a means of

thrombus prevention given the close relationship between stroke and AF, is one of the key components in the management of patients with AF.

1.8.2 Risk of Stroke Following Ablation

It is not clear if eliminating AF will result in a reduction in stroke risk.[17] Despite this a large multicentre registry has demonstrated that successful elimination of AF following ablation resulted in lower stroke rates than those treated medically, indeed the rates of stroke and mortality were indifferent from the general population.[389] Similarly another study has shown favourable outcomes with comparable stroke rates between those following ablation and those without AF.[390] A meta-analysis assessing the impact AF ablation has in reducing stroke in comparison to anti-arrhythmic therapy revealed in thirteen randomised control trial demonstrated that there was no difference in the rate of stroke or TIA between the ablation and drug therapy group.[391] Several studies have looked at risk of stroke, a large Danish cohort study evaluated the risk of thromboembolism and serious bleed following anticoagulation use and ablation. This found over almost three and a half years of follow-up and the rate of thromboembolism with (0.56, 95%CI 0.40-0.78) and without (0.64, 95% CI 1.25-3.35) anticoagulation were comparable, with an incidence of 1.8% cases identified.[392] The Swedish national health registry reports that 30% of patients had discontinued anticoagulation therapy within the first year following catheter ablation. This resulted in patients with a CHA_2DS_2-VASc score having a higher rate of ischemic stroke following discontinuation of warfarin, 1.6% versus 0.3% per year compared to those who remained on warfarin.[393] A large multicentre study assessing cessation at 3-6 months following ablation demonstrated during follow up 0.07% of those off anticoagulation and 0.45% on anticoagulation had an ischemic stroke (p=0.06). While non-randomised

this does suggest a benefit to continuation of anticoagulation following successful AF ablation.[394]

A sub-study of the TRENDS study demonstrated in patients who were monitored at the time of their stroke, only 30% were in AF at the time of the event.[395] However, a recent meta-analysis has suggested that this lack of temporal association with arrhythmia may be a consequence of the type of data collection that was included.[396] This suggested that subclinical AF predicts clinical AF and is associated with increased risk of stroke albeit lower than the risk descried for clinical AF. Therefore, perhaps while ablation reduces AF one of the leading causes of stroke this may not be related to a subsequent reduction in stroke risk. While cessation of anticoagulation following apparent successful ablation seems relatively safe, there still remains a lack of conclusive data, particularly in the absence of large randomised clinical studies.

The answer may come when we see the results of the Optimal Anti-Coagulation for Enhanced-Risk Patients Post-Catheter Ablation for Atrial Fibrillation (OCEAN) trial.[397] This is a prospective, multicentre, open-label, randomized trial, with a primary endpoint being composite of clinically overt stroke, systemic embolism, and convert stroked based on MRI. This study is currently enrolling patients and may assist with some of the answers to the optimal antithrombotic regimen after successful AF ablation.

Chapter 2: Screening Australia Wide for overAll pREvalence of Atrial Fibrillation: AWARE-AF Study

2.1 INTRODUCTION

It is well established that atrial fibrillation (AF) is emerging as a global epidemic with approximately 33.5 million individuals affected worldwide.[1] In the Asia Pacific region, the prevalence of AF is higher compared to the rest of the world due to the proportionally higher aged population and the established increase in AF risk by age.[251] A recent review has estimated that there will be over 70 million people with AF in the Asia Pacific region by the year 2050, which is 12-fold higher than what is predicted for the United States.[2,251,252] In Australia, the prevalence of AF has only been estimated based on international epidemiological studies.[5] Ball et al applied the international AF prevalence statistics to Australian adult population and predicted an AF prevalence of 6.4% (600,000 individuals) by 2034.

Given there is a large percentage of the population who have asymptomatic AF estimated at approximately one-third of patients, screening potentially enables the detection of AF in these patients.[15,16] Multiple studies have been undertaken to screen for AF; the majority were observational, with variable detection rates based on the population screened ranging from 0.8% up to 5.33% of detected AF.[398,399] The prevalence of detected AF varied from 0.5% to over 5%, when these are combined the weight average for newly detected AF was around 0.9% (95% CI; 0.7-1.1).[14] In addition to detection of individual cases, screening for AF undertaken by organisations like Arrhythmia Alliance, StopAfib and Hearts4Heart which partner with patients, government and medical organisations, help increase public awareness. In Australia,

as part of the Heart Rhythm Society AF awareness week to raise knowledge of the disease and associated risk factors in conjunction with screening for individual cases, we collected prospective data on risk profile, predictive risk and screened individuals for AF.

In this study, we report on the clinical characteristics and outcomes of screening that took place in Australia and New Zealand over 2016-2018. We aimed to evaluate the risk prediction of AF in the general population through the use of the CHARGE-AF risk score,[400] determine the detection rate of AF on single point ECG screening, and assess blood pressure (BP) control in the community and describe the distribution of different stages of hypertension as per the European Society of Cardiology guidelines.[56]

2.2 METHODS

2.2.1 AF Screening Setting

Screening was performed as part of AF Awareness Week, which is an annual event undertaken across Australia and New Zealand. This campaign was established by the APHRS/HRS and undertaken with the assistance of Hearts4Heart a patient advocacy group for heart rhythm disorders in Australia.

Screening stations were positioned in hospital foyers and pharmacies throughout Australia and New Zealand inviting the general public. If agreeable, a participant was seated, consented to the process and the following was recorded: an automated BP, a single lead ECG on a handheld device and a health questionnaire. ECG recording, BP measurement and education delivery were undertaken voluntarily by doctors, nurses, pharmacists and allied professionals. Of note due to the number of

centres (186) undertaking screening, some pharmacies (64) were limited to BP and questionnaire completion only with no access to ECG recording. The study was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital and the University of Adelaide, Adelaide, Australia.

2.2.2 Definitions

Atrial Fibrillation: AF was defined as a supraventricular arrhythmia that is characterized by rapid and irregular activation in the atria without discrete P waves on the surface ECG.[401] Diagnosis was confirmed by an electrophysiologist blinded to the individuals clinical characteristics.

Exercise: Exercise was categorised using the criteria from the validated international physical activity questionnaire (IPAQ)[402] as vigorous which included aerobics, running, fast cycling or fast swimming; and moderate which included brisk walking, moderate cycling and moderate swimming.

Alcohol Intake: Alcohol intake was determined by self-reported number of standard drinks consumed on a weekly basis.

Blood Pressure: To classify hypertension we used the current ESC guidelines as follows: systolic BP (SBP) <140 mmHG as normal; SBP 140-159 mmHG as grade 1 hypertension; SBP 160-170 mmHG as grade 2 hypertension; and SBP >180 mmHG as grade 3 hypertension.[56]

2.2.3 AF Detection

Two devices were used for ECG recording and analysis. One was the AliveCor KardiaMobile (AliveCor Inc., USA) which is a validated device for detecting atrial fibrillation[29] and is used by placing fingers on small electrodes and recording a 30 second single lead ECG on a smart phone. The other device used was the PM-10 ECG device (Contec Medical Systems, China; Figure 1). All ECGs were reported by a cardiologist and suspected AF episodes were manually adjudicated by two electrophysiologists. All participants were provided a copy of their risk score and a recommendation to follow. This included focusing on their individual risk factors and in the event of AF detection seeking a review from their general practitioner.

2.2.4 Health Condition Questionnaire

In order to calculate an AF risk score, patients were asked to complete a questionnaire regarding their individual health status (Figure 2). Collected information included date of birth, height, weight, smoking status, prior diagnoses of hypertension, diabetes, heart failure, myocardial infarction, stroke, obstructive sleep apnoea, cardiac surgery, device implant, or prior AF diagnosis. Physical activity levels and alcohol intake were also recorded.

2.2.5 AF Risk Score Calculation

Individualised 5-year AF risk score was calculated, and participants were provided with a graphical risk of AF (Figure 3). To establish risk of AF development, the CHARGE-AF scoring system was used.[400,403] This simple, validated scoring system provides a 5-year AF risk prediction based on age, race, height, weight, smoking,

systolic and diastolic BP, hypertension treatment, diabetes, history of heart failure and history of myocardial infarction. The CHARGE-AF has two models; the simple model which utilises the above measures and the advanced model which requires a 12 lead ECG. The simple model was used in this study.

Additionally, the CHA_2DS_2-VASc score was used to predict the annual risk of stroke for patients with AF. Patients scored 1 point for chronic heart failure, hypertension, diabetes, vascular disease, age 65-74 years and female sex, and 2 for age ≥75 and prior stroke/transient ischemic attack/embolism. Women without other stroke risk factors were scored 0.[404]

2.2.6 Statistical Analysis

Categorical variables are represented as frequencies and percentages. Continuous variables are summarized as mean ± standard deviation (SD) or median and interquartile range as appropriate. For categorical variables, differences between groups was compared using a Chi-squared test. Continuous variables were compared by independent t-test or Mann-Whitney U test where appropriate. A p-value of $p<0.05$ was considered statistically significant. All statistical analysis was performed with SPSS version 24.0 (SPSS, Inc., Chicago, IL, USA).

2.3 RESULTS

2.3.1 Baseline Characteristics

A total of 2586 participants undertook screening. Of those, 2338 had complete data and were included in this analysis (Figure 4). Mean age was 53.2 ± 16.3 and the majority were female (68.4%). Mean body mass index (BMI) was 27.2 ± 5.4 Kg/m^2

and 26.3% were obese (BMI≥30 Kg/m^2) (Table 1). Mean BP measured 131.4 ± 17.8 mmHG systolic and 79.8 ± 10.9 mmHG diastolic.

2.3.2 AF Detection

AF was detected in 4 participants, 3 of whom had a prior diagnosis and 2 were already on oral anticoagulants. The proportion of detected AF using the screening program was 0.2%. Of the detected AF cases (n=4), 2 were female and the mean age was 72 ± 9 years and the mean BMI was 29.9 ± 6.1. Three patients had hypertension, mean BP for them was 134/84 mmHG.

In terms of other findings on the day, there were 36 participants who had isolated ectopic beats, 106 in sinus tachycardia, 77 in sinus bradycardia, 19 had intraventricular conduction delay, 1 participant had an atrial couplet and 1 patient had a short non-sustained run of ventricular bigeminy.

2.3.3 Prior Diagnosis of AF

Participants were asked in the questionnaire if they had a prior history of AF. In total 77/2338 (3.3%) of the cohort had a prior diagnosis of AF, 46 (59.7%) were female, 31 (40.3%) male. Mean age 64 ± 13, with a mean BMI 29 ± 6. Not unsurprisingly, AF risk factors were more common in patients with a prior diagnosis of AF. For those with AF compared to without AF the prevalence was: hypertension 50.6% versus 21% ($p<0.0001$), diabetes 14.3% versus 7.3% ($p=0.05$), OSA 15.6% versus 5.9% ($p=0.005$). Those with AF also had a higher prevalence of prior stroke 14.3% versus 1.6% ($p<0.0001$), prior surgery 16.9% versus 2.9% ($p<0.0001$) and pacemaker implant 5.2% versus 0.5% ($p=0.001$) and BP of 135/82 versus 131/80 mmHG.

2.3.4 Risk Factors by Race

Previous studies have demonstrated the importance of race in developing AF, with Caucasian race being associated with higher risk.[403] In our study, the majority of the cohort were Caucasian (69%), followed by Asian (10%), and Indian (5%) with 10% not reported (Figure 5). Compared to non-whites, whites/Caucasians were significantly older (54.8 ± 16.1 versus 49.7 ±16.3 years, p<0.001) and had a significantly higher BMI (27.6 ± 5.6 versus 26.4 ± 5.1 Kg/m^2, p<0.001). While there was no significant difference in hypertension prevalence (p=0.28), whites had a higher mean BP on the day 132.9±17.9 compared to 128±17.2 (p<0.001). Non-whites had a higher prevalence of diabetes 11.6% compared to 7.5% in whites (Table 1).

2.3.5 CHARGE-AF Score

Based on the questionnaire the median CHARGE-AF score for the population was 0.54% [0.14-2.11]. This was significantly higher in whites 0.59 [0.17-2.2] compared to non-whites 0.41 [0.1-1.66] (p<0.001). This was reflective of a relatively low risk population, as demonstrated by the age and risk factors seen in these participants. Of interest when stratified by sex, males presented with a higher median risk of AF 1.05 [0.23-4.25] compared to females 0.45 [0.11-1.42] (p<0.001; Figure 6). Similarly, males presented older 55 ± 17 versus 52 ± 16 (p=0.001), with higher mean blood pressure 136/82 versus 129/79, more sleep apnoea 18% versus 5.5% (p<0.001), diabetes (12% versus 7% (p<0.001) and myocardial infarction 6% versus 1% (p<0.001) compared to females (Table 2).

2.3.6 Hypertension Control

As part of AF risk factor awareness, we aimed to assess participants' BP control to raise awareness of hypertension and assess BP control across an unselected cohort. Of those with no prior diagnosis of hypertension, 76.6% had a normal BP, 19.7% had BP readings consistent with grade 1 hypertension, and 3.1% had grade 2 and 0.6% had grade 3 hypertension. Of those with a prior diagnosis of AF, 48.9% had normal BP's on the day, while 36.4% had grade 1 hypertension and a further 14.7% had BP measurements consistent with grade 2 or 3 hypertension, indicating poor BP control despite self-reporting a diagnosis of hypertension (Figure 7).

2.3.7 CHA_2DS_2-VASc Score

Of the 77 patients with a prior diagnosis of AF, the mean CHA_2DS_2-VASc score was 3 ± 2 with 6 (7.8%) having a CHA_2DS_2-VASc of 0. 19 (24.7%) participants had a CHA_2DS_2-VASc score of 1. 18 (23.4%) had a score of 2. 13 (16.9%) had a score of 3, and 21 (27.3%) scoring 4 or more. In this cohort 71 (92.2%) had a CHA_2DS_2-VASc score of ≥1. Of these who had a CHA_2DS_2-VASc >1, 44 (61.9%) were not on oral anticoagulation.

2.3.8 Performance of Automated ECG Analysis

The total number of ECGs performed in this event was 2089. 948 were screened using the AliveCor device and the remainder with the PM-10 device. Of those screened with AliveCor, 381 were excluded either due to short duration of recording below 30 seconds (n=186), or due to inability to accurately match the ECG to the participants (n=195). Of the remaining 567 ECGs that were included, the automated algorithm

accurately detected the rhythm in 496 ECG, reported AF in 16, failed to classify the ECG in 55 participants. Following manual adjudication, only 2 of the suspected 16 AF cases were diagnosed as AF. When able to provide a classification (90% of the ECGs), the AliveCor automated algorithm had a sensitivity of 100% and specificity of 97.5% for detection of AF, with a positive predictive value of 12.5%.

A further 1141 were performed using the PM-10 device. This did not display a machine generated diagnosis therefore there were no incorrect machine generated interpretation. 1016 were interpretable, and a further 123 were unable to be accurately interpreted due to artefact.

2.4 DISCUSSION

2.4.1 Major Findings

There is a paucity of data on the community risk of AF in Australia. In addition, the utility of population screening is questioned. This study provides context in the setting of community awareness screening, identifying the following:

1. Detection rate of AF following community screening is relatively low;
2. The 5-year risk of developing AF as characterised by CHARGE-AF score was generally low (0.54%)
3. The predictive 5-year risk was significantly higher in the Caucasian population compared to non-Caucasian. Similarly males presented with a higher risk compared to females
4. A significant proportion of participants with a prior diagnosis of hypertension had poor (grade 2, 11.4%) or very poor (grade 3 3.3%) BP control at the time of screening.

5. Of the patients who had a history of AF, 60% who had a CHA_2DS_2-VASc >1 were not on oral anticoagulation.
6. The type of device used and process in which the ECG is attained is important due to significant amounts of artefact, with the AliveCor having a positive predictive value of 12.5%.

2.4.2 Current Guideline Recommendations

The European Heart Rhythm Association Consensus Statement in 2017 defines types of screening and recommends this as a useful way to detect undiagnosed AF.[14] The 2016 the European Society of Cardiology (ESC) AF management guidelines included a class 1 level B recommendation for opportunistic screening for AF for patients >65 by use of pulse or ECG rhythm strip, and additionally a class IIb level B recommendation for systematic ECG screening in those >75 years old or those who are at high risk of stroke.[17]

2.4.3 Screening Studies for Identification of AF

There have been many screening studies over the last two decades largely due to the advances in technology over this time. It has been shown that the use of BP monitors, handheld ECG recording devices, and smartphone applications are superior forms of detection when compared with pulse palpation.[23] AF detection large depends on the type of screening, population and number screened as shown by the differing rates of detection in previous studies. Proietti et al looked at over 52,000 participants as part of a voluntary community AF screening campaign in Belgium and found 1.1% new AF cases detected.[18] Similarly, LePage undertook screening of the general public

following a media campaign and yielded only a 0.2% detection of AF.[405] To date there has only been three studies from Australia assessing feasibility opportunistic screening.[19-22] One was performed across 10 pharmacies of 1000 participants who were aged ≥65 undertaken using handheld ECG, and found the proportion of new AF individuals to be 1.5%.[22] The Busselton Study of 1770 participants found a prevalence of 4.9% in those aged over 60 years. A recent study of 8,272 individuals in the AusDiab study reported 1.4% of baseline ECG's were in AF.[7] The prevalence in New Zealand was 1.7%, this rose to approximately 5% for those aged over 55 years.[406] In Australia the prevalence is estimated to be between 1.4 and 5%.[5-7]

2.4.4 Tools Used for Screening

While detection of AF can be facilitated by regular pulse checks, other irregularities can be mistaken for AF. Common tools used for screening with various sensitivity and specificities include the Zenicor EKG® (Zenicor Medical Systems), sensitivity 96% and specificity 97%. The MyDiagnostik (Applied Biomedical Systems BV, The Netherlands), sensitivity 95% and specificity 93%. The Omron HCG (Model HCG-801, Omron Healthcare Europe, the Netherlands) monitor, 98.7% sensitivity and specificity 76.2%. The AliveCor (AliveCor Inc., USA), sensitivity 98% and specificity 97%.[13,26-29] In our study, the AliveCor was able to provide an ECG classification in 90% of ECGs, with a sensitivity of 100% and specificity of 97.5% for detecting AF.

2.4.5 CHARGE-AF Score

Interestingly in this study by using the predictive 5-year CHARGE-AF score we were able to demonstrate that Caucasians were significantly more likely to develop AF

compared to non-Caucasians. Additionally, we found that by use of the risk score males presented with more risk factors compared to females, this also corresponded with a significantly greater risk of AF. This has not been demonstrated previously in an Australian and New Zealand population.

2.4.6 Blood Pressure Screening in the Community

While a single time-point BP measurement in a less-than-ideal screening situation may not truly reflect the individual's BP control, it was of interest that a significant proportion (3.3%) of patients with a prior diagnosis of hypertension had a systolic BP of >180 mmHg. This potentially indicates inadequate management of hypertension and further highlights the importance of ongoing engagement with health care practitioners.

2.5 LIMITATIONS

As with all opportunistic screening events, this study comes with innate selection bias. While providing potentially useful information regarding prevalence in a non-selected population, the screening was not performed in a systematic approach to allow epidemiological inferences. The individual AF detection could have been higher had there been more ECG-recording facilities more widely available across the screening sites. However, it is important to recognise that the aim of the campaign was not purely for individual AF detection, but also to improve public awareness for AF and its risk factors. The dynamic nature of BP makes assessing global BP control by a single time-point BP reading very difficult. However, it remains alarming that a significant number of participants with prior diagnosis of hypertension had very high BP readings on

screening, and a further proportion likely have undiagnosed hypertension and were advised to seek medical attention. While this study was inclusive of all races, a much larger cohort would be required to establish AF prevalence, particularly in the Aboriginal, Torres Strait Islander and Maori ethnic groups who are generally under-represented in such studies.

2.6 CONCLUSIONS

Screening for AF provided an opportunity to assess detection of AF in an Australian and New Zealand the general population. Screening enabled further awareness and education of AF and risk factors. This screening event found a very low detection of AF in the Australian and New Zealand population. Additionally, while the overall 5-year risk prediction of AF was relatively low, males presented with a stronger risk of AF than females. The limitations identified in the detection and evaluation of risk provides important information to be used in any future screening approach for AF.

2.7 TABLE AND FIGURE LEGEND

TABLE 1: PARTICIPANTS CHARACTERISTICS

Overall baseline characteristics of the participants, with the risk factors dichotomised by race

TABLE 2: PREDICTIVE 5-YEAR AF RISK BY SEX

FIGURE 1: TECHNOLOGY USED FOR SCREENING

Example of the 2 devices used for screening along with the ECG tracing they produce. 1A is the PM-10 developed by Contec Medical, this is used by placing the hands over the sensors to record ECG. 1B is the AliveCor Kardia device, this is used as displayed by placing fingers onto the sensors to record the tracing.

FIGURE 2: EXAMPLES OF QUESTIONNAIRE

Example of the original questionnaire used as well as an example of one of the Apps used for the questionnaire to establish risk factors for the participants. This provides an example of how the selection of exercise and alcohol were able to be selected. The guide for taking the ECG at the required time point and shown is the final outcome of risk of AF for the participant based on the CHARGE-AF scoring system.

FIGURE 3: EXAMPLE OF APP USED

Example of the application used for the screening, participants answered each question before it proceeded to the next one. The answers were then presented to the patient in an image to demonstrate to them the risk of developing AF over the next 5 years based on the CHARGE-AF score

FIGURE 4: FLOW DIAGRAM

Flow diagram of the participants screened and final cohort used for analysis.

FIGURE 5: DISTRIBUTION OF ETHNICITY

Pie chart with the breakdown of the participants based on the ethnicity.

FIGURE 6: PREDICTIVE 5-YEAR RISK OF AF BY SEX

Scatter plot demonstrating predictive 5-year risk of AF development stratified by sex

FIGURE 7: RESULTS OF HYPERTENSION SCREENING

Pie charts demonstrating the distribution of hypertension graded by normal, grade 1-

TABLE 1: PARTICIPANTS CHARACTERISTICS

CHARACTERISTIC	TOTAL POPULATION N: 2338	WHITE/CAUCASIAN N: 1620	NON-WHITE/CAUCASIAN N: 718	P VALUE
Age	53.2 ± 16.3	54.8 ± 16.1	49.7 ± 16.3	<0.001
Female gender (%)	1599 (68.4)	1117 (69)	482 (67.1)	0.38
Body mass index	27.2 ± 5.4	27.6 ± 5.6	26.4 ± 5.1	<0.001
Smoking (%)	338 (14.5)	260 (16)	78 (10.9)	0.003
Hypertension (%)	597 (25.5)	424 (26.2)	173 (24.1)	0.28
Systolic blood pressure (mmHg)	131.4 ± 17.8	132.9 ± 17.9	128 ± 17.2	<0.001
Diastolic blood pressure (mmHg)	79.8 ± 10.9	80 ± 10.8	79.6 ± 11.1	0.21
Diabetes (%)	204 (8.7)	121 (7.5)	83 (11.6)	<0.001
Heart Failure (%)	46 (2)	29 (1.8)	17 (2.4)	0.35
Myocardial Infarction (%)	68 (2.9)	50 (3)	18 (2.5)	0.44
CHARGE AF Risk Score	0.54 [0.14 - 2.11]	0.59 [0.17 - 2.2]	0.41 [0.1 - 1.66]	<0.001
Known AF (%)	77 (3.3)	60 (3.7)	17 (2.4)	0.09
AF on ECG (%)	4 (0.2)	3 (0.2)	1 (0.1)	0.92
Sleep Apnea (%)	170 (7.3)	112 (6.9)	58 (8.1)	0.31
Prior stroke (%)	54 (2.3)	42 (2.6)	12 (1.7)	0.17
Surgery (%)	90 (3.8)	69 (4.3)	21 (2.9)	0.12
Pacemaker (%)	17 (0.7)	12 (0.7)	5 (0.7)	0.91

TABLE 2: PREDICTIVE 5-YEAR AF RISK BY SEX

CHARACTERISTIC	MEN	WOMEN	P VALUE
Risk Score (median)	1.05 [0.23-4.25]	0.45 [0.11-1.42]	<0.001
Age	55 ± 17	52 ± 16	0.001
Body Mass Index	27.6 ± 4.7	27 ± 5.8	0.019
SBP (mmHg)	136 ± 17	129 ± 18	<0.001
DBP (mmHg)	82 ± 11	79 ± 11	<0.001
Sleep Apnea (%)	82 (11.1)	88 (5.5)	<0.001
Smoking (%)	131 (17.7)	207 (12.9)	0.002
Myocardial (%)	46 (6.2)	22 (1.4)	<0.001
Heart Failure (%)	24 (3.2)	22 (1.4)	0.002
Hypertension (%)	200 (27.1)	397 (24.8)	0.249
Diabetes (%)	88 (11.9)	116 (7.3)	<0.001
SBP=systolic blood pressure; DBP=diastolic blood pressure			

FIGURE 1: TECHNOLOGY USED FOR SCREENING

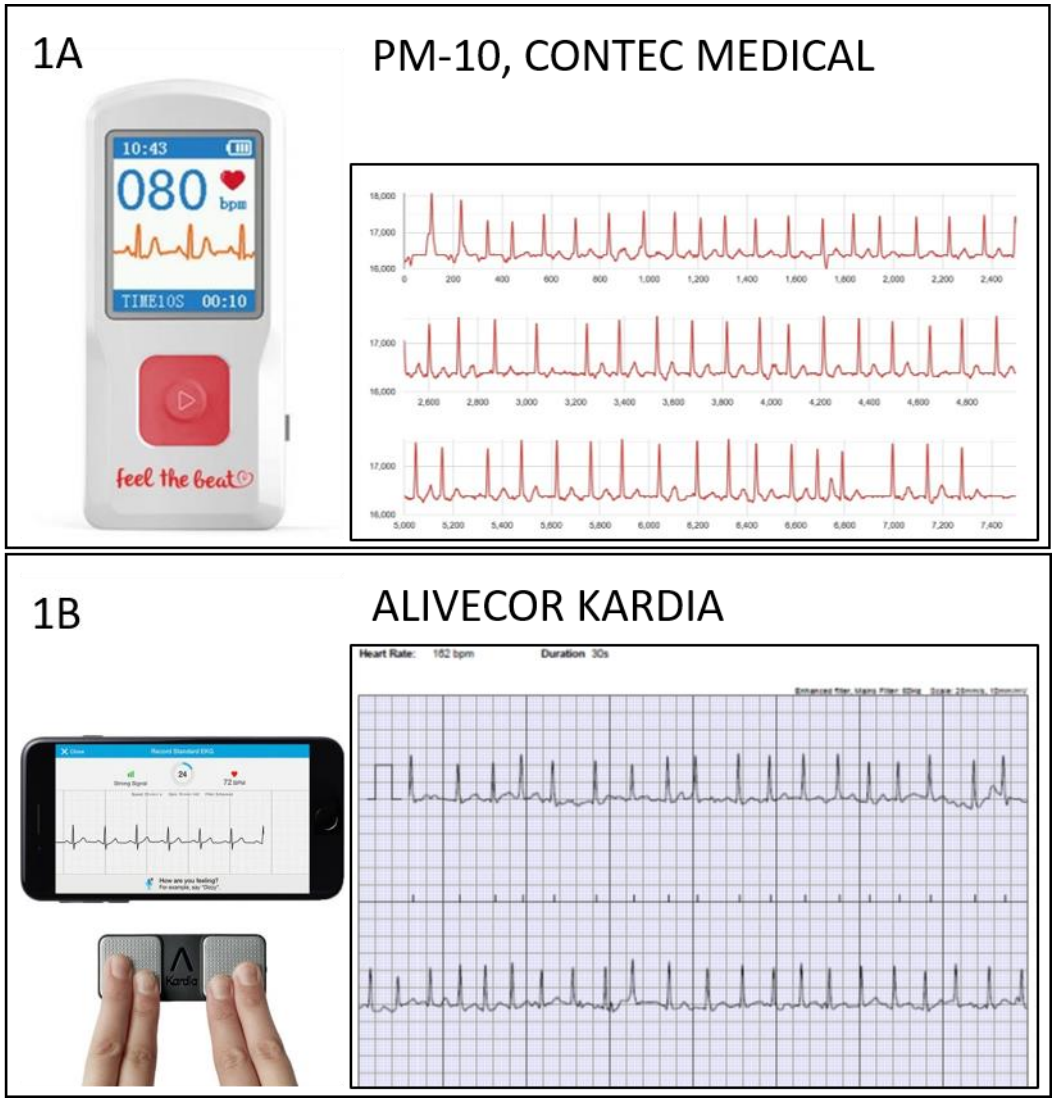
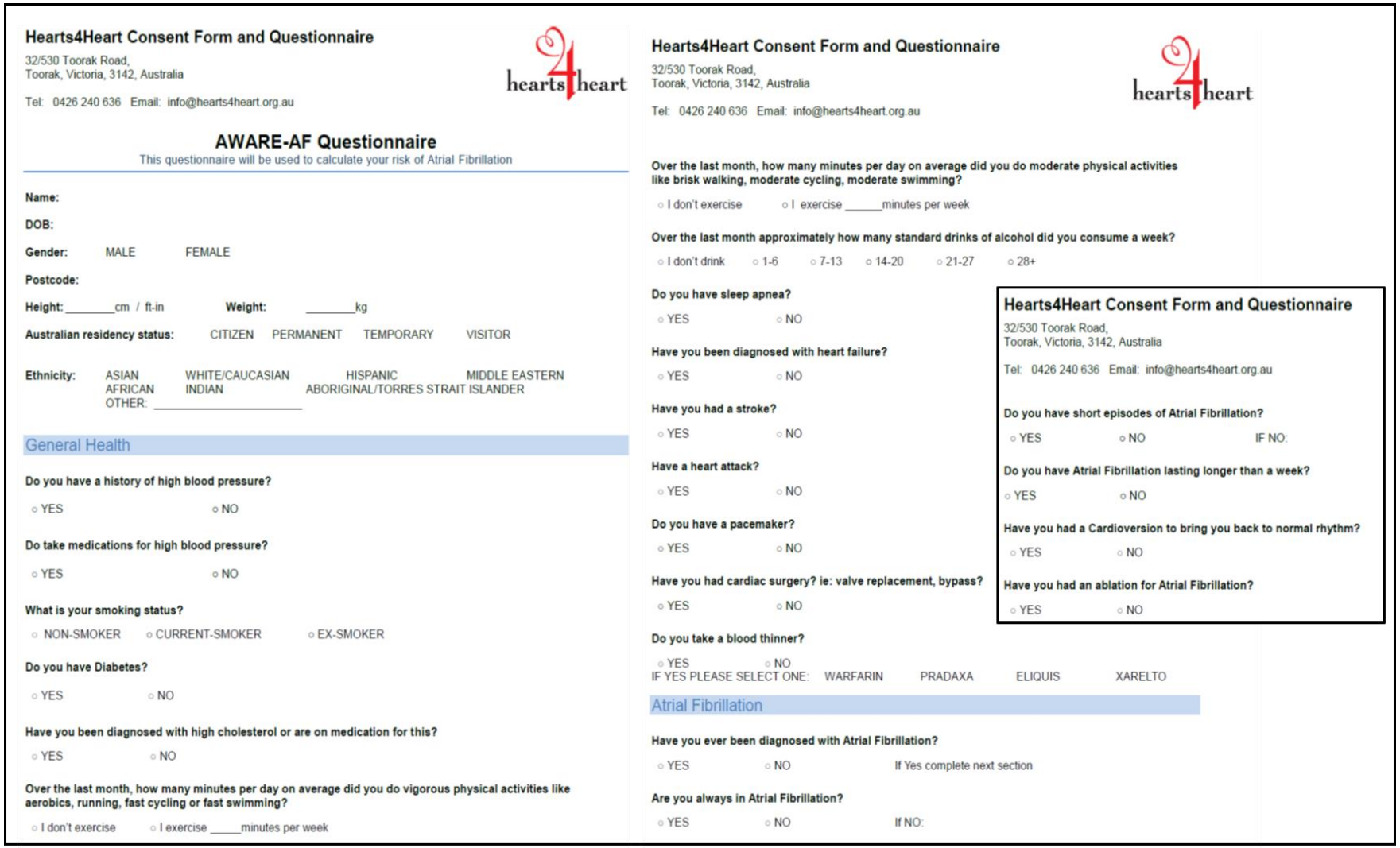


FIGURE 2: EXAMPLES OF QUESTIONNAIRE



Hearts4Heart Consent Form and Questionnaire

32/530 Toorak Road,
Toorak, Victoria, 3142, Australia

Tel: 0426 240 636 Email: info@hearts4heart.org.au

AWARE-AF Questionnaire

This questionnaire will be used to calculate your risk of Atrial Fibrillation

Name:

DOB:

Gender: MALE FEMALE

Postcode:

Height: _____cm / ft-in **Weight:** _____kg

Australian residency status: CITIZEN PERMANENT TEMPORARY VISITOR

Ethnicity: ASIAN WHITE/CAUCASIAN HISPANIC MIDDLE EASTERN
AFRICAN INDIAN ABORIGINAL/TORRES STRAIT ISLANDER
OTHER: _____

General Health

Do you have a history of high blood pressure?

○ YES ○ NO

Do take medications for high blood pressure?

○ YES ○ NO

What is your smoking status?

○ NON-SMOKER ○ CURRENT-SMOKER ○ EX-SMOKER

Do you have Diabetes?

○ YES ○ NO

Have you been diagnosed with high cholesterol or are on medication for this?

○ YES ○ NO

Over the last month, how many minutes per day on average did you do vigorous physical activities like aerobics, running, fast cycling or fast swimming?

○ I don't exercise ○ I exercise _____minutes per week

Hearts4Heart Consent Form and Questionnaire

32/530 Toorak Road,
Toorak, Victoria, 3142, Australia

Tel: 0426 240 636 Email: info@hearts4heart.org.au

Over the last month, how many minutes per day on average did you do moderate physical activities like brisk walking, moderate cycling, moderate swimming?

○ I don't exercise ○ I exercise _____minutes per week

Over the last month approximately how many standard drinks of alcohol did you consume a week?

○ I don't drink ○ 1-6 ○ 7-13 ○ 14-20 ○ 21-27 ○ 28+

Do you have sleep apnea?

○ YES ○ NO

Have you been diagnosed with heart failure?

○ YES ○ NO

Have you had a stroke?

○ YES ○ NO

Have a heart attack?

○ YES ○ NO

Do you have a pacemaker?

○ YES ○ NO

Have you had cardiac surgery? ie: valve replacement, bypass?

○ YES ○ NO

Do you take a blood thinner?

○ YES ○ NO
IF YES PLEASE SELECT ONE: WARFARIN PRADAXA ELIQUIS XARELTO

Atrial Fibrillation

Have you ever been diagnosed with Atrial Fibrillation?

○ YES ○ NO If Yes complete next section

Are you always in Atrial Fibrillation?

○ YES ○ NO If NO:

Hearts4Heart Consent Form and Questionnaire

32/530 Toorak Road,
Toorak, Victoria, 3142, Australia

Tel: 0426 240 636 Email: info@hearts4heart.org.au

Do you have short episodes of Atrial Fibrillation?

○ YES ○ NO IF NO:

Do you have Atrial Fibrillation lasting longer than a week?

○ YES ○ NO

Have you had a Cardioversion to bring you back to normal rhythm?

○ YES ○ NO

Have you had an ablation for Atrial Fibrillation?

○ YES ○ NO

FIGURE 3: EXAMPLE OF APP USED

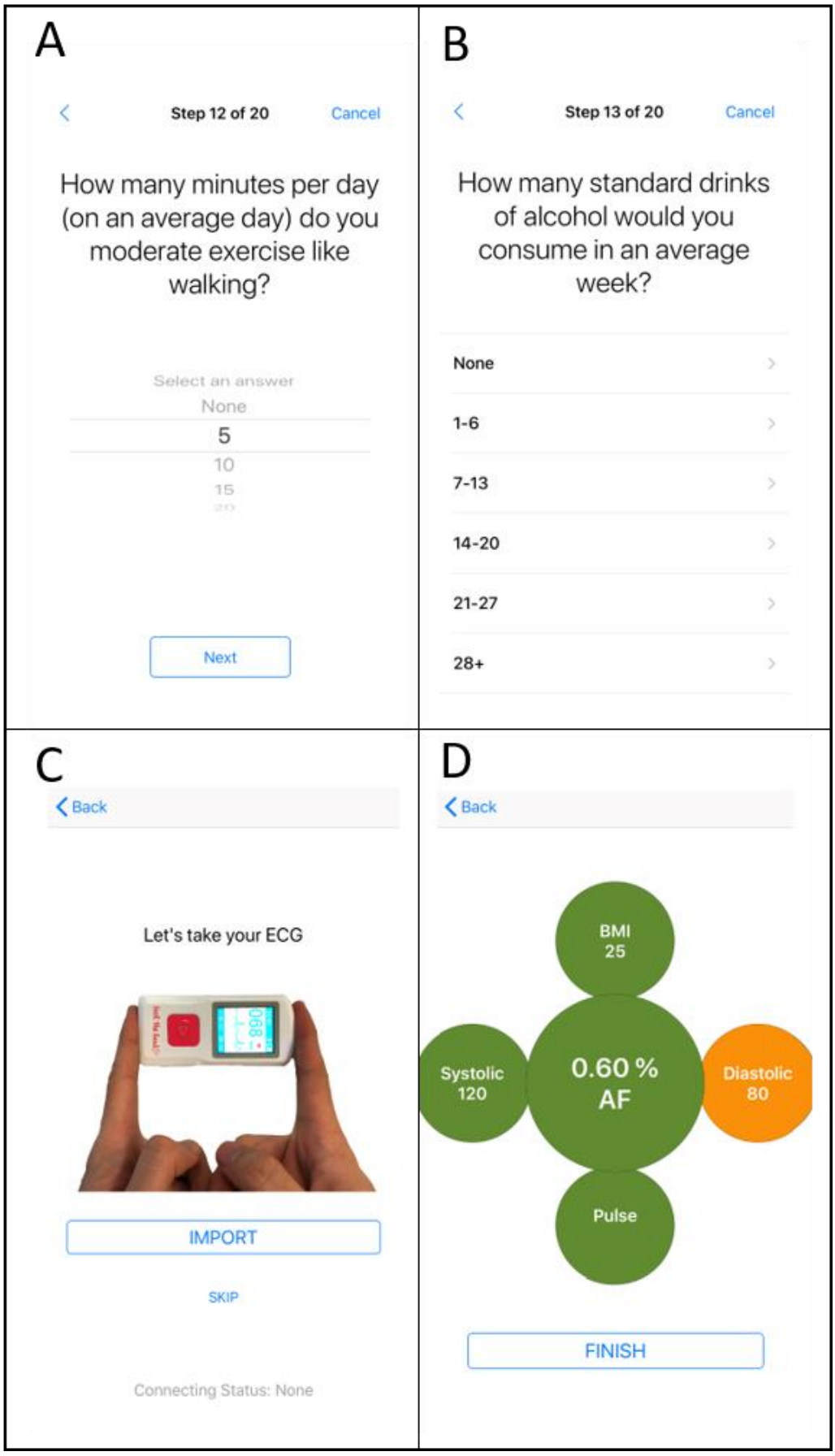


FIGURE 4: FLOW DIAGRAM

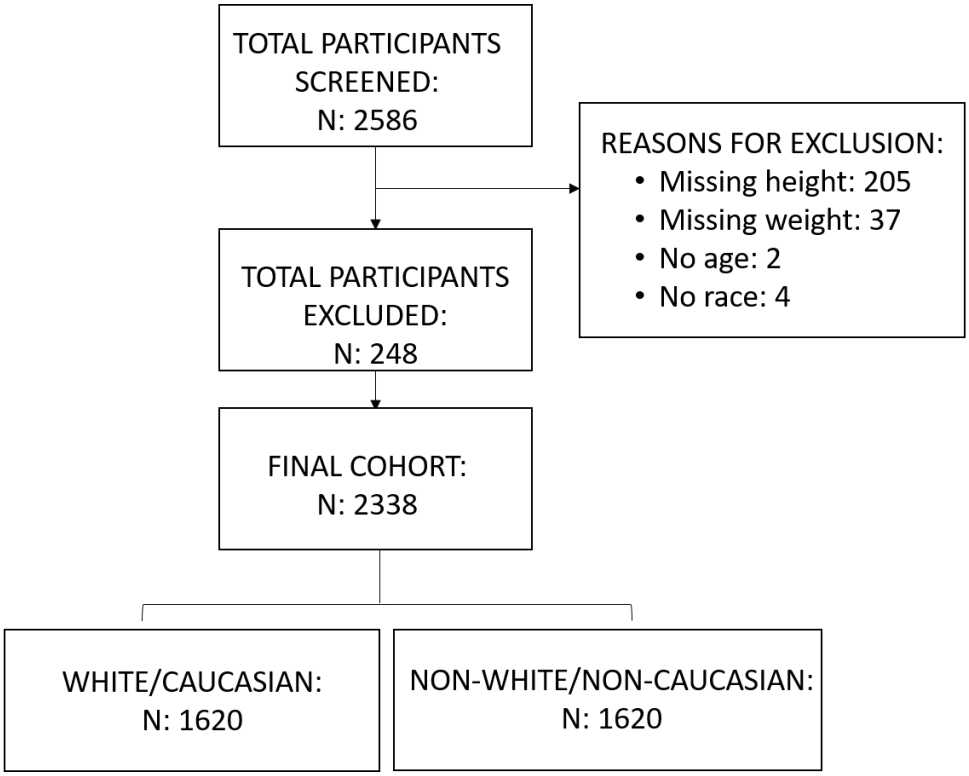


FIGURE 5: DISTRIBUTION OF ETHNICITY

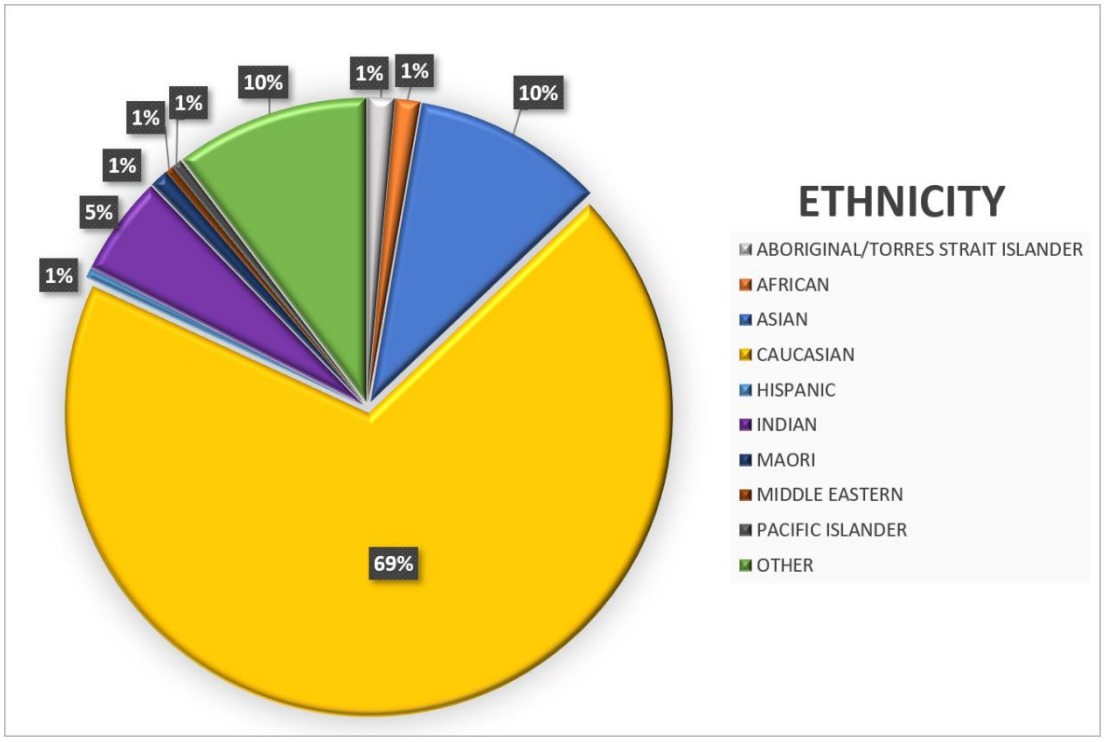


FIGURE 6: PREDICTIVE 5-YEAR RISK OF AF BY SEX

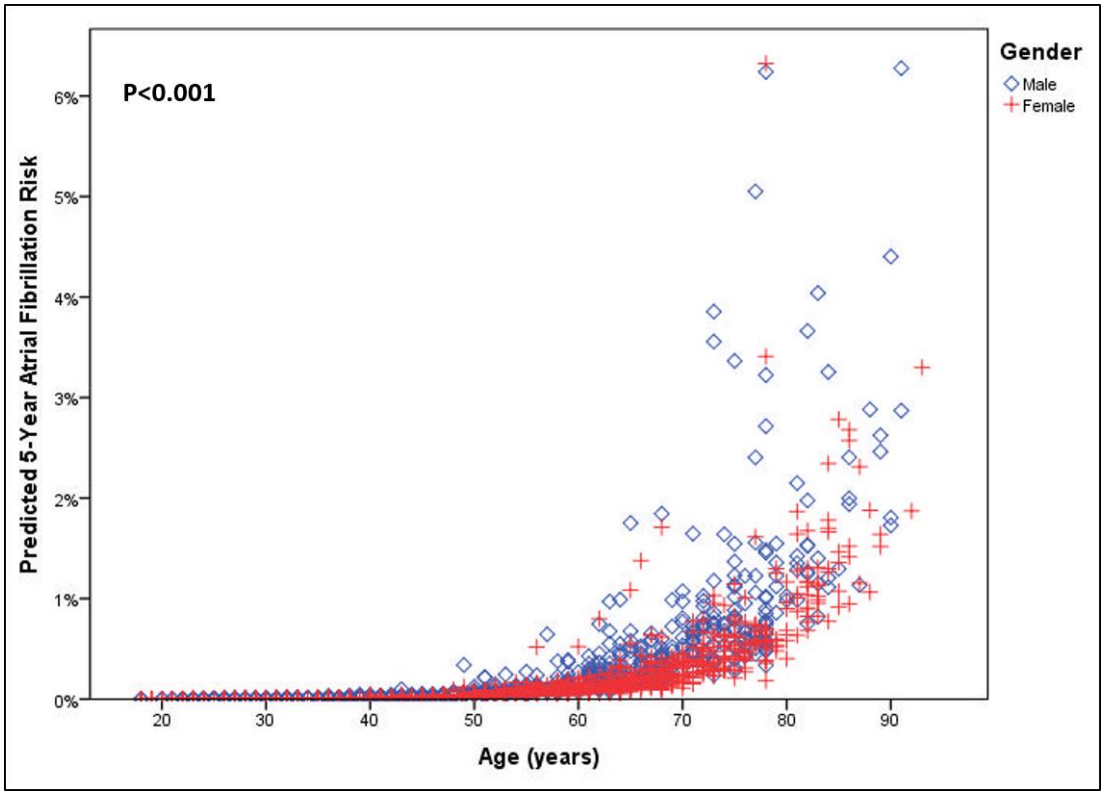
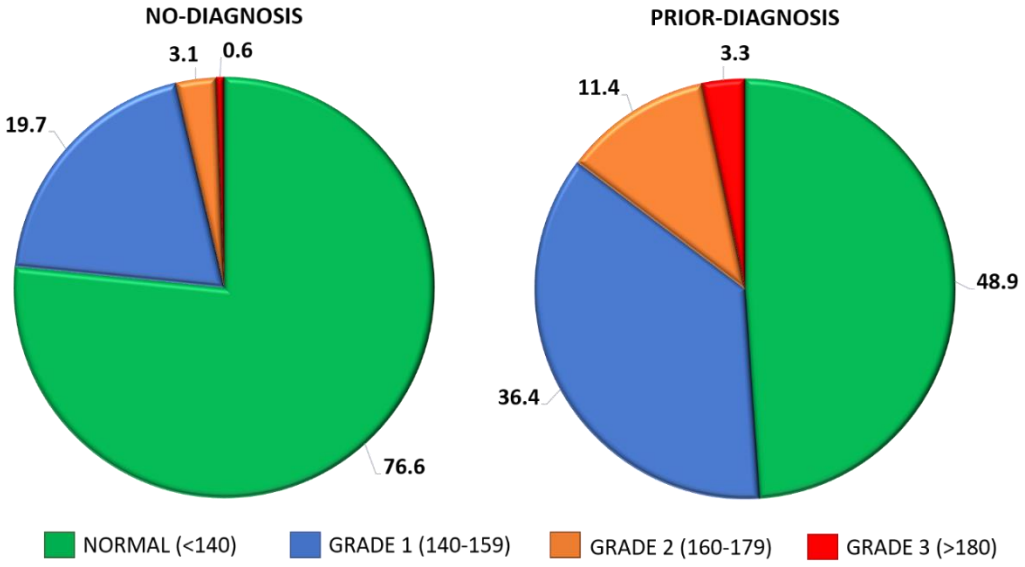


FIGURE 7: RESULTS OF HYPERTENSION SCREENING



Chapter 3: RegReSsive Effect of weight-loss and risk factor modification on AF: The REVERSE-AF Study

3.1 INTRODUCTION

Atrial Fibrillation (AF) is a progressive disease. Over the course of time, many patients progress from paroxysmal to persistent AF and eventually more sustained forms of AF.[35,87,203] The association of cardiovascular risk factors with the development of AF has been known for some time.[407] Whilst this phenomenon was initially considered to be part of the arrhythmic process,[203] more recent data suggests that both the type of AF and the likelihood of progression to more persistent forms of AF, are determined by the number of concomitant risk factors that are harboured.[35,205] Indeed, progressive atrial remodelling has been documented in patients after successful AF ablation, implicating a detrimental role of persistent risk factors.[207] Previous studies have looked at risk factors that contribute to the progression of AF to more persistent forms; however, none of these assessed the impact of treating risk factors to reverse AF disease.

In the Long-Term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort: A Long-Term Follow-Up (LEGACY) Study,[107] we demonstrated that intensive weight and risk factor management had a dose-dependent effect on overall long-term freedom from AF. The impact of weight and risk factor modification on the progression of AF has not yet been characterized. Here we hypothesize that weight-loss and concurrent risk factor management not only reduces patient AF symptoms and recurrence, but also has potential to "reverse" the disease process.

3.2 METHODS

3.2.1 Study Population

This study comprised consecutive patients with symptomatic AF referred to the Centre for Heart Rhythm Disorders at the University of Adelaide, Australia. The details of the study registry have been presented in the LEGACY study[408]. In brief, patients included in the analysis had a body mass index (BMI) $\geq 27 kg/m^2$. The study excluded those who had a history of myocardial infarction or cardiac surgery in the previous 12 months, significant cardiac valvulopathy or ventricular dysfunction, active malignancy, auto-immune or systemic inflammatory diseases, severe renal or hepatic failure, and <24 months of follow-up.

The study was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital and the University of Adelaide, Adelaide, Australia. ANZCTR Clinical Trial Registration: ACTRN12614001123639.

3.2.2 Weight-loss and Risk Factor Management

All patients were offered participation in a dedicated physician-led clinic focused on weight and risk factors. The weight and risk factor management program used by our clinic has been previously presented[408,409]. This is a goal-directed, motivational, structured program where patients received one on one individualized counselling. Weight was initially managed by providing a tailored program. Patients maintained a lifestyle journal and were provided with a meal plan with an initial target of >10% weight-loss. Meal replacement was prescribed if patients lost <3% at 3 months. Patients were advised to undertake 30 minutes of exercise 3-4 times a week with the aim to increase this to 200 minutes per week. Hypertension was managed with salt

restriction and pharmacotherapy as required. Patients were encouraged to monitor blood pressure 2-3 times a day. We aimed for 80% of home blood pressure readings to be <130/80 mmHg, with the blood pressure during rest and exercise consistently <130/80mmHg and <200/100mmHg, respectively. This was corroborated by in office blood pressure readings, exercise stress testing screening for exercise-induced hypertension, 24-hour ambulatory monitoring and echocardiography to ensure the resolution of left ventricular hypertrophy. Cholesterol and glucose intolerance was managed initially with lifestyle measures; however, if this was not achieved pharmacotherapy was prescribed. Patients underwent sleep study with continuous positive airway pressure therapy prescribed if their apnea-hyopnea index ≥30/hour. Smoking cessation was encouraged along with alcohol reduction to ≤30g/week is advised.

3.2.3 Weight-loss Definition

As per LEGACY study,[107] weight-loss groups were divided as follows:

- **Group-1:** <3% weight-loss or weight gain;
- **Group-2:** 3-9% weight-loss; and
- **Group-3:** ≥10% weight-loss.

Importantly, the degree of weight loss was used as a marker of overall control of risk factors.

3.2.4 Categorisation of Atrial Fibrillation

Type of AF: Based on the patients clinical history and 7-day Holter monitoring results patients were divided into the following groups as defined by the Heart Rhythm Society Consensus Statement:[410]

- Paroxysmal AF: AF episodes that are self-terminating and last less than 1 week;
- Persistent AF: AF episodes either lasting >7 days or requiring termination by cardioversion, either with pharmacotherapy or by direct current cardioversion (DCC) after this time.

To assess the change in AF type, AF type was taken according to the clinical status over the preceding 12 months.

Burden of AF: To further categorize type of AF based on AF burden, episodes were divided per duration at baseline and in the last 12 months of follow up:

- Paroxysmal AF: Episodes lasting ≤48 hours (Short PAF) and episodes lasting >48 hours but <1 week but spontaneously reverted to sinus rhythm (Long PAF).
- Persistent AF: Episodes lasting ≥1 week (Short PrsAF) and <3 months and episodes lasting ≥3 months (Long PrsAF).

3.2.5 Arrhythmia Management

Management of AF was undertaken in a separate dedicated AF clinic independent of the weight management clinic. Usage of rate and rhythm control strategies was at the discretion of the treating physician. Sotalol and Flecainide were preferred anti-

arrhythmic drugs (AAD). Amiodarone was not routinely used. Ablation was advocated in patients who remained symptomatic despite use of AAD and risk factor management. The ablation technique utilized at our institution has been previously described.[411] AF type and burden was determined by at least annual clinical review, 12-lead electrocardiogram, device interrogation, and 7-day Holter monitoring. In patients undergoing ablation, procedural success was determined after a 3-month blanking period. Recurrent arrhythmia was defined as any atrial arrhythmia ≥30 seconds. The earliest date with documented AF was set as the date of arrhythmia recurrence. Follow-up was standard for our clinic with a follow-up duration for each group 48.4±18.2, 46.0±16.7, and 48.3±18.4 months respectively (p: 0.3).

3.2.6 Study Outcomes

Primary outcome was change in AF category from baseline to the last year of review. AF status was determined by patient symptoms, 7-day Holter monitoring, ECG or implantable device. Secondary outcomes included AF episode burden as assessed by 7-day Holter, need for single or multiple AF ablation procedures, AV node ablation and pacemaker implantation.

3.2.7 Statistical Analysis

Categorical variables are represented as frequencies and percentages. Continuous variables are summarized as mean ± SD. Differences between the weight-loss groups were assessed using ANOVA procedures for baseline characteristics. A repeated measure ANOVA was used to assess change over time. For categorical variables, change in status at follow-up was compared between groups using a Chi-squared test.

Two-tailed $p<0.05$ was considered statistically significant. Statistically significant predictor of progression of AF was assessed using a logistic regression model. Candidate variables with $p<0.1$ in univariate analyses were considered in multivariate regression models. Statistical analysis was performed with SPSS version 21.0 (SPSS, Inc., Chicago, IL, USA).

3.3 RESULTS

3.3.1 Baseline Characteristics

As described in LEGACY,[107] of the 1415 consecutive patients with symptomatic AF, 825 patients had a BMI ≥27 kg/m2. After screening for exclusion criteria, the final cohort consisted 355 patients (Figure-1): 116 in Group-1 (<3% weight-loss), 104 in Group-2 (3-9% weight-loss) and 135 in Group-3 (≥10% weight-loss). Baseline characteristics and follow-up duration (48.3±18.4, 46.0±16.7 and 48.4±18.2 months respectively, p=0.3) were similar for all groups (Table-1).

3.3.2 Effect of Weight-loss by AF Type

Table-2 shows the effect of weight-loss on AF type. At baseline, Group-1: Paroxysmal 61 (53%) and Persistent 55 (47%); Group-2 had: Paroxysmal 62 (60%) and Persistent 42 (40%); and Group-3: Paroxysmal 73 (54%) and Persistent 62 (46%). At final follow up, Group-1: 48 (41%) progressed AF disease from paroxysmal to persistent; whereas only 1 (1%) patient went from persistent to paroxysmal AF, 37 (32%) had no change in AF type, and 30 (25%) were free from AF at final follow up. Group-2 had: 33 (32%) progressed from paroxysmal to persistent, 18 (17%) who reversed from persistent to

paroxysmal AF and 20 (19%) had no change in AF type, while 33 (32%) were free from AF at final follow up. Group-3: 4 (3%) patients progressed from paroxysmal AF to persistent AF, while 49 (36%) reversed AF disease from persistent to paroxysmal AF, 12 (9%) had no change in AF type, with 70 (52%) patients free from AF over the final year of follow up (p=0.001) (Figure 2 and 3).

Weight-loss was a significant univariate and multivariate predictor of AF regression (p=0.001). On multivariate analysis, >10% weight-loss with accompanied risk factor modification was associated with significantly greater likelihood of transition from persistent to paroxysmal AF (OR 4.3 CI: 2.7-6.8, p<0.001). At baseline, there was no difference in mean number of AAD between the three groups: Group-1 0.8±1.0, Group-2 0.7±0.8, Group-3 1.0±0.9 (p=0.1). At final follow up, while all the groups had reduced AAD use, Group-1 0.4±0.6 (p=<0.001), Group-2 0.5±0.6 (p=<0.001), this was significantly greater in Group-3 0.1±0.4 (p=<0.001; Table 2).

3.3.3 Effect of Weight-loss on AF Burden

In Group-1 with paroxysmal AF, 95% (19/20 patients) had progression from Short PAF to Long PAF and only 7% (3/41 patients) went from Long to Short PAF group (p<0.001). Those with persistent AF, 47% (19/40 patients) of Short PrsAF had an increase in episode duration to Long PrsAF and only 20% (3/15 patients) Long PrsAF went to short PrsAF (p<0.001).

Patients in Group-2 with paroxysmal AF, 61% (8/13 patients) had progression from Short PAF to Long PAF and 69% (34/49 patients) went from Long to Short PAF group (p<0.001). Those with persistent AF, 58% (21/36 patients) of Short PrsAF had an increase in episode duration to Long PrsAF and 80% (4/5 patients) Long PrsAF went to short PrsAF (p<0.001).

In Group-3, none of the 21 patients progressed from short PAF group to Long PAF group and large number of patients had reduction in AF burden with 85% (44/52 patients) who previously had Long PAF reducing to Short PAF group ($p<0.001$). All 13 patients with Long PrsAF at baseline, had a reduction in burden and went into short PrsAF group and only 20% (10/49 patients) who previously had short PrsAF went into Long PrsAF ($p<0.001$).

3.3.4 Pacemaker, AV Node Ablation or AF Ablation

Weight-loss had a dose dependent effect on freedom from AF. At final follow-up in the overall total arrhythmia-free patients: 45 (39%) patients in Group-1 (5 [13%] without ablation, 15 [34%] with 1 ablation, and 25 [53%] with multiple ablations); 69 (67%) patients in Group-2 (15 [22%] without ablation, 32 [46%] with 1 ablation, and 22 [32%] with multiple ablations) were free from AF; and in Group-3, 116 (86%) patients were free from AF (53 [45.5%] without ablation, 44 [37.5%] with 1 ablation, and 19 [17%] with multiple ablations; Table 2). There were no differences in the number of patients requiring AV node ablation or pacemaker implantation between the three groups (p=NS).

3.4 DISCUSSION

3.4.1 Major Findings

This study demonstrates that in over-weight and obese individuals with symptomatic AF, sustained obesity is associated with progression of the AF disease while progressive weight-loss has a dose dependent “reversal” of the AF disease process.

Weight-loss was associated with increased long-term freedom from AF, and a reduction in the need for ablation and the need for multiple procedures.

3.4.2 Progression of AF

AF is a progressive disease with the majority of patients progressing from paroxysmal to persistent and then permanent AF over time[87,412]. There are dynamic adaptive changes in the atria, enhancing the ability of the AF not only to sustain itself, but also to recur ("AF begets AF")[32]. Although postulated that early cardioversion would prevent the remodeling due to AF and allow "sinus rhythm to beget sinus rhythm", restoration of sinus rhythm with early repeated cardioversion reversed electrical remodeling but did not impact the maintenance of sinus rhythm[413]. Thus the role of a "second factor", an atrial substrate responsible for propagation of AF has been implicated[412]. Indeed, abnormal atrial changes have been observed even in patients with apparently 'lone AF'[411]. A recent study has observed a progressive atrial substrate even after successful catheter ablation of AF[207]. These findings argue in favor of an underlying atrial substrate responsible for AF that is promoted by inadequately treated or unrecognized risk factors[414]. Cardiac risk factors such as hypertension, diabetes mellitus, obesity and sleep apnea have been independently shown to increase incidence of AF[40,69,74,131]. Importantly, these have been associated with structural and electrical remodeling of the atria that forms the substrate leading to the development and progression of AF[46,77,78,128,415]. This study confirms these observations. We found that AF has a more progressive course when associated with cardiac risk factors.

3.4.3 Weight Reduction and Risk Factor Management Effect on Reversal and Outcomes

It has been shown that patients on rhythm control medications are much less likely to progress to more persistent forms of AF as opposed to those on rate control[416,417]. However, successful ablation alone did not halt the progression of the AF substrate[207,418]. Whether earlier intervention may alter disease progression is a subject of ongoing evaluation. In the current study, aggressive weight and risk factor management was associated with reversal in AF progression. We found ≥10% weight-loss with management of associated risk factors was associated with significant reversal of the disease state with 88% of AF patients having significant reduction in burden and reversing to paroxysmal AF or experiencing no further AF. In addition, weight reduction was associated with significant reduction in need for AF ablation; ≥10% weight-loss was associated with 45% patients not requiring any ablation and further 37% requiring only single ablation.

3.4.4 Risk Factor Management as Future Strategy for AF Reversal

The recognition of AF as a progressive disease, determined by ongoing remodelling consequent to the various underlying risk factors, calls for early and aggressive weight and risk factor intervention. This study adds to a growing body of evidence that risk factor management to treat the primary cause of the disease halts this vicious cycle and improves the long-term freedom from AF (Figure 4). Given the rising epidemic of obesity and AF, primary and secondary prevention strategies need to be urgently implemented.[419]

3.5 LIMITATIONS

Findings from this study are subject to biases that are inherent in observational studies. Measurement bias has been minimized through standardized processes in our clinic and the evaluation by operators blinded to the patient's weight management strategy. AF burden assessment using 7-day Holter may incompletely detect AF episodes, especially in patients with low AF burden. Continuous monitoring was not available in all patients, so this may lead to asymptomatic AF not able to be captured. This method was utilized in both groups and thus unlikely to introduce detection bias. Ascertainment bias was reduced through the collection of outcomes via routine data sources. Given the observational nature of the data being registry based the outcomes were not pre-specified apriori, this is a limitation which will be addressed in a randomized control study. This study looks at the association of weight loss on progression of AF. Considering the study design, it was statistically impossible to run a multivariate analysis or logistic regression with so many co-variates and therefore was avoided. Weight-loss results in improvement in various associated risk factors such as sleep apnea and hypertension, no adjustments for applied rhythm control therapies were made, which may have also influenced progression of AF. This study does not provide insight into the cause-effect relationship of individual risk factors to the change in AF type.

3.6 CONCLUSIONS

AF is a progressive disease. Sustained obesity is associated with progression from paroxysmal to persistent AF; however, weight-loss and management of risk factors may reverse the natural progression of AF disease, resulting in those with persistent

AF more frequently transiting to either paroxysmal AF or no AF. These findings provide insight to the role of upstream intervention to alter the AF disease process.

3.7 TABLE AND FIGURE LEGEND

TABLE 1: BASELINE CHARACTERISTICS

Baseline characteristics of the 3 patient groups dichotomised by degree of weight-loss

TABLE 2: WEIGHT-LOSS

Table demonstrating overall follow up results of weight-loss on AF progress and reversal, episode duration, and requirement for procedures.

FIGURE 1: PATIENT SELECTION

Consort diagram of the patient selection. AF=atrial fibrillation, BMI=body mass index, WL=weight-loss, Parox=paroxysmal, Persis=persistent.

FIGURE 2: CHANGE IN AF TYPE BETWEEN GROUPS

Pie graphs demonstrating baseline and follow up of patients change in AF type. Demonstrative of impact of risk factor management, those who achieve optimal weight loss reverse the AF type to paroxysmal or no AF as shown in the green and grey.

FIGURE 3: AF DISEASE PROGRESSION AND REVERSAL

Bar charts showing change in AF type at following weight-loss. With green representing Group 1, blue representing Group 2 and orange Group 3. There was a stepwise decline in progression of AF based on the degree of weight loss. Similarly there was a step wise improvement, those who lost <3% weight less likely to reverse AF disease compared to those who lost ≥10% weight.

FIGURE 4: AF DISEASE PROGRESSION AND REVERSAL WITH WEIGHT-LOSS

Showing the process of AF disease progression with increase weight-loss to BMI >27 demonstrating the transition from paroxysmal to persistent. Following weight-loss and

risk factor management we see a reversal of AF type, from persistent to paroxysmal or no AF.

TABLE 1: BASELINE CHARACTERISTICS

	<3%WL Group-1 N= 116	**3-9%WL Group-2 N = 104**	**≥10%WL Group-3 N = 135**	**P Value**
Age (years)	61 ± 11	63 ± 11	65 ± 11	0.06
Male gender, n (%)	83 (71%)	65 (63%)	86 (64%)	0.37
Anthropometric Measures and Blood Pressure				
BMI (Kgm^{-2})	32.9±4.8	32.7±4.4	33.6±4.7	0.24
SBP (mmHg)	146 ± 17	144 ± 17	147 ± 17	0.33
Atrial Fibrillation Type				
Paroxysmal AF, n (%)	61 (53%)	62 (60%)	73 (54%)	0.55
Non-Paroxysmal, n (%)	55 (47%)	42 (40%)	62 (46%)	
Atrial Episode Burden				
48 hours	29 (25%)	13 (13%)	24 (18%)	0.39
<1 Week with No DCC	48 (41%)	49 (47%)	56 (42%)	
>1 Week OR DCC	35 (30%)	37 (36%)	49 (36%)	
3 Months	4 (3%)	5 (5%)	6 (4%)	
Metabolic Risk Factors				
Hypertension, n (%)	90 (78%)	75 (73%)	109 (81%)	0.30
DM, n (%)	34 (29%)	28 (27%)	41 (30%)	0.35
IGT, n (%)	8 (7%)	8 (8%)	18 (13%)	
Hyperlipidemia, n (%)	56 (48%)	45 (44%)	66 (49%)	0.70
Coronary artery disease, n (%)	11 (9%)	12 (12%)	21 (16%)	0.31
AHI>30, n (%)	61 (52%)	52 (50%)	69 (51%)	0.97
Alcohol excess (>30g/week), n	34 (29%)	35 (34%)	42 (31%)	0.73
Smoker, n (%)	47 (40%)	41 (40%)	50 (37%)	0.86
Medication Use				
Mean no. of Anti-Arrhythmic	0.9±0.8	1.0±0.7	1.1±0.7	0.10
Mean no. of Anti-Hypertensive	1.1 ±1.0	1.0±0.8	1.0±0.9	0.08

BMI = body mass index; SBP = systolic blood pressure; DCCV = direct current; DM = diabetes mellitus; IGT = impaired glucose tolerence; AHI = apnea-hypopnea index

TABLE 2: WEIGHT-LOSS

Risk Factors		<3% WL Group; N = 116			3-9% WL Group; N = 104			≥10% WL Group; N = 135			P value†
		Baseline	Follow Up‡	P value*	Baseline	Follow Up‡	P value*	Baseline	Follow Up‡	P value*	
BMI (Kgm^{-2})		33.0±4.9	33.5±5.3	<0.001	32.7±4.4	30.8±4.2	<0.001	33.7±4.7	28.4±4.0	<0.001	<0.001
Mean SBP (mmHg)		146±17	139±15	<0.001	144±17	134±14	<0.001	147±17	129±12	<0.001	<0.001
Medication Use											
Mean no. of Anti-HTN, n		0.8±1.0	1.0±0.7	0.01	0.7±0.8	0.7±0.6	0.74	1.0±0.9	0.5±0.6	<0.001	<0.001
Mean no. of AAD, n		0.8±0.8	0.4±0.6	<0.001	1.0±0.7	0.5±0.6	<0.001	1.1±0.7	0.1±0.4	<0.001	<0.001
AF Type											
Paroxysmal AF, n (%)		61 (53%)	-		62 (60%)	-		73 (54%)	-		0.55
Persistent AF, n (%)		55 (47%)	-		42 (40%)	-		62 (46%)	-		
Paroxysmal to Persistent AF		-	48 (41%)		-	33 (32%)		-	4 (3%)		<0.001
Persistent to Paroxysmal AF		-	1 (1%)		-	18 (17%)		-	49 (36%)		
No Change in AF Type		-	37 (32%)		-	20 (19%)		-	12 (9%)		
No AF		-	30 (25%)		-	33 (32%)		-	70 (52%)		
Last AF Episode Duration											
Paroxysmal AF	48hrs, n (%)	20 (17%)	1 (1%)		13 (14%)	5 (5%)		21 (15%)	21 (15%)		<0.001
	Δ to <1wk		19 (16%)			8 (8%)		-	0 (0%)		
	<1wk, n (%)	41 (35%)	38 (33%)		49 (47%)	15 (14%)		52 (39%)	8 (6%)		
	Δ to 48hrs, n (%)		3 (3%)			34 (33%)		-	44 (33%)		
Persistent AF	>1wk, n (%)	40 (34%)	21 (18%)		36 (34%)	15 (14%)		49 (36%)	39 (29%)		
	Δ to >3m, n (%)		19 (16%)			21 (20%)		-	10 (7%)		
	>3m, n (%)	15 (13%)	12 (10%)		5 (5%)	1 (1%)		13 (10%)	0 (0%)		
	Δ to >1wk, n (%)		3 (3%)			4 (4%)		-	13 (10%)		

TABLE 2: WEIGHT-LOSS CONT.

	<3% WL Group; N = 116			3-9% WL Group; N = 104			≥10% WL Group; N = 135			P value†
Total AF Freedom and Ablation										
Total Freedom from AF	-	45 (39%)		-	69 (67%)		-	116 (86%)		<0.001
• No AF Ablation	-	5 (13%)		-	15 (22%)		-	53 (45.5%)		0.001
• Single AF Ablation	-	15 (34%)		-	32 (46%)		-	44 (37.5%)		0.8
• Multiple AF Ablation	-	25 (53%)		-	22 (32%)		-	19 (17%)		0.007

*p-Value refers to within group differences (baseline to follow-up). †p-Value refers to difference between groups over time (group-time interaction). ‡Median follow up 48.3±18.4, 46.0±16.7 and 48.4±18.2 months respectively
BMI = body mass index; SBP = systolic blood pressure; HTN = hypertension; AAD = anti-arrhythmic drug

FIGURE 1: PATIENT SELECTION

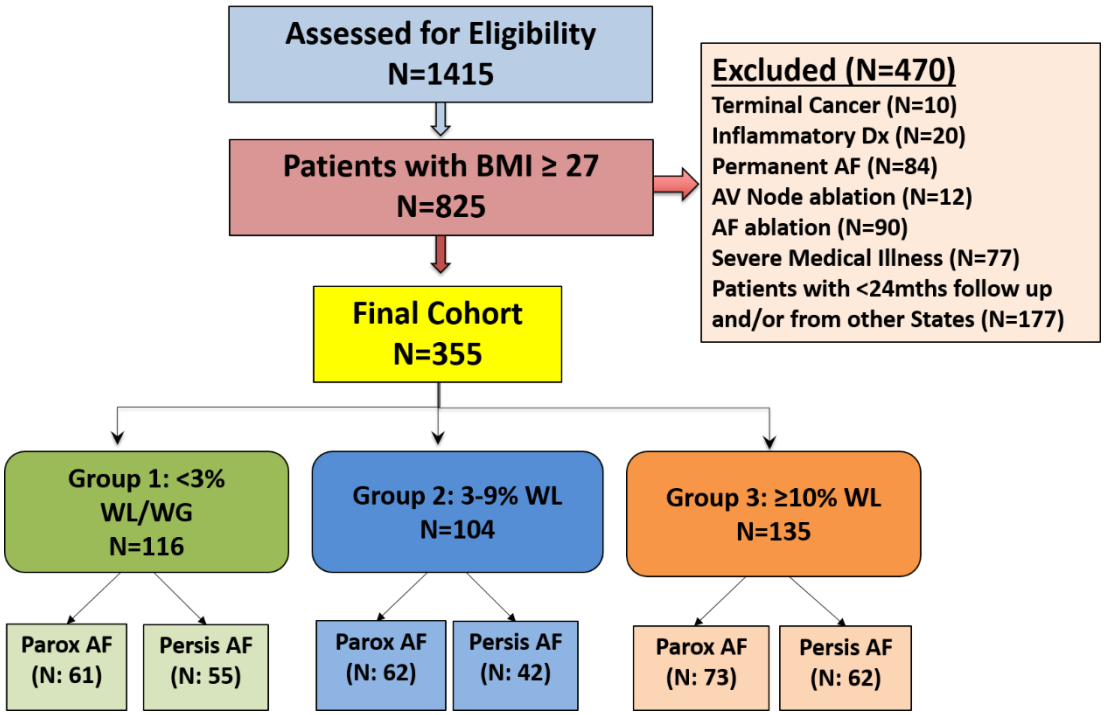


FIGURE 2: CHANGE IN AF TYPE BETWEEN GROUPS

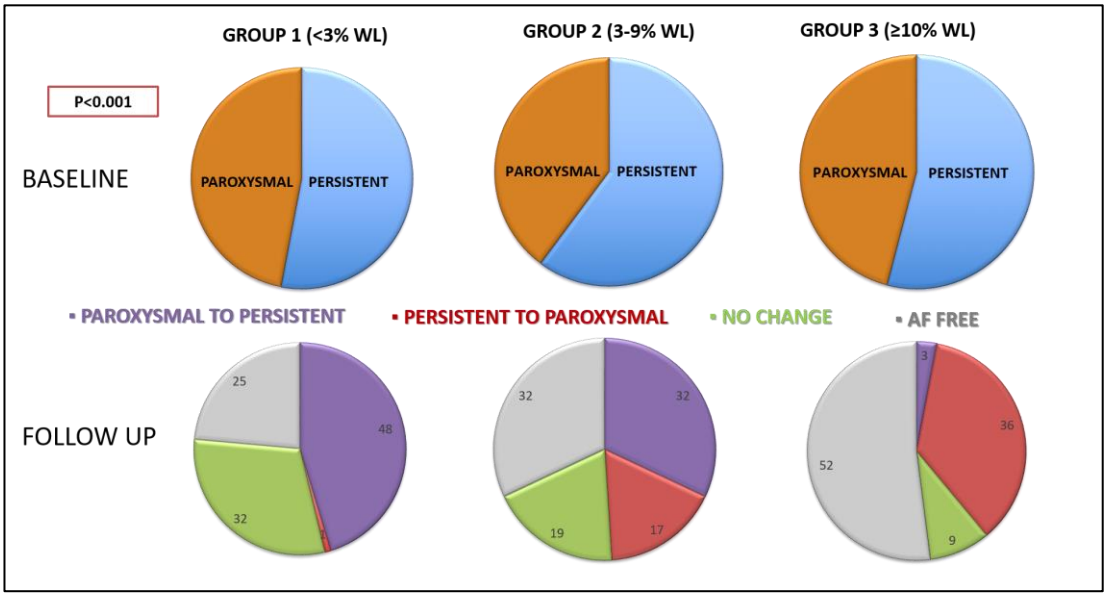


FIGURE 3: AF DISEASE PROGRESSION AND REVERSAL

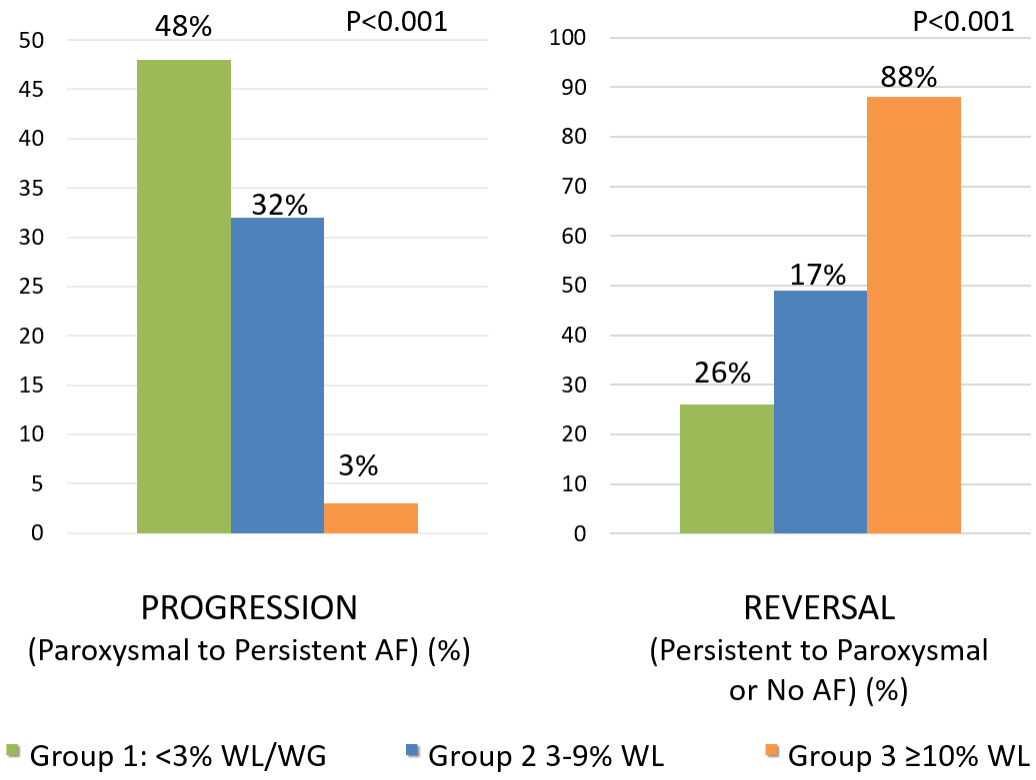
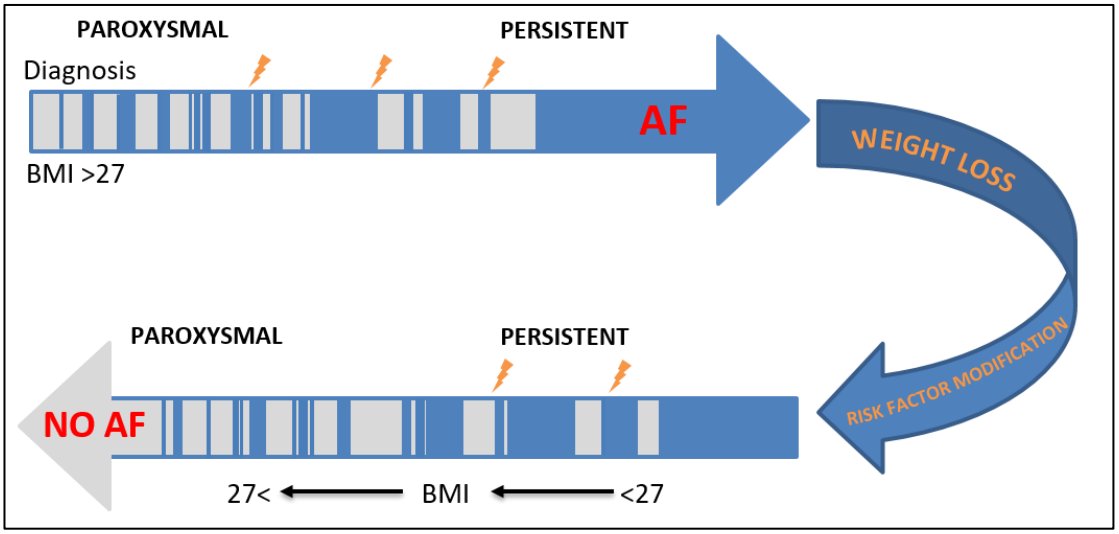


FIGURE 4: AF DISEASE PROGRESSION AND REVERSAL WITH WEIGHT-LOSS



Chapter 4: SoCio-EcoNomic StatUS Impact on Risk Factor Management in Atrial Fibrillation: CENSUS-AF Study

4.1 INTRODUCTION

The association between socioeconomic status (SES) and atrial fibrillation (AF) has not been well characterised. Several studies have shown various links to AF, with early studies suggesting the link between life events, behaviour and stress impacting recurrence and reversion of AF.[420] The AFFIRM study assessed some socioeconomic factors and found that asymptomatic patients had a higher quality of life using the 'Ladder-of-life' based on questionnaire ($p=0.005$) compared to symptomatic patients. Although there were no significant differences in work and living situations, patients in the asymptomatic group trended to possess higher education level ($p=0.06$).[421] The Atherosclerosis Risk in Communities (ARIC) Study demonstrated that lower income was associated with a higher risk of AF. In addition, the same study showed the link between lower education level was associated with increased AF risk in females.[218] A large Swedish AF cohort has shown that there was a higher relative risk of all-cause mortality in men living in low SES neighbourhood (HR 1.49, 95% CI; 1.13-1.96) compared to middleclass neighbourhoods, and that time to death was shorter for those in the middle SES compared to low SES areas.[422]

In 2015, the American Heart Association released an eloquent statement on social determinants of risk and outcomes for cardiovascular disease, they focused on the social determinants of health such as socioeconomic position, race/ethnicity, social support, culture, access to care and residential environment. Additionally, this looked

at the markers for socioeconomic position such as income, health, education, access to activities, political voice, social connections, environment and physical insecurity. While this was not centred on AF but cardiovascular disease, it suggested that to treat this we need to broaden and improve study designs, research programs and policies to focus on the social determinants of health as these may be important contributors to cardiovascular disease.[211]

Similarly, the relationship between obesity and SES has been shown both internationally and within Australia.[220-222] The World Health Organization has also demonstrated that obesity rates in high income countries have not risen as fast as those in low and middle income countries.[423] Given the impact socioeconomics has on obesity and subsequently can have on various health conditions we hypothesised that lower SES would adversely affect risk factor management in obese individuals. We aimed to evaluate this in patients with AF undergoing a structured risk factor clinic focusing on weight and individual risk factors and therefore AF burden

4.2 METHODS

4.2.1 Study Population

This study comprised consecutive patients with symptomatic AF referred to the Centre for Heart Rhythm Disorders at the University of Adelaide, Australia. The details of this registry have been previously presented in the LEGACY registry,[408] this study is a sub-analysis of the LEGACY cohort. In brief, patients included in the analysis had symptomatic AF referred for catheter ablation and a baseline body mass index (BMI) $\geq 27 kg/m^2$ plus at least one other cardiovascular risk factor. The study excluded those who had a history of myocardial infarction or cardiac surgery in the previous 12

months, significant cardiac valvulopathy or ventricular dysfunction, active malignancy, auto-immune or systemic inflammatory diseases, severe renal or hepatic failure, and <24 months of follow-up and/or from other states.

The study was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital and the University of Adelaide, Adelaide, Australia. ANZCTR Clinical Trial Registration: ACTRN12614001123639.

4.2.2 AF Freedom

AF freedom was determined by review of the clinical history, 12 lead ECG or device interrogation, and 7-day Holter monitoring. AF freedom was defined as the absence of atrial arrhythmia >30 seconds with the earliest documented date of AF deemed recurrence of atrial arrhythmia.

4.2.3 Weight-loss Definition

In order to assess the overall risk factor outcomes, weight-loss was used as an objective measure. Weight-loss (WL) groups were divided as follows:

- **Group-1:** <3% WL or weight gain;
- **Group-2:** 3-9% WL); and
- **Group-3:** ≥10% WL.

4.2.4 Socioeconomic Status Definition

Patients were grouped based on their socioeconomic status according to the Australian Bureau of Statistics Socio-Economic Indexes for Areas (SEIFA) rankings which are

comprised from the Australian Census data. Individuals were ranked according to postcode with suburbs in the lowest socioeconomic ranking ranked 1 in the most disadvantaged area to those ranked 10 in the most advantaged. This score reflects household's incomes, employment, education, qualifications and assets. To enable appropriate analysis of this cohort we divided our patients into:

- Group 1 (ranking 1-3): Low SES Area;
- Group 2 (ranking 4-7): Medium SES Area; and
- Group 3 (ranking 8-10): High SES Area.

4.2.5 Questionnaire

The questionnaire was presented to all patients and was voluntary with patients completing this either in person or via interview. Patients were given the option not to answer all questions if they did not wish to disclose this information relating to their income. Socioeconomic factors which were covered in the questionnaire included: marital status, number of children, birthplace, number of siblings, education level, employment status, type of employment, hours worked per week, annual income level, retirement status, housing status, parental ethnicity, parental cardiac health, sibling's cardiac health, awareness of other relatives with AF or sudden cardiac death.

4.2.6 Statistical Analysis

Categorical variables are represented as frequencies and percentages. Continuous variables are summarized as mean ± SD. Differences in normally distributed continuous variables between SES groups were assessed using ANOVA procedures. For categorical variables, between-group differences in baseline proportions were

compared using the Chi-squared test. Two-tailed $p<0.05$, with adjustment for multiple comparisons where appropriate, was considered statistically significant. To investigate the influence of baseline socioeconomic variables on AF freedom, a using Cox proportional hazards regression model was used, with adjustment for age and gender. Statistical analysis was performed with SPSS version 21.0 (SPSS, Inc., Chicago, IL, USA).

4.3 RESULTS

4.3.1 Baseline Characteristics

Of the 1415 consecutive patients with symptomatic AF, 825 patients had a BMI ≥27 kg/m2. Baseline characteristics as defined in the LEGACY Study and follow-up duration (48.3 ± 18.4, 46.0 ± 16.7 and 48.4 ± 18.2 months respectively, p=0.3) were similar for all groups. Of the 355 patients, 318 completed the questionnaire (Refused: 33, moved overseas: 2, English difficulties: 1). Patients were divided into their SE area (SEA) levels, Low SEA (Group 1; 64), Medium SEA (Group 2; 116) and High SEA (Group 3; 138).

There was no significant difference in age across the three groups, 67 ± 10, 67 ± 11, and 67 ± 11 (p=0.92) for low, medium and high SES respectively. There were less females than males 30 (46.9%), 40 (34.5%) and 41 (29.7%) (p=0.058) for low, medium and high SES respectively. Body mass index across the groups is 32 ± 3.7, 33.8 ± 5.2 and 32.8 ± 4.4 (p=0.07) for low medium and high SES respectively. There were no significant differences across all other risk factors as shown in table 1.

4.3.2 Questionnaire Outcomes

Of the 318 patients who completed the questionnaire, 228 (71.7%) were born in Australia. Majority of the patients in the cohort were married (68%), mean number of children was 2 ± 1.2, 61% completed secondary school as their highest level of education, with a further 28% completing higher degrees, 54% patients had retired with majority of the remainder 33% working full time. For those who worked over half (57%) worked more than 40 hours a week. Income levels varied with 66% earning <$80,000/annum, 35% earned $80-200,000/annum, and 9% earning $200,000+ (Figure 1).

In terms of parental background, majority of patient's fathers were white/Caucasian (301), Aboriginal (3), Asian (1), Hispanic (1), Middle Eastern (3). Mothers were also majority white/Caucasian (304), Aboriginal (0), Asian (1), Hispanic (2), Middle Eastern (2). Many parents were born overseas, fathers: 125 (39%), mothers: 118 (37.1%). While not all patients were aware of their parent's health, those who knew reported their father having: Hypertension (64), diabetes (35), coronary artery disease (44), AF (25), myocardial infarction or transient ischemic attack (85), cancer of various forms (44) and other heart conditions such as pacemaker insertion, valve replacements, bypass (37). For their mother they reported: Hypertension (78), diabetes (44), coronary artery disease (24), AF (57), mitral infarction or transient ischemic attack (68), cancer of various forms (42) and other heart conditions such as pacemaker insertion, valve replacements, bypass (32).

4.3.3 Outcomes in Weight Loss and SES

Based on the degree of weight-loss, there was no difference between the SES groups (p=0.4; Figure 2). However, based on degree of weight-loss, marital status was associated with more weight loss (Figure 3A). Relative weight loss was significantly higher for married patients compared to those who were not married (8.2±8.4 versus 5.9±8.3%, p=0.02; Figure 3B). There was no significant difference in the extent of weight loss for patients grouped by SES (p=0.45), retirement (p=0.37), income (p=0.45), full-time employment (p=0.34) or education level (p=0.95; Figure 4).

4.4 SOCIOECONOMIC FACTORS AND AF FREEDOM

4.4.1 Total AF Freedom

Marriage status, income, working hours, retirement status or education level did not contribute to determining freedom from AF (Figure 5). Additionally, there was no significant influence of socioeconomic area on total AF freedom (p=0.84). Furthermore, the proportion of patients undergoing AF ablation did not differ between patients stratified by SEA (p=0.66; Figure 7).

4.4.2 Ablation-Free, Drug-Free (AFDF) Freedom

There was a significant association between socioeconomic status groups and AFDF outcomes. Participants in the middle SEA group were significantly less likely to be in AF at follow-up (HR: 0.60, 95% CI; 0.42-0.84) compared to those in the low SEA group (Figure 6). The association between high SEA and AFDF outcomes did not reach statistical significance (HR: 0.75, 95% CI; 0.54-1.04; Figure 8). There was no

significant association between marriage status, employment, income, retirement status, and level of education with AF freedom, without rhythm control.

4.5 DISCUSSION

4.5.1 Major Findings

In this prospectively collected registry of risk factor management in consecutive overweight or obese patients with symptomatic AF referred for catheter ablation, there was no association between socioeconomic factors such as income level, education level, employment status, marital status and degree of weight loss or long-term AF recurrence. Long-term AF freedom was significantly lower in the middle SES compared to low or high SES groups. Interestingly those who were married were more likely to have successful weight loss and better overall risk factor management compared to those who were not married.

4.5.2 Cardiovascular Disease and SES

Cardiovascular disease has been associated with four markers of SES: income, education, employment and environment.[424] Previous studies have demonstrated low socioeconomic neighbourhoods are associated with increased heart disease and mortality.[422] Similarly, the impact that SES has with obesity has been previously shown.[220-222] To date it has been shown that following adjustment there is a lower risk of stroke if you reside in a higher socioeconomic neighbourhood (HR: 0.87, 95% CI; 0.7-0.96) conversely if you are in a low socioeconomic neighbourhood you had a higher risk of ischemic stroke (HR: 1.16, 95% CI; 1.06-1.27).[425]

4.5.3 Obesity and Role of Socioeconomic Status

Additionally, obesity which in turn leads to cardiovascular disease and atrial fibrillation has been rising significantly. Our previous studies have shown that undertaking dedicated risk factor clinics can not only reduce AF symptom burden but also result in maintenance of sinus rhythm following ablation.[309,408] However trying to assess which patients are most likely to achieve adequate weight loss or best respond to these have not been presented. By undertaking this analysis, it was anticipated that it would help with perhaps providing the insight into which patients to target or provide more directed risk factor management to ensure all patients achieve optimal results.

4.5.4 Socioeconomic Factors that Results in Risk Factor Modification in AF

Unfortunately, despite assessing the primary factors for SES: Income, education, employment, environment[424], and the many factors included in the questionnaire we have not been able to identify specific factors that could assist in providing targeted counselling suggesting that perhaps there may be more character or behavioural influences that could provide further insight. While we did see a relationship with those in the middle-socioeconomic group and AF freedom, it is hard to fully appreciate the causal relationship of this. To our knowledge there is limited data on the impact of socioeconomic status on risk factor modification for patients with AF.

4.5.5 Role of Marital Status in Risk Factor Management

Importantly, we did see the role of marital status on optimal risk factor management. Indeed, perhaps family support or the support of a partner to provide motivation may translate in the ability to achieve the better outcomes. This however did not translate

into reduction in AF burden, possibly due to the low number of patients in the study. This perhaps suggests further research in this area is warranted to better understand the patients who can achieve optimal results and those who may require more input into their strategies.

4.6 LIMITATIONS

Findings from this study are subject to biases that are inherent in observational studies. As this is a single centre cohort from one State in Australia there is limited racial differences as seen in other countries. The clinic did see patients from all levels of socioeconomic levels. AF burden assessment using 7-day Holter may incompletely detect AF episodes, especially in patients with low AF burden. Continuous monitoring was not available in all patients, so this may lead to asymptomatic AF not able to be captured. As this was based on patient knowledge, particularly of family members, this may have underestimated some of the health conditions. Ascertainment bias was reduced through the collection of outcomes via routine data sources.

4.7 CONCLUSION

Socioeconomic determinants of health are increasingly recognised. In this study on risk factor management in individuals with symptomatic AF we were able to demonstrate individuals who were married were significantly more likely to achieve more weight-loss and risk factor modification. This suggest perhaps the importance of immediate family to provide support and motivation to achieve the adequate goals. However, this did not translate into meaningful reduction in AF burden. Interestingly, individuals from middle socioeconomic areas had greater AF freedom compared to

those who were in a low-socioeconomic area. Further studies are required to determine what influence socioeconomic status has on patients with AF.

4.8 TABLE AND FIGURE LEGEND

TABLE 1: BASELINE CHARACTERISTICS

Baseline characteristics of patients as dichotomised by socioeconomic status.

FIGURE 1: RESULTS OF QUESTIONNAIRE

Pie charts showing break down of marital status, number of children, level of education, employment status, hours worked, and income of patients. Majority of patients were married had between 2-3 children, completed secondary school were retired. For those that worked 57% worked 40+ hours and 57% were middle to high income earners.

FIGURE 2: WEIGHT-LOSS BASED ON SES

Bar chart weight-loss based on the SES group. There was no significant difference in the degree of weight-loss achieved based on the SES of the individuals.

FIGURE 3: WEIGHT-LOSS BASED ON MARITAL STATUS

Bar charts figure 3A demonstrates those married based on the degree of weight-loss, being married was associated with greater weight-loss. Figure 3B demonstrates the amount of weight-loss with those who were married able to achieve a greater degree of weight-loss.

FIGURE 4: WEIGHT LOSS BASED ON EDUCATION AND EMPLOYMENT

Bar charts demonstrating the impact education status, employment and retirement status had on the overall degree of weight-loss. There was no significant difference based on an individual's level of education or employment status.

FIGURE 5: AF FREEDOM BASED ON SES PARAMETERS

Bar chart demonstrating that no individual SES parameter resulted in greater AF freedom.

FIGURE 6: AF FREEDOM BASED ON SES GROUP

Patients with medium socioeconomic status was associated with a greater likelihood of AF freedom compared to low or high socioeconomic status.

FIGURE 7: TOTAL AF FREEDOM

This Kaplan-Meier curve shows the total AF freedom over the duration of the study, there was no significant difference between the three groups based on socioeconomic status area.

FIGURE 8: AF FREEDOM – ABLATION AND DRUG FREE

Kaplan-Meier curve demonstrating AF free survival without the use of ablation or antiarrhythmic therapy, there was no significant differences across the three groups. However, there was significantly more freedom for patients in the medium socioeconomic status area compared to the low socioeconomic status area.

TABLE 1: BASELINE CHARACTERISTICS

	LOW SE GROUP N= 64	MEDIUM SE GROUP N = 116	HIGH SE GROUP N = 138	P Value
Age (years)	67 ± 10	67 ± 11	67 ± 11	0.92
Female gender, n (%)	50 (46.9)	40 (34.5)	41 (39.7)	0.06
BMI (Kgm^{-2})	32.3 ± 3.7	33.8 ± 5.2	32.8 ± 4.4	0.07
Metabolic Risk Factors				
Hypertension, n (%)	52 (81.3)	94 (81)	100 (73)	0.23
DM, n (%)	14 (21.9)	28 (24.1)	20 (14.5)	0.19
Hyperlipidemia, n (%)	31 (49.2)	52 (46.1)	60 (44.1)	0.80
Coronary artery disease, n (%)	8 (12.5)	15 (12.9)	17 (12.3)	0.99
Obstructive sleep apnoea, n (%)	28 (43.8)	65 (56)	66 (47.8)	0.23
Alcohol excess (>30g/week), n	18 (18.1)	28 (24.1)	49 (35.5)	0.29
Smoking status: Current, n (%): Former, n (%):	 2 (3.1) 23 (5.9)	 7 (6) 38 (35.5)	 5 (3.6) 46 (43)	0.86
BMI = body mass index; DM = diabetes mellitus; IGT = impaired glucose tolerence; AHI = apnea-hypopnea index				

FIGURE 1: RESULTS OF QUESTIONNAIRE

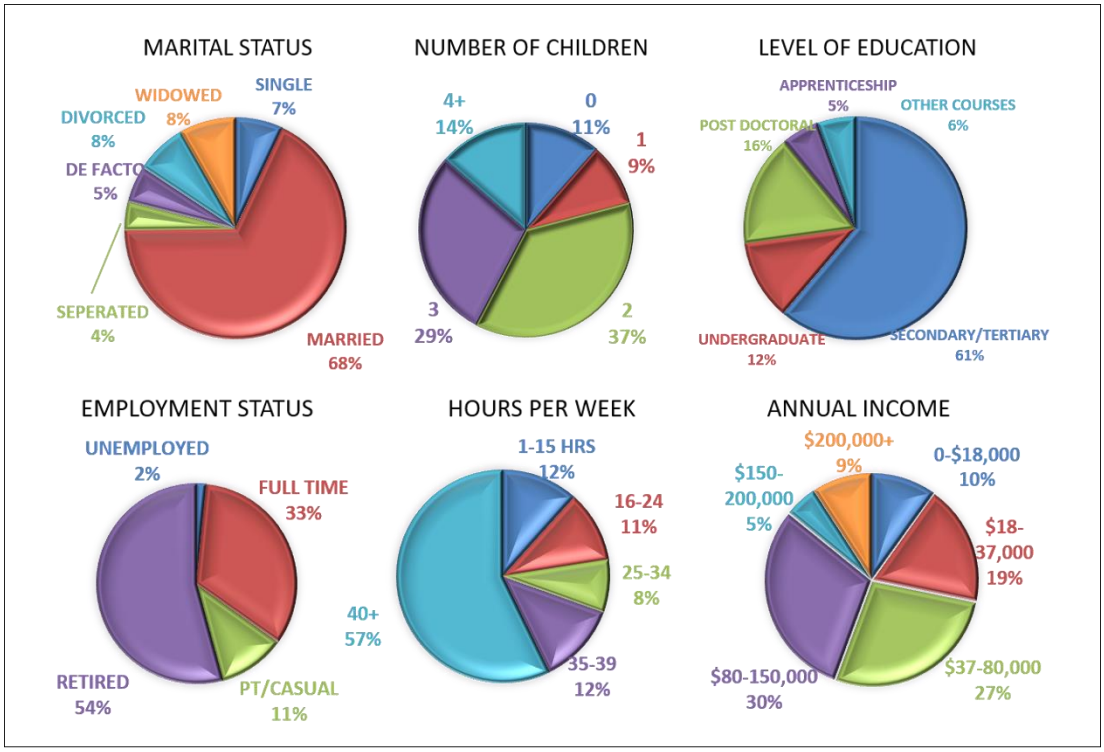


FIGURE 2: WEIGHT-LOSS BASED ON SES

Bar chart weight-loss based on the SES group. There was no significant difference in the degree of weight-loss achieved based on the SES of the individuals.

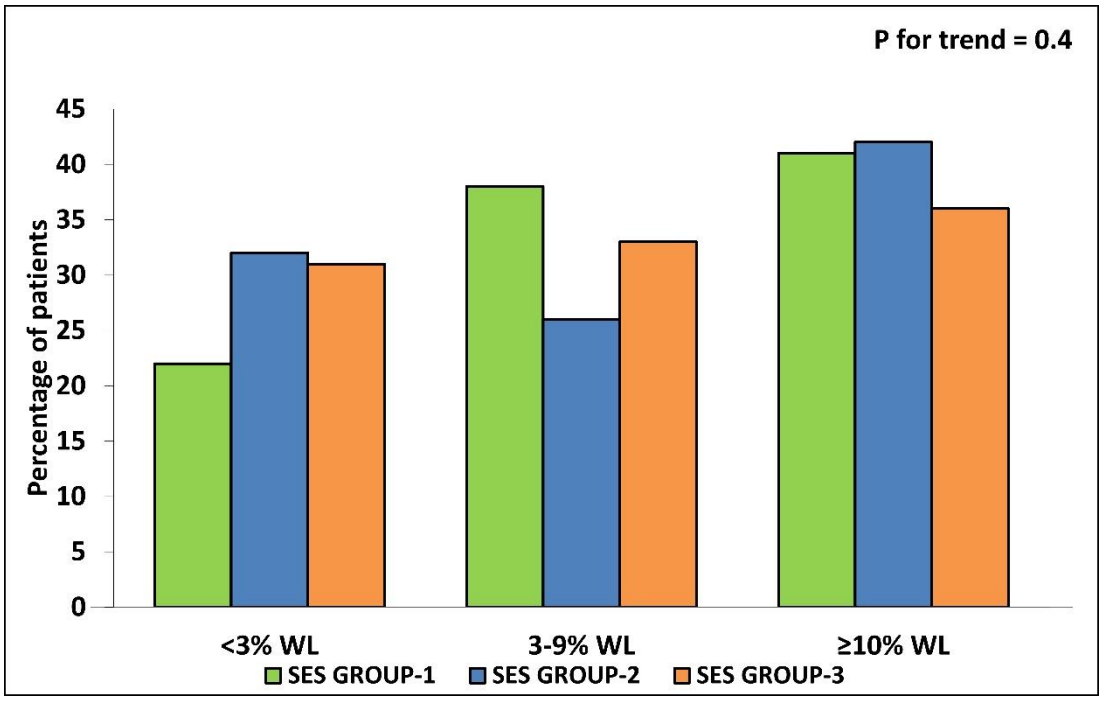


FIGURE 3: WEIGHT-LOSS BASED ON MARITAL STATUS

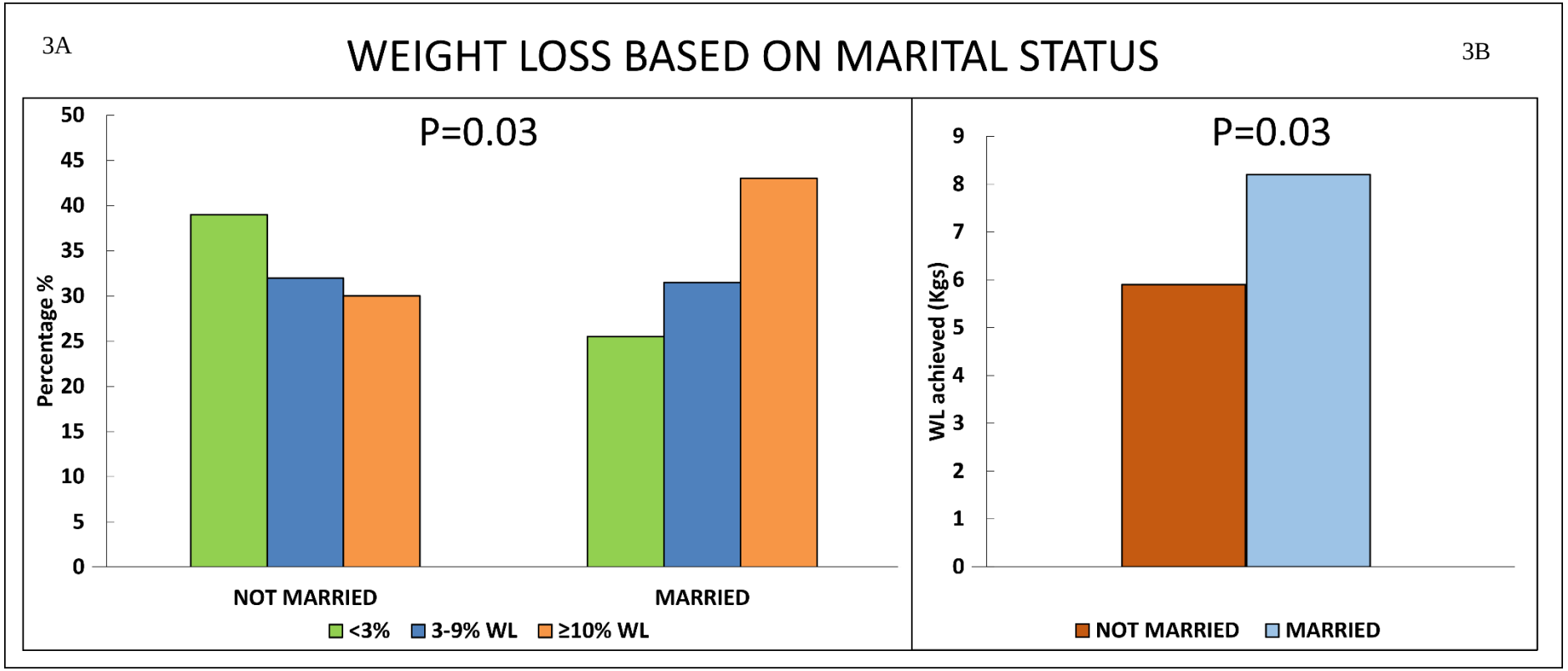


FIGURE 4: WEIGHT LOSS BASED ON EDUCATION AND EMPLOYMENT

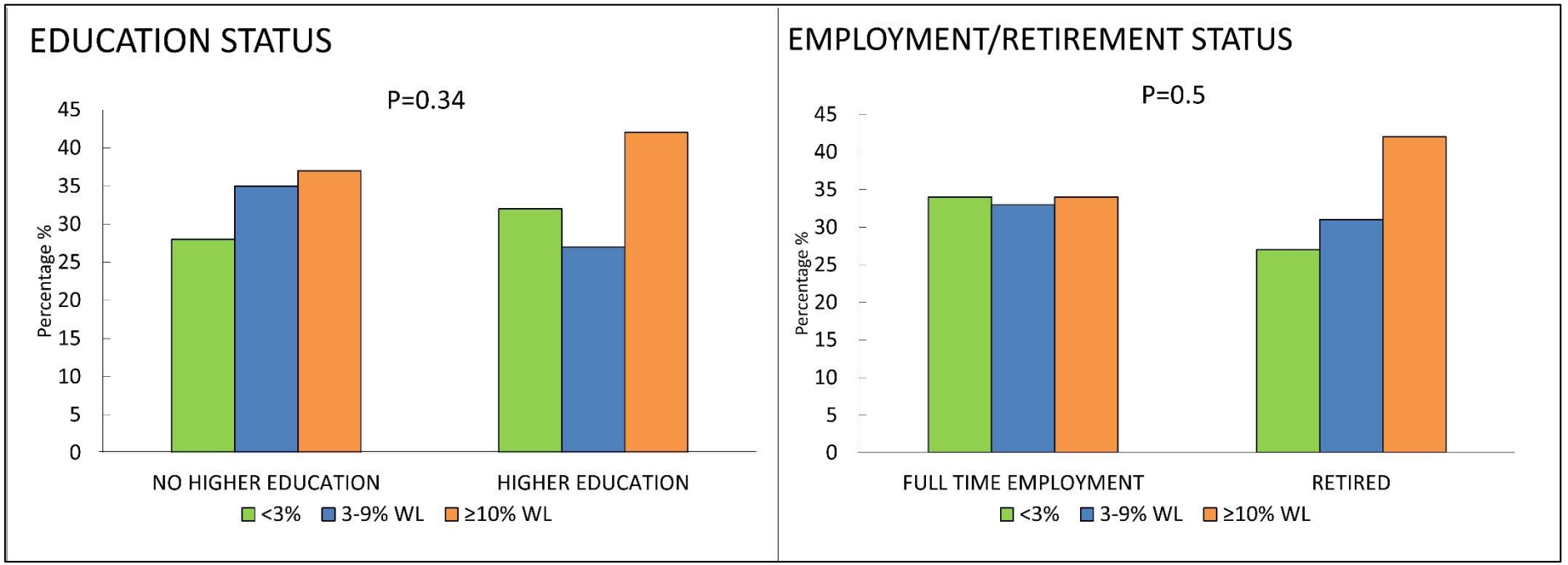


FIGURE 5: AF RECURRENCE BASED ON SES PARAMETERS

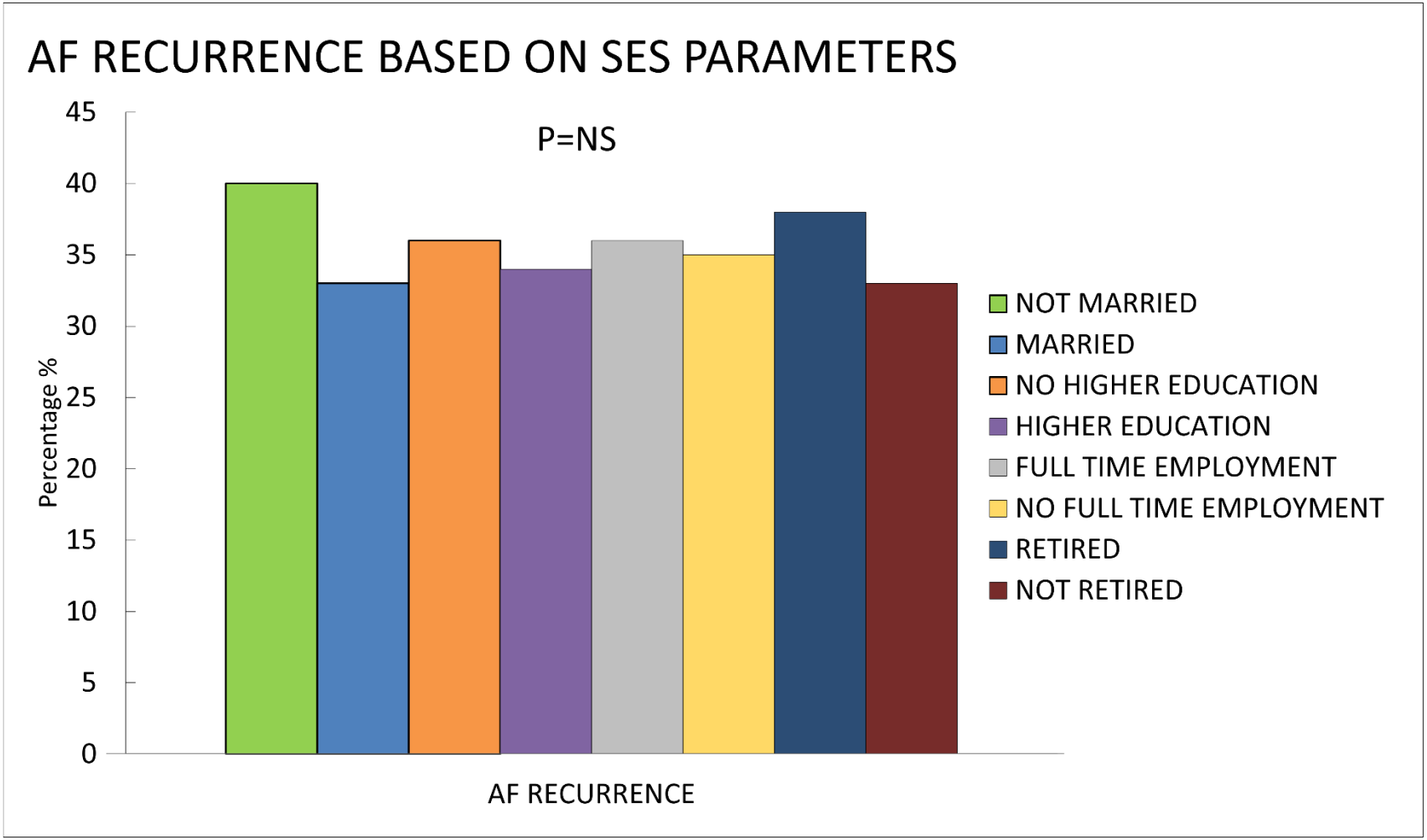


FIGURE 6: AF FREEDOM BASED ON SES GROUP

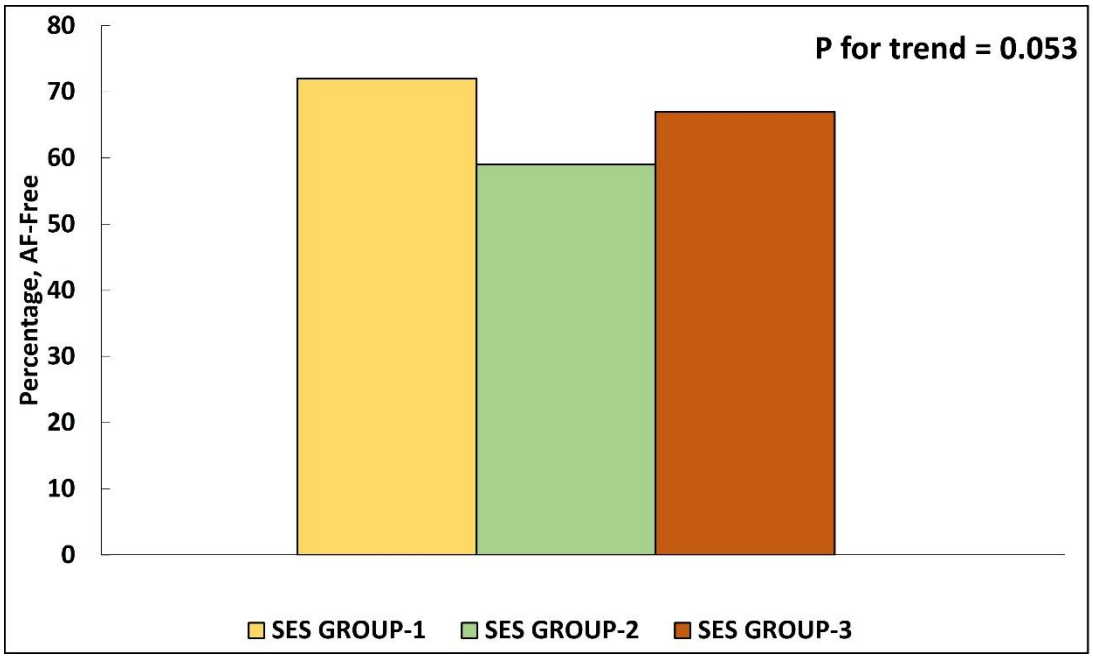


FIGURE 7: TOTAL AF FREEDOM

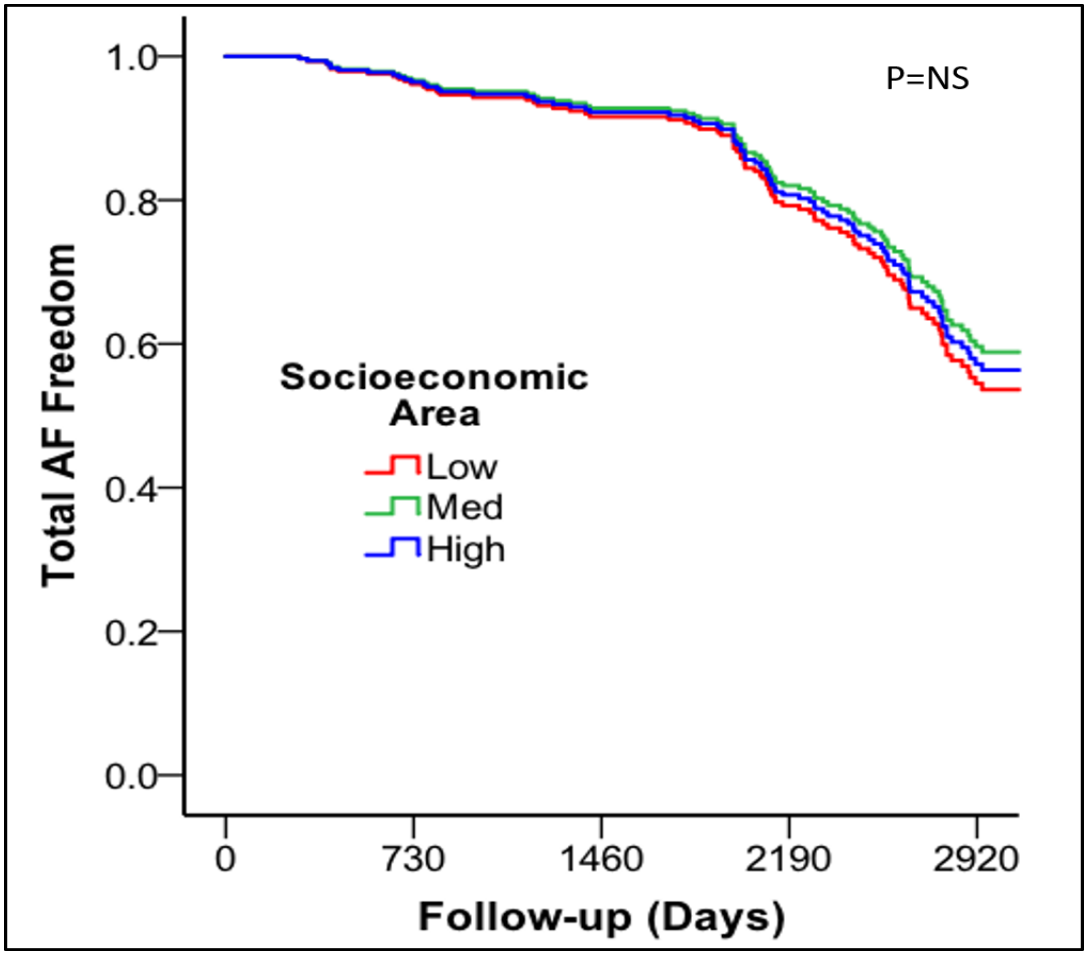
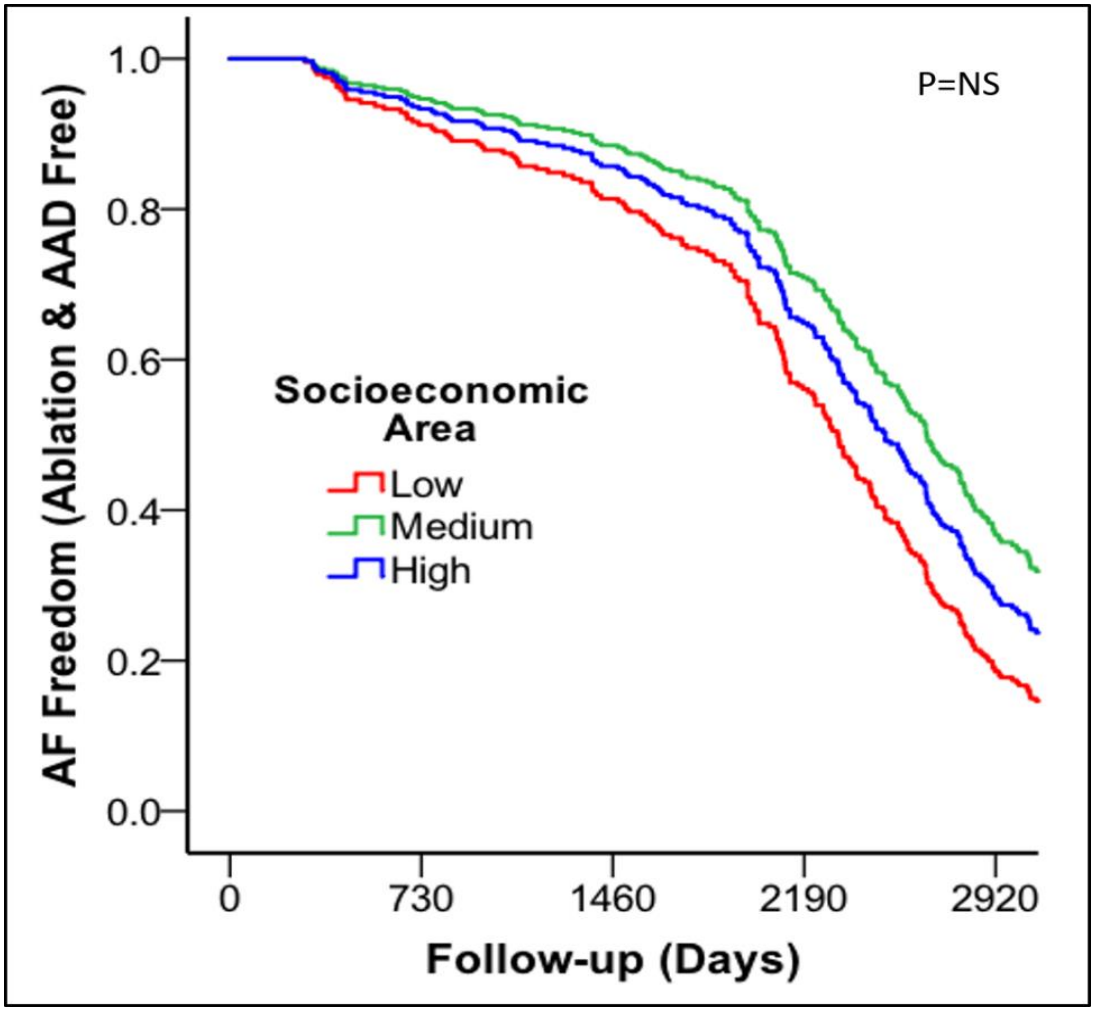


FIGURE 8: AF FREEDOM – ABLATION AND DRUG FREE



Chapter 5: Role of GENDER in Long-term Outcomes of Atrial Fibrillation Ablation: GENDER-AF

5.1 INTRODUCTION

Atrial fibrillation (AF) is fast reaching epidemic numbers worldwide, estimated to affect more than an estimated 33 million individuals, and over 12 million of these being female.[1] Female patients with AF are typically older, more symptomatic and carry a significantly stronger risk of stroke, cardiovascular and all-cause mortality.[273,275-277] These observations perhaps justify the aggressive treatment of AF and its risk factors in women, yet large registry data suggests that women with AF have a lower history of rhythm control, including cardioversion and catheter ablation[275] and may proceed to AF ablation at a later stage.[258]

Catheter ablation is an effective rhythm control strategy in patients with symptomatic AF, refractory to anti-arrhythmic medications. Given the gender differences in clinical characteristics of AF patients, including more advanced age and burden of comorbidities, the outcomes of AF ablation may differ between males and females. Large registry data suggests that in patients undergoing radiofrequency ablation of paroxysmal or persistent AF, females may be referred later for ablation and have lower success rates in males.[259,305] Similarly, the Fire and Ice trial demonstrated women had lower success rate with an almost 40% increased risk of recurrence and a 36% increase risk of cardiovascular rehospitalisation post procedure, suggesting despite the ablation technique used, women still have worse outcomes.[306]

Although a number of smaller additional studies have attempted to compare procedural outcomes from AF ablation between men and women,[307] these findings

should be interpreted with some caution due to the differing blanking periods, follow up durations, numbers of females, and limited description of baseline clinical characteristics. Indeed, many studies have included <70 females[301,303,426,427] and blanking periods less than 3 months.[301,305] Despite the advantage of larger sample sizes with registry data, these studies can be limited by the lack of baseline patient-level characteristics and/or standardized follow-up.[258,259,275]

Based on the current short-term data we hypothesised that women would have worse outcomes to men. This study aimed to evaluate the long-term impact of gender on baseline clinical characteristics, single and multiple procedure outcomes in a single centre cohort of patients undergoing radiofrequency catheter ablation for paroxysmal or persistent AF.

5.2 METHODS

5.2.1 Study Population

This study is an analysis of prospectively collected registry data and comprised consecutive AF patients from the Centre for Heart Rhythm Disorders at the University of Adelaide, Australia who were undergoing AF ablation. Patients who had less than 12-months follow-up were excluded from the analysis. Baseline, follow-up, echocardiographic, and complication data was collected on patients, CHADs Scoring were calculated to assess stroke risk in patients in place of CHA_2DS_2-VASc, in order to avoid gender bias shown in CHA_2DS_2-VASc. All patients who were symptomatic and had failed anti-arrhythmic therapies were referred for AF ablation. This study has been approved by the Human Research Ethic Committee of the Royal Adelaide Hospital.

5.2.2 Ablation Technique

The technique used for ablation in our laboratory has previously been described.[411] In brief, all patients underwent pulmonary vein isolation. Additional substrate ablation in the form of linear ablation, targeting triggers or potential sources of AF was undertaken in individuals with non-paroxysmal AF, longest atrial dimension of >57 mm or if they had concurrent structural heart disease. The type and extent of substrate modification was undertaken at the operating physician's discretion.

All patients had a planning computed tomography prior to ablation. Intracardiac or trans-oesophageal echocardiogram was undertaken to ensure no thrombus was present at the time of the procedure. During ablation, radiofrequency energy was delivered at 15-40 Watts and was temperature limited to 48 degrees. Patients underwent oesophageal temperature monitoring and ablation on the posterior wall was interrupted with any rise in temperature of >0.5 degrees. Cryoablation was not used in this cohort. Echocardiogram was performed following ablation to ensure there was no pericardial effusion.

5.2.3 Echocardiogram Protocol

Transthoracic echocardiograms were undertaken using a 3.5 MHz probe. Measurements taken were a per the standardised protocol according to American Society of Echocardiography guidelines.[428]

5.2.4 Follow-up Protocol

This study had a blanking period of 90 days from ablation in keeping with the Heart Rhythm Society Consensus Statement.[410] Arrhythmia recurrence was determined by symptoms and ambulatory monitoring. In addition, asymptomatic arrhythmia recurrence was based on 12-lead electrocardiogram, and 7-day Holter monitoring or device interrogation performed every 3 months for the first year and then 6 monthly. Echocardiography and symptom limited exercise stress testing was performed at 6 and 12 months and subsequently on a yearly basis. Patients symptoms were assessed using the AF Symptom Severity Score as described by the University of Toronto, every 3 months for the first-year post-ablation, and every 6 to 12 months thereafter.

5.2.5 AF Freedom Definition

AF recurrence was defined as any documented atrial arrhythmia lasting >30 seconds in duration, in keeping with the Heart Rhythm Society Consensus Statement.[410] The date of arrhythmia recurrence was defined as the earliest date with documented AF following the blanking period. AF freedom was determined by review of the clinical history, 12 lead ECG and 7-day Holter monitoring.

5.2.6 Study Outcomes

The primary outcome of this study was AF freedom differences between sexes off anti-arrhythmic medication following a single ablation procedure. This was determined by patient reported symptoms, 7-day Holter monitoring, or ECG. Secondary outcomes included requirement for multiple ablations off and on anti-arrhythmic medications, and procedural complications

5.2.7 Statistical Analysis

Categorical variables are represented as frequencies and percentages. Continuous variables are summarized as mean ± SD or median and interquartile range as appropriate. For categorical variables, differences between groups was compared using a Chi-squared test. Continuous variables were compared by independent t-test or Mann-Whitney U test where appropriate. To investigate the impact of gender on ablation outcomes, a Cox proportional hazards regression model was used. The impact of gender was assessed using age and type of AF in model 1, with the additional of left atrial size and concomitant risk factors (coronary artery disease, obstructive sleep apnoea, hypertension, BMI, diabetes mellitus) in model 2. A p-value of $p<0.05$ was considered statistically significant. All statistical analysis was performed with SPSS version 24.0 (SPSS, Inc., Chicago, IL, USA).

5.3 RESULTS

5.3.1 Patient Population

A total of 699 consecutive patients undergoing de novo primary ablation of AF were studied. Median follow-up was 6.1 [1-12.7] years. Of these 74 patients had <12 months follow-up. Six patients died within the first year of follow-up, 42 lived interstate or overseas, and 26 patients had <12 months follow-up. Of the remining 625 patients there were 207 (33.1%) females and 418 (66.9%) were male. Figure 1 presents the CONSORT figure for recruitment and follow up.

5.3.2 Baseline Characteristics

At the time of first ablation, males were significantly younger than females 59 ± 10 versus 62 ± 10.5 (p=<0.0001). Females were more likely to present with paroxysmal AF compared to males (70.5% versus 59%, p<0.001), have less obstructive sleep apnoea (7.7% versus 15.6%, p=0.006), less alcohol excess (21.5% versus 3.4%, p<0.0001) and less coronary artery disease (6.8% versus 11.2%, p=0.076). There were no other significant differences in baseline parameters between sexes. There was no difference seen in pharmacotherapy use between the sexes. Table 1 presents the differences in baseline characteristics between the genders.

5.3.3 Echocardiography Differences

In terms of echocardiographic measures, females presented with less ventricular wall thickening IVsd (1.0 ± 0.6 versus 1.1 ± 0.2, p=0.01), smaller left atrial diameter (3.7 ± 0.6 versus 4.3 ± p=0.6), left atrial volume (61.5 ± 23.6 versus 77.5 ± 26.3, p<0.0001), left atria area (21.5 ± 2.9 versus 24.8 ± 7.5, p<0.0001), and a greater left ventricular ejection fraction (61 ± 9 versus 59 ± 11, p=0.02) compared to males (Table 1).

5.3.4 AF Ablation Outcomes

5.3.4.1 Number of procedures

The mean number of procedures undertaken in this cohort was 1.6 ± 0.7. There was no significant difference in the number undertaken in females compared to males. In terms of number of procedures undertaken in each gender, 100 (48.3%) females had 1 procedure, 88 (42.5%) had 2 procedures, 18 (8.7%) had 3 procedures and 1 (0.5%)

underwent 4. For males there was a similar result: 210 (50.2%) underwent single procedure, 157 (37.6%) had 2, 43 (10.3%) had 3 and 8 (1.9%) had 4.

In terms of other outcomes, there was a similar number of females and males who underwent subsequent pacemaker implantation, 58 (28%) versus 100 (23.9%) (p=0.39). Also, those who require AV nodal ablation females 16 (7.7%) males 12 (2.9%) (p=0.13).

5.3.4.2 Single Procedure Outcomes – Males Compared to Females

There was no statistical difference between sexes for single procedure success drug free (M: 28.9% versus F: 26.6%, p=0.57) or (M: 31% versus F: 32%, p=0.86) drug assisted. As demonstrated in table 2, in univariate analysis, female gender was not associated with single procedure recurrence either drug assisted (HR: 1.06, 95% CI: 0.86-1.29) or drug free (HR: 1.14 .95% CI: 0.93-1.38). Furthermore, in adjusted analyses female gender was not associated with single procedure outcomes either drug assisted (Model 1, HR: 1.09, 95% CI: 0.92-1.44) or drug free (Model 1, HR: 1.17, 95% CI: 0.95-1.43). However, in a fully adjusted model, female gender was associated with an elevation in risk of AF recurrence drug free following a single procedure (HR: 1.26, 95% CI: 1.01-1.58).

5.3.4.3 Multiple Procedure Outcomes– Males Compared to Females

Women fared worse following multiple procedure (68.6% versus 76.3%, p=0.041) drug assisted and (46.9% versus 54.4%, p=0.074) drug free. In univariate analysis, female gender was associated with multiple procedure recurrence drug assisted (HR: 1.46 .95% CI: 1.06-1.99) and but not drug free (HR: 1.25, 95% CI: 0.98-1.58). In

adjusted analyses female gender was associated with multiple procedure recurrence drug assisted (Model 1, HR: 1.43, 95% CI: 1.03-1.98) but not drug free (Model 1, HR: 1.21, 95% CI: 0.95-1.55). In a fully adjusted model, female gender was associated with a significantly increased risk of AF recurrence drug assisted following a multiple procedure (HR 1.53, 95% CI: 1.04-2.24).

5.3.4.4 Predictors of AF Recurrence

In multivariate regression model, age, type of AF and OSA were independent predictors of AF recurrence for single procedure drug assisted. These were also the predictors, along with gender for single procedure drug free. For multiple procedure, gender, age and type of AF were independent predictors of AF recurrence drug assisted, and age, type of AF and OSA for those drug free (Table 3).

5.3.5 Complication Data

Given previous studies have demonstrated females often present with more post-procedural complications we assessed this within out cohort. There was a total of 51 (8.1%) complications, there was no difference between genders (M: 35, 8.4% versus F: 16, 7.7%; p=0.9). There were no significant differences between the sexes in either major or moderate complications (Table 4).

5.3.6 Mortality

Over the course of follow-up, a total of 28 (4.5%) patients died, 11 were female. Two patients died as a result of atrio-esophageal fistula following the procedure. A further

9 died from carcinoma, 9 due to various non-cardiac conditions, 6 due to chronic heart failure, and 2 due to unknown reasons.

5.4 DISCUSSION

5.4.1 Major Findings

In this single centre prospective cohort with detailed patient level data, and long-term data on ablation outcomes of up to 10 years we found the following:

1. Women presented with more paroxysmal AF, smaller left atria and had more sleep apnoea;
2. There was no difference in the antiarrhythmic use, number or procedures or pacemaker implantation between the sexes;
3. Following adjustment for risk factors women had worse outcomes following multiple procedures and an increased risk of recurrence drug assisted

5.4.2 Difference in Risk Factors Between Sexes

Gender differences in disease profiles, treatment availability and outcomes have been determined about several cardiovascular conditions. There is emerging data from large registries that have suggested that there may be undertreatment of women with AF. In this cohort, 70.5% of women had paroxysmal AF, this was significantly higher than males 49%. Women had a significantly smaller left atria, were older and more sleep apnoea. Previous studies have demonstrated females are typically older and present with more risk factors including a higher prevalence of persistent AF, resulting in more

AF recurrence when they undergo AF ablation,[259,302,305,429,430], The large German Ablation Registry which has one of the largest cohorts of females undergoing ablation.[259] This study also demonstrated women had a greater presence of paroxysmal AF but were less likely to have freedom from AF following ablation and more complications post procedure. Of note however, this was a short-term study with data was taken after only 1 year of follow-up and was taken from a registry which lacked the basic patient level information. The current study provides long-term patient level follow-up which demonstrates a higher risk of recurrence in females only following adjustment, in addition there was no apparent difference in post procedural complications.

5.4.3 Difference in Management Strategies Between Sexes

Several registries have found women are undertreated with rhythm control and more likely to undergo AV nodal ablation.[257,259,298] This data however is taken from registries and does lacks significant follow-up from a clinical perspective. The current study was able to show that management strategies between sexes was markedly similar. There were similar rates of ablation performed, no differences in the use of anti-arrhythmic therapies, no difference in females undergoing pacemaker implantation or AV nodal ablation. This is different to what has previously been suggested in which women are more likely to be undertreated.

5.4.4 Outcome Differences Between Sexes

As demonstrated by Vallakati et al the strength of data in the area of gender and AF ablation outcomes is very weak.[307] This meta-analysis pooled together 20 studies

assessing gender difference in ablation outcomes. This demonstrated that women were significantly more likely to have less freedom from AF following ablation. Of significance is that when looking closer at the studies, 35% had short-term follow-up of around 12 months, and perhaps more strikingly, 65% of the studies included had <100 females. Winkle et al where they also showed that while women had the same rates of AF freedom as males following the initial ablation overall they success rates were lower[302], highlighting there the success rates of females may indeed be approximately 10% lower than that of males undergoing ablation. Zhang et al once again presented a cohort of only persistent AF and in a relatively small cohort, however they demonstrated that women were more likely to present with lone AF but yet had a lower initial ablation success rate (HR: 1.66, 95% CI: 1.11-2.49).[303] These studies however were not long-term and included small numbers of females. In the current long-term study, we were able to demonstrate overall there was no difference following single procedure outcomes, however women were more likely to fail multiple procedures. Women had a significantly higher risk of recurrence following multiple procedures on AAD. Similarly following adjustment for common factors which would influence AF recurrence women were more likely to experience recurrent following ablation.

5.4.5 Complication Differences Post Ablation

Complications following ablation have previously been shown to differ, in studies several it has been demonstrated that females have predominately more complications [259,305,430], while other studies have reported similar complication rates.[302,303,427] Our study however concurred with the later where we did not see any significant difference between males and females in terms of post procedural related complications.

These have mostly had relatively small cohorts and short follow-up. This study presents a large cohort over a long-follow up and shows outcomes between genders is equivocal to what has been published. It is interesting to note that despite studies highlighting that women have a higher risk of recurrence, mortality and strokes[305,307,429] there is still a large discrepancy in the literature regarding women and ablation outcomes highlighting a clear gap in knowledge.

5.5 LIMITATIONS

This is a single centre cohort and observational study; however, the data emerges from a prospectively collected clinical registry. Measurement bias was reduced by use of standardised processes in the clinic. Additionally, while many of the patients had implantable devices, for those without the silent or asymptomatic AF could have occurred without our knowledge. Use of 7-day Holter monitoring and review of all implantable device checks was undertaken to enable us to capture AF recurrence as much as possible.

5.6 CONCLUSION

Data on gender outcomes has been varied and is predominantly taken from small cohorts of short duration. This study provides the longest follow-up of gender outcomes demonstrating that females present with more paroxysmal AF and a smaller atrium. Despite this, women are more likely to have AF recurrence following ablation. This data adds further weight for biological differences in gender outcomes and AF management.

5.7 TABLE AND FIGURE LEGEND

TABLE 1. BASELINE CHARACTERISTICS

TABLE 2. RISK OF AF RECURRENCE

Table demonstrating univariate and multivariate risk of AF recurrence for single and multiple procedures.

TABLE 3. MULTIVARIATE PREDICTORS OF AF RECURRENCE

Table demonstrating the multivariate predictors for single and multiple drug free and drug assisted outcomes.

TABLE 4. TABLE OF COMPLICATION

Table demonstrating the differences in complications post AF ablation between men and women, there was no significant difference between the groups.

FIGURE 1: CONSORT DIAGRAM

Consort diagram demonstrating the final cohort of patients included in the study. Also shown is the number of patients who underwent follow-up at 2-yearly intervals.

FIGURE 2. KAPLAN MEIER CURVE AF FREEDOM OFF AAD

Kaplan Meier curves demonstrating outcomes between genders for AF freedom off anti-arrhythmic drugs for single and multiple procedures.

FIGURE 3. KAPLAN MEIER CURVE AF FREEDOM ON AAD

Kaplan Meier curves demonstrating outcomes between genders for AF freedom on anti-arrhythmic drugs for single and multiple procedures.

TABLE 1. BASELINE CHARACTERISTICS

	MALES N=418	**FEMALES N=207**	**P-VALUE**
Age	59 ± 10	62 ± 10.5	<0.0001
BMI	29.5 ± 4.9	30 ± 6.8	0.4
Type of AF: Paroxysmal AF (%) Persistent AF (%)	 105 (49) 213 (51)	 146 (70.5) 61 (29.5)	 <0.0001
Hypertension (%)	208 (49.8)	123 (59.4)	0.02
Diabetes Mellitus (%)	31 (7.4)	20 (9.7)	0.3
Obstructive Sleep Apnoea (%)	65 (15.6)	16 (7.7)	0.006
Alcohol excess (>30g/week)	90 (21.5)	7 (3.4)	<0.0001
Smoking Never Current Ex-smoker	 292 (69.8) 16 (3.8) 108 (25.8)	 168 (81.2) 5 (2.4) 34 (16.6)	 0.01
Hyperlipidaemia (%)	150 (35.9)	75 (36.2)	0.9
Coronary Artery Disease (%)	47 (11.2)	14 (6.8)	0.08
ANTIARRHTYHMIC USE			
Flecainide (%)	78 (18.7)	44 (21.3)	0.4
Sotalol (%)	117 (28.1)	52 (25.1)	0.6
Amiodarone (%)	56 (13.4)	33 (15.9)	0.4
ECHOCARDIOGRAPHIC MEASURES			
IVersusd (cm)	1.1 ± 0.2	1.0 ± 0.6	0.01
LVID (cm)	29.5 ± 4.9	30 ± 6.8	0.1
LVEF (%)	59 ± 11	61 ± 9	0.02
LA Diameter (cm)	4.3 ± 0.6	3.7 ± 0.6	<0.0001
LA Volume (mls)	77.5 ± 26.3	61.5 ± 23.6	<0.0001
LA Area (cm^2)	24.8 ± 7.5	21.5 ± 2.9	<0.0001
LA Major (cm)	6.1 ± 2.9	5.5 ± 0.7	0.008
LA Minor (cm)	4.6 ± 2.3	4.2 ± 0.7	0.02

TABLE 2. RISK OF AF RECURRENCE

	UNIVARIATE	ADJUSTED HR* (95% CI)	ADJUSTED HR*ǂ (95% CI)
SINGLE PROC, DRUG ASSISTED	1.06 (0.86-1.29)	1.09 (0.88-1.34)	1.15 (0.92-1.44)
SINGLE PROC, DRUG FREE	1.14 (0.93-1.38)	1.17 (0.95-1.43)	1.26 (1.01-1.58)
MULTI PROC, DRUG ASSISTED	1.46 (1.06-1.99)	1.43 (1.03-1.98)	1.53 (1.04-2.24)
MULTI PROC, DRUG FREE	1.25 (0.98-1.58)	1.21 (0.95-1.55)	1.28 (0.97-1.68)
Reference group is male. *Model 1: Adjusted for age and type of AF. *ǂ Model 2: Adjusted for model 1 and coronary artery disease, obstructive sleep apnoea, hypertension, BMI, diabetes mellitus, left atrial diameter			

TABLE 3. MULTIVARIATE PREDICTORS OF AF RECURRENCE

	ODDS RATIO	95% CI	P-VALUE
SINGLE PROCEDURE, DRUG FREE			
GENDER	1.23	1.01-1.58	0.04
AGE	1.15	1.01-1.03	0.005
TYPE OF AF	1.33	1.12-1.72	0.002
OSA	1.37	1.08-1.92	0.012
SINGLE PROCEDURE, DRUG ASSISTED			
AGE	1.01	1.00-1.02	0.18
TYPE OF AF	1.35	1.15-1.77	0.001
OSA	1.39	1.09-1.98	0.01
MULTI PROCEDURE, DRUG FREE			
AGE	1.02	1.01-1.04	0.001
TYPE OF AF	1.37	1.12-1.89	0.005
OSA	1.56	1.24-2.45	0.001
MULTI PROC PROCEDURE, DRUG ASSISTED			
GENDER	1.42	1.04-2.24	0.03
AGE	1.03	1.01-1.05	0.004
TYPE OF AF	1.41	1.05-2.2	0.03

TABLE 4. TABLE OF COMPLICATIONS

	MALES (n=418)	FEMALES (n=207)	P-VALUE
Major Complications	**19 (4.5)**	**5 (2.4)**	**0.27**
Fistula	2	0	
Tamponade	2	3	
Stroke/TIA	2	0	
Pericarditis/Dresslers Syndrome	13	2	
Moderate Complications	**16 (3.8)**	**11 (5.3)**	**0.4**
Pulmonary (Edema/Pneumonia)	5	2	
Groin Haematoma	7	5	
Major Effusion requiring intervention	2	0	
Asystole/PPM Requirement	2	4	
Total Complications, n (%)	**35 (8.4)**	**16 (7.7)**	**0.9**

FIGURE 1: CONSORT DIAGRAM

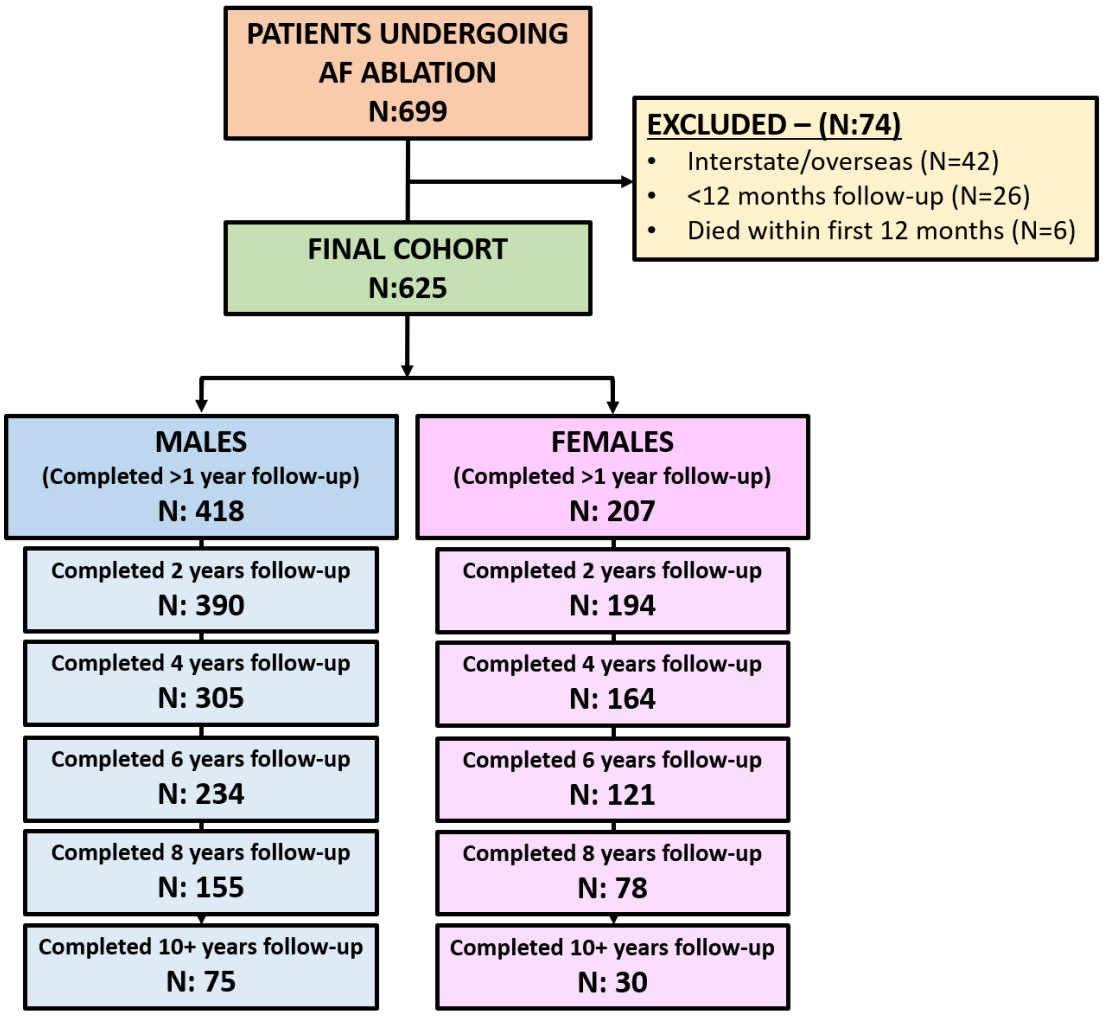


FIGURE 2. KAPLAN MEIER CURVE AF FREEDOM OFF AAD

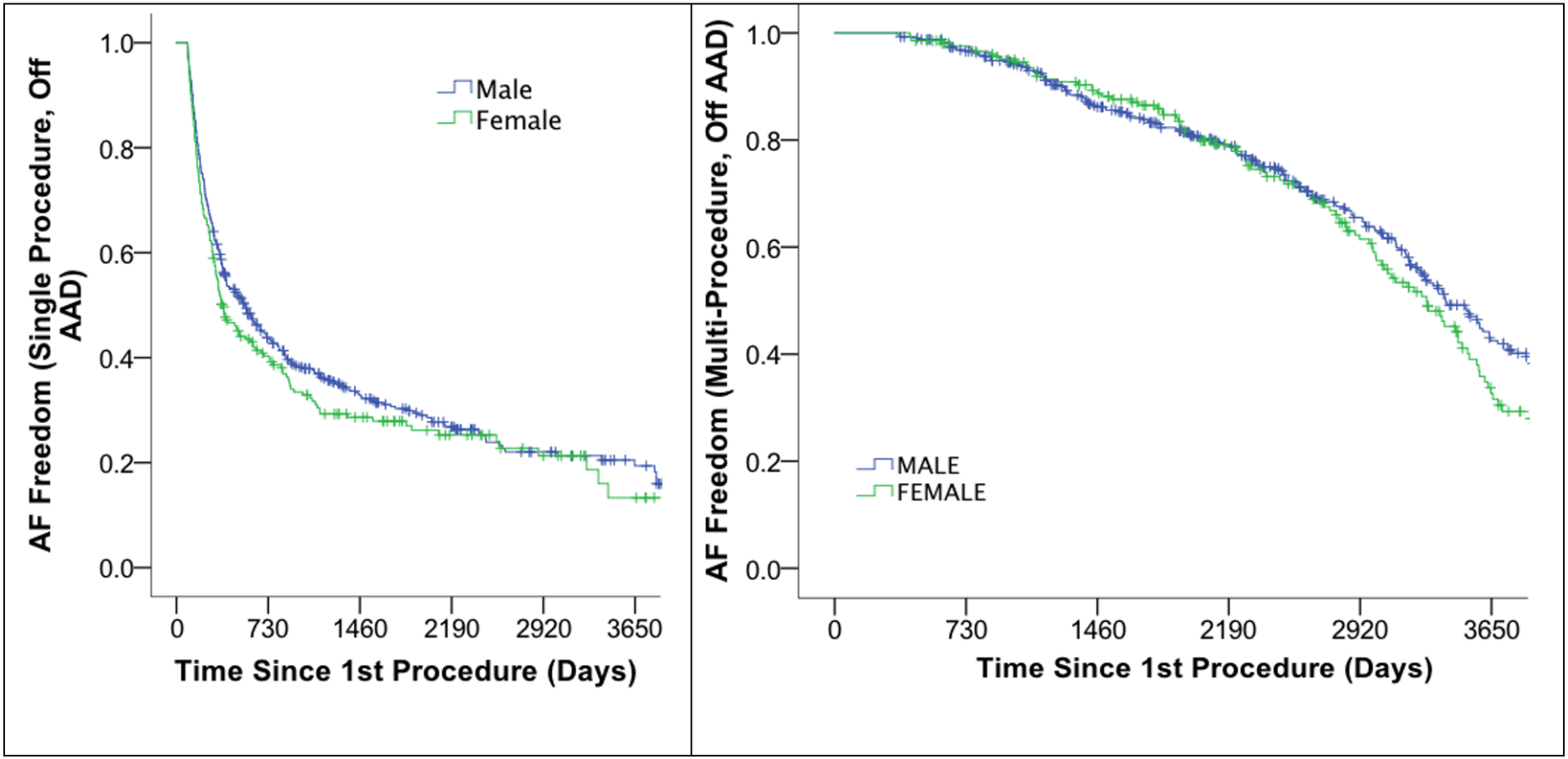
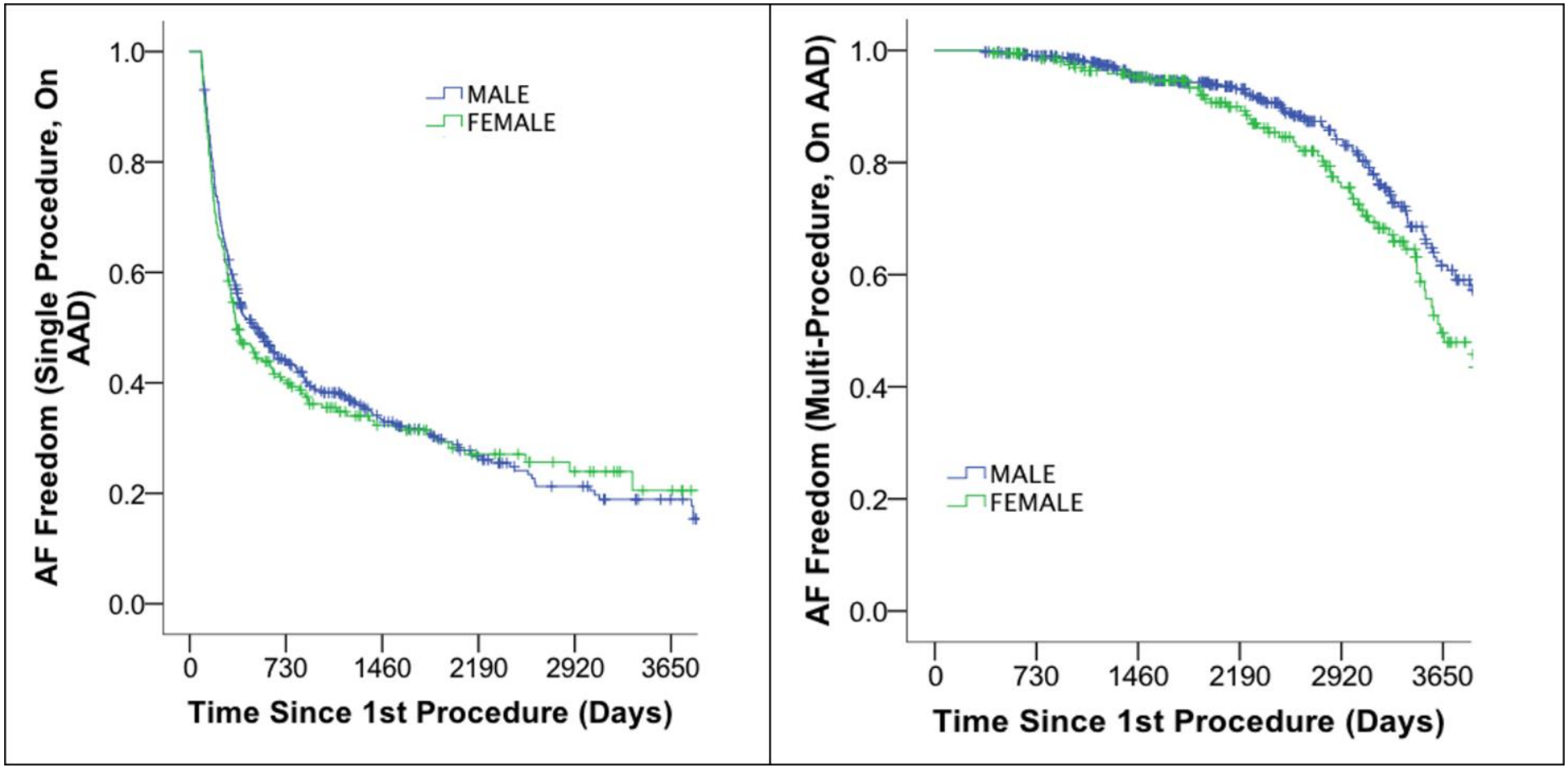


FIGURE 3. KAPLAN MEIER CURVE AF FREEDOM ON AAD



Chapter 6: ThrombogeneSIs Risk LatE FollowiNg AF AblaTion – SILENT Study

6.1 INTRODUCTION

Among the multiple complications resulting from AF, stroke remains the most devastating. It has been demonstrated that AF is responsible for one third of ischemic strokes.[385] Whether the risk of stroke persists following successful ablation of AF and total elimination of arrhythmic episodes remains unknown.[17] The mechanisms of thrombus formation are somewhat complex and poorly understood, factors such as mechanical dysfunction, endothelial dysfunction, clotting, inflammation and platelet activation as potential contributors.[387] It has been described in Vichow's triad that there are three factors responsible for thrombus development being abnormal blood flow and stasis, hypercoagulability and endothelial dysfunction.[388] Further it suggests perhaps it is not only the abnormal blood flow but resultant due to the fibrillation in the left atrium.

Several studies have assessed the risk of thromboembolism following AF ablation. Oral et al demonstrated a risk of TE to be 1.1% with these events all occurring within the first 12 months following ablation.[431] A large registry has shown that AF elimination as a result of ablation did result in lower stroke rates than those medically treated, the rates were no different to the general population.[389] A large multicentre study assessing cessation at 3-6 months following ablation demonstrated during follow up 0.07% of those off anticoagulation and 0.45% on anticoagulation had an ischemic stroke (p=0.06). While non-randomised this does suggest a benefit to continuation of anticoagulation following successful AF ablation.[394] More recently, data has been

variable with one study suggesting that following successful ablation at 3 months, switching to aspirin in patients with a CHA_2DS_2-VASc ≥2 is as safe as long-term anticoagulation.[432] Conversely a national survey performed in Canada demonstrated that 89% of physicians continued anticoagulation even after no AF recurrence at 12 months.[433] A recent study has demonstrated the rates of thromboembolic events beyond 3 months following ablation are quite low when compared to a non-ablation cohort.[392] Additionally, it found that the risk of serious bleeding associated with anticoagulation outweighed the benefit of thromboembolic event. It has also been suggested that perhaps the type of AF is an important consideration with a meta-analysis demonstrating that the risk of thromboembolism was higher in those with persistent AF.[434] A recent meta-analysis addressing the role of subclinical 'silent' AF has found that this is a predictor of clinical AF, while it does pertain a risk of stroke it was demonstrated that this was indeed lower than that of subclinical AF.[396] Noseworthy et al have demonstrated that the overall risk of stroke post ablation is low. While discontinuation of anticoagulation was common, they were able to show that this was associated with an increased risk of cardioembolism within the first 3 months for all patients, however for high-risk patients this was also a long-term risk.[435]

It is not clear if the stroke risk is eliminated by catheter ablation of AF. We hypothesised despite eliminating AF in a population undergoing ablation, there would still be individuals who experience a thrombogenic event. As such, the aim of this study was to characterise the stroke risk following AF ablation in a large single centre prospectively collected cohort.

6.2 METHODS

6.2.1 Study Population

The study comprised consecutive patients undergoing AF ablation at the Centre for Heart Rhythm Disorders at the University of Adelaide, Australia. Patients who had less than 12-months follow-up were excluded from the analysis. Baseline, follow-up, echocardiographic, and complication data was collected on patients. As per the ESC guidelines, women with a CHA_2DS_2-VASc score of 1 for sex with no other stroke risk factors were scored 0.[17] All patients were symptomatic and had failed anti-arrhythmic therapies were referred for AF ablation. This study had a blanking period of 90 days from ablation in accordance with the Heart Rhythm Society Consensus Statement.[410] Patients who experienced a thromboembolic event were recorded and the characteristics of the event along with investigations were collected. These events were established over the time course of the patient's follow-up. Patient records including ECG, Holter Monitoring and device interrogations were obtained to establish if the event occurred due to arrhythmia or in the absence of arrhythmia. This study has been approved by the Human Research Ethic Committee of the Royal Adelaide Hospital.

6.2.2 Ablation Technique

The techniques used for ablation in our laboratory have previously been described.[411] In brief, all patients underwent pulmonary vein isolation. Additional substrate ablation in the form of linear ablation, targeting triggers or potential sources of AF was undertaken in individuals with non-paroxysmal AF, longest atrial dimension of >57 mm or if they had concurrent structural heart disease. The extent and type of substrate modification undertaken was at the operating physician's discretion.

All patients had computed tomography prior to ablation. Intracardiac or trans-oesophageal echocardiogram was undertaken to ensure no thrombus was present at the time of the procedure. During ablation, radiofrequency energy was delivered at 15-40 Watts and was temperature limited to 48 degrees. Patients underwent oesophageal temperature monitoring and ablation on the posterior wall was interrupted with any rise in temperature of >0.5 degrees. Cryoablation was not used in this cohort.

6.2.3 Follow-up Protocol

Arrhythmia recurrence was undertaken with 12-lead electrocardiogram, 7-day Holter monitoring and/or device interrogation every 3 months for the first-year post-ablation, and every 6 months thereafter. Anticoagulation was ceased in all patients with a CHADS2 <2 at 3 months following ablation. In all other patients the decision to stop anticoagulants was made on an individual basis after the absence of any arrhythmia for ≥12 months.

6.2.4 AF Freedom

AF recurrence was defined as any atrial arrhythmia lasting >30 seconds in duration in accordance with the Heart Rhythm Society Consensus Statement.[410] The date of arrhythmia recurrence was defined as the earliest date with documented AF following the blanking period. AF freedom was determined by review of the clinical history, 12 lead ECG and 7-day Holter monitoring.

6.2.5 Thromboembolic Event Definition

Events of stroke, transient ischaemic attack (TIA), or cerebrovascular attack (CVA) were captured at either routine follow-up or hospitalisation. Stroke was defined as a neurological deficit lasting longer than 24 hours due to cerebrovascular emboli. A TIA was defined as a neurological deficit lasting less than 24 hours due to cerebrovascular emboli. All patients underwent cerebral imaging to confirm diagnosis with CT or MRI and in some cases patients underwent transoesophageal echo or carotid ultrasound to rule out atheroma and carotid stenosis. All patients underwent review by a Neurologist who made the diagnosis.

Patients were defined as having a late event if this occurred more than 12 months following the ablation.

6.2.6 Statistical Analysis

Categorical variables are represented as frequencies and percentages. Continuous variables are summarized as mean ± standard deviation (SD) or median and interquartile range as appropriate. For categorical variables, differences between groups was compared using a Chi-squared test. Continuous variables were compared by independent t-test or Mann-Whitney U test where appropriate. A p-value of $p<0.05$ was considered statistically significant. All statistical analysis was performed with SPSS version 24.0 (SPSS, Inc., Chicago, IL, USA).

6.3 RESULTS

6.3.1 Baseline Characteristics

A total of 700 consecutive patients undergoing de novo AF ablation were prospectively followed. A total of 628 patients completed at least 12 months of follow-up and were included in the analysis (Figure 1). Median follow-up was 2411 days [365-4645]. Table 1 presents the baseline characteristics of the cohort. Mean age of the cohort was 66 ± 11, 419 were male, the mean BMI 30.2 ± 5.6. There were 56.4% of the cohort with paroxysmal AF, and 52.7% had hypertension.

6.3.2 Clinical Factors Associated with Stroke

No significant differences were present in baseline characteristics between patients who had embolic events (n=15) compared with those without events (n=613; Table 1). There were no major echocardiographic differences in LA sizes nor was there any significant difference in anticoagulation use between the groups. The mean CHA_2DS_2-VASc was 1.6 ± 1.3, with non-stroke patient CHA_2DS_2-VASc 2 ± 1 and stoke patients CHA_2DS_2-VASc 3 ± 1. This was not statistically different between the groups (Table 1).

6.3.3 Timing of Events

Of the 628 patients with at least 12 months follow up, a total of 15 (2.4%) presented with thromboembolic event following AF ablation. Two (13%) occurred within 12 months of ablation; a further 5 (27%) within 1-2 years and 8 (60%) >2 years after ablation (Figure 2). One patient had an event within 48 hours of undergoing an ablation.

6.3.4 Events and Arrhythmia

There were 9 (60%) patients who experienced an event in the absence of arrhythmia following successful ablation. These patients underwent a median of 1176 [504-13870] hours of monitoring for asymptomatic arrhythmias. These occurred at a median of 801 [421-2956] days post ablation. Five (55.5%) occurred very late, more than 2 years following successful AF ablation in the absence of arrhythmia. Two patients had implantable pacemakers which confirmed the absences of arrhythmia. The remainder of the patients had ECG and were undergoing regular Holter monitoring as part of their post ablation follow-up. Figure 3 demonstrates example of the pacemaker interrogation. One patient had a CHA_2DS_2-VASc score of 4, three had a CHA_2DS_2-VASc score of 3, four patients had a CHA_2DS_2-VASc score of 2 and one patient had a score of 1. Majority of patients scored for hypertension which was treated in all patients (Table 2).

There were six patients (40%) who had an embolic episode related to AF recurrence. This was documented on pacemaker interrogation, ECG and patient symptoms. Two patients had CHA_2DS_2-VASc score of ≥ 2, two patients had CHA_2DS_2-VASc score of 1 and two patients had CHA_2DS_2-VASc score of 0. These scores were predominantly due to hypertension (Table 3).

6.3.5 Anticoagulation at Time of Event

Eight patients who had no AF had ceased long-term anticoagulation for a mean of 6.9±6.1 months prior to the thromboembolic event. Of note, one patient experienced his event while taking rivaroxaban despite appropriate dosage and compliance with

this medication. Two patients had ceased their anticoagulation for 1 week due to undergoing non-cardiac surgery (Table 2).

For those who had AF recurrence, two patients (13.3%) experienced an event due to anticoagulation non-compliance. One patient had his event directly following his ablation while on anticoagulation, one patient had ceased his anticoagulation for 30 days, one for 228 days, and one patient was on anticoagulation at the time of the event (Table 3).

6.3.6 Type of Event

In the patients who had an event in the absence of arrythmia, five patients experienced CVA, three had a TIA, and 1 patient had a gastrointestinal ischemic event. Symptoms for the patients were typical of CVA/TIA presentation, with dysphasia, left sided weakness and amaurosis fugax (Table 2).

For those who had AF recurrence two experienced CVA and three had a TIA. Symptoms for the patients were typical of CVA/TIA presentation, with dysphasia, left sided weakness and diplopia (Table 3).

6.3.7 Details of Investigations

All patients underwent neurological evaluation to confirm diagnosis of stroke and exclude the possibility of lacunar infarcts based on the cerebral imaging. All patients underwent brain computed tomography (CT) and/or magnetic resonance imaging (MRI) to confirm diagnosis.

Of those who had no AF eight underwent CT with four also undergoing MRI evaluation. In one patient only MRI imaging was undertaken to confirm the diagnosis.

Two patients were unable to have MRI due to non-MRI compatible pacemakers insitu, one patient refused to have MRI (Figure 3).

In the patients who had AF recurrence, three had CT scan, two didn't have this as diagnosis made on MRI, one patient was overseas and therefore the CT was not performed. Four patients underwent MRI, with two patients were unable to have MRI due to non-MRI compatible pacemakers insitu (Figure 3).

6.3.8 Management of Patients

In total, two patient received acute thrombolysis. Transoesophageal echo (TEE) was performed in 5 patients: No intra-cardiac clot was seen but mild arch atheroma was seen in 3 patients, one patient had significant arch atheroma and one patient had no significant findings. Carotid ultrasound on 4 of the 6 patients did not demonstrate any significant carotid artery stenosis.

In the group who had no AF recurrence, patients had repeat rhythm monitoring with 7-day Holters and ECGs except for 2 patients with implantable pacemakers. No AF was seen from these investigations with device interrogations also showing no evidence of atrial arrhythmia recurrence (Figure 4).

Following the event, all patients who had an event were anticoagulated (5 with Warfarin and 10 with a non-vitamin K antagonist).

One patient died as a result of the event. Fortunately, all remaining 14 patients have recovered neurologically without functional deficits.

6.4 DISCUSSIONS

6.4.1 Major Findings

This study has some important findings:

1. There were no significant baseline characteristics that contributed to a thromboembolic event following ablation.
2. Events following ablation occur late with 27% occurring 1-2 years post ablation and 60% occurring more than two years post ablation
3. A significant proportion of patients experienced an event in the absence of arrhythmia

This study has shown that in patients undergoing ablation for AF, the risk of stroke remains low over a long-term follow-up. However, it also demonstrates that these events can present quite late following the apparent successful ablation in the absence of arrhythmia. It argues for meticulous monitoring and careful consideration if anticoagulant cessation is considered.

6.4.2 Stroke Post AF Ablation

The risk of AF recurrence following an apparent successful procedure confers an inherent risk of increased thromboembolic complications should anticoagulation be ceased based on initial results.[436] Indeed, despite having had "successful" AF ablation, stroke risk may still be present given that the constellation of risk factors that led to AF in the same patients are also known risk factors for stroke and data is limited in this area.[17] Saad et al demonstrated there was a low to moderate risk if a patient had a $CHADS^2$ score of ≤ 3 but that remained on antiplatelets and that risk factors would need to be assessed to establish risk of stroke, they did however have 3 patients in their

cohort who experienced strokes whilst on anticoagulation.[437] Yagishita et al suggests that with patients who maintained sinus rhythm following ablation there was a low risk from >3 years follow-up suggesting that AF ablation reduces the risk irrespective of the outcome, once again suggesting anticoagulation to be used based on risk factors.[438] A large multi-centre study demonstrated that those off anticoagulation had a higher rate of thromboembolic events in a short-term follow-up following AF ablation.[394] More recently Gaita et al published an observational study with a low incidence of thromboembolic events over 60.5 months of follow-up.[439] They noted the incidence was lower in those who underwent AF ablation compared with the general population of anticoagulated patients. In their cohort they documented 6 of 267 patients who had events whist still anticoagulated and 5 of 499 patients who ceased their anticoagulation experienced events. The current study demonstrates that 87% of events occurred more than 1 year following their ablation. Of this 53% occurred more than 3 years following the procedure. The same held true for those who had an event in the absence of arrhythmia with 88% of the events occurring greater than 12 months follow successful ablation.

6.4.3 Subclinical AF and Stroke

A recent meta-analysis assessing the temporal association between subclinical AF and stroke found that following excluding patients without AF, only 17% strokes occur in the presence of ongoing AF.[396] The type of AF has also been suggested as a potential to predict events post ablation, with persistent AF patients more likely to experience an event.[434] This was demonstrated in a recent meta-analysis has demonstrated the unadjusted risk for thromboembolism in persistent compared to paroxysmal AF was 1.355 (95% CI: 1.17-1.57, $p<0.001$). The risk of stroke being related to the burden of

AF has important implications. In the context following catheter ablation, in the absence of detectable arrhythmia, the risk of stroke could be considered low.

6.4.4 Clinical Implications

Perhaps due to the low number of events, this study was unable to isolate any individual risk factors that increased the risk of an event. It could be suggested that due to these patients receiving protocolised care with regular long-term follow-up this could indeed result in fewer events. This cohort has demonstrated that despite the absence of AF, cryptogenic stroke risk exists, and thromboembolic management needs to be considered following ablation. This study however does demonstrate that there is potentially the risk of a thrombogenic atria despite elimination of AF. While cessation of anticoagulation following apparent successful ablation seems relatively safe, there still remains a lack of conclusive data, particularly in the absence of large randomised clinical studies.

6.5 LIMITATIONS

This is a single centre cohort and observational study; however, the data was is obtained from a prospectively collected clinical registry. Measurement bias was reduced by use of standardised processes in the clinic. Additionally, while two of the patients had implantable devices which demonstrated no AF, for those without a device, silent/asymptomatic AF could have occurred without our knowledge. Standard protocolised follow-up with the use of 7-day Holter monitoring, ECGs and review of all implantable device checks was undertaken to provide the ability to capture AF recurrence as much as possible.

6.6 CONCLUSION

Although AF ablation is a well-regarded treatment for AF, “successful” ablation does not abolish the risk of stroke. In this study a significant number of events occurred in the absence of arrythmia with two of these continuously monitored by pacing. This suggest that perhaps the thrombogenic atria exists despite sinus rhythm maintenance. Additionally, these events occurred quite late following successful ablation suggesting, while the risk seems low, caution is needed about cessation of anticoagulation following AF ablation. Further studies are needed to determine the ideal strategy of anticoagulation management following successful AF ablation.

6.7 TABLE AND FIGURE LEGEND

TABLE 1. PATIENT CHARACTERISTICS

TABLE 2. CHARACTERISTICS OF PATIENTS WHO HAD EVENTS IN THE ABSENSE OF AF

Table demonstrating the patients divided by those who had event in the absence of arrhythmia.

CHARACTERISTICS OF PATIENTS WHO HAD EVENTS WITH AF RECURRENCE

Table demonstrating the patients divided by those who had event with AF recurrence.

FIGURE 1. CONSORT DIAGRAM

Diagram of patient selection

FIGURE 2. TIMING OF EVENTS

Pie chart demonstrating distribution of time of event occurring following ablation. With over half events occurring after 2 years post ablation.

FIGURE 3. ACUTE MANAGEMENT FLOW DIAGRAM

Patient management flow for patients who had stroke, evaluation undertaken and diagnosis.

FIGURE 4. PACEMAKER INTERROGATION

Pacemaker interrogation from patient who had event in the absence of arrhythmia. This demonstrates no AF in the lead up to the TIA, highlighted in red, and no AF following.

TABLE 1. PATIENT CHARACTERISTICS

	TOTAL COHORT N=628	NON-EVENT N=613	EVENT N=15	P-VALUE
AGE	66 ± 11	59.8 ± 10.4	62.7 ± 7.6	0.3
BODY MASS INDEX	28.9 ± 5.6	29.8 ± 5.6	28 ± 4.5	0.27
MALES (%)	419 (66.7)	409 (66.7)	10 (66.7)	0.98
TYPE OF AF (%) **PAROXYSMAL** **PERSISTENT**	 354 (56.4) 275 (44)	 344 (56) 270 (44)	 10 (66.7) 5 (33.3)	0.41
PRIOR STROKE (%)	48 (7.6)	47 (7.7)	1 (6.7)	0.87
PRIOR MI (%)	21 (3.3)	21 (3.4)	0 (0)	0.47
OSA (%)	81 (13)	79 (12.9)	2 (13.3)	0.96
HYPERTENSION (%)	331 (52.7)	322 (52.5)	9 (60)	0.57
HYPERLIPIDAEMIA (%)	224 (35.7)	220 (36)	4 (26.7)	0.46
CORONARY ARTERY DISEASE (%)	60 (9.6)	60 (9.8)	0 (0)	0.2
SMOKING (%) **NEVER** **CURRENT** **EX-SMOKER**	 418 (66.6) 34 (5.4) 176 (28)	 408 (66.4) 32 (5.2) 173 (28.2)	 10 (66.7) 2 (13.3) 3 (20)	0.34
DIABETES MELLITUS (%)	51 (8.1)	51 (8.3)	0 (0)	0.24
CHA_2DS_2-VASc Score	1.6 ± 1.3	2 ± 1	3 ± 1	0.71
ECHOCARDIOGRAM MEASURES				
LA VOLUME (mls)	72 ± 27	72 ± 27	61 ± 15	
LA AREA (cm^2)	24 ± 7	23.8 ± 6.9	22.3 ± 6.6	0.4
LA DIAMETER (cm)	4.1 ± 0.7	4.14 ± 0.67	3.93 ± 0.74	0.23
LVEF (%)	60 ± 10	60 ± 10	62 ± 7	0.5
ANTICOAGULATION USE				
NONE/ASPIRIN (%)	261 (41.6)	256 (41.7)	5 (33.3)	0.46
WARFARIN (%)	311 (49.5)	302 (49.3)	9 (60)	
NOAC (%)	55 (8.8)	54 (8.8)	1 (6.7)	

AF = atrial fibrillation; MI = myocardial infarction; OSA = obstructive sleep apnoea; LA = left atrial; LVEF = left ventricular ejection fraction; NOAC = non-vitamin K antagonist

TABLE 2. CHARACTERISTICS OF PATIENTS WHO HAD EVENTS IN THE ABSENSE OF AF

ID	SEX	AGE	EVENT TYPE	DAYS OFF OAC	MONTHS POST ABLATION	CHA2D2-VASc Score	TYPE OF AF	EVIDENCE OF AF	SYMPTOMS	MONTHS AF FREEDOM
1	M	66	TIA	360	84	2 – HTN, AGE	Paroxysmal	Holters/ECG's performed (no AF)	Amaurosis fugax	96
2	F	66	CVA	442	52	3 – HTN, AGE, FEMALE	Paroxysmal	Holters/ECG's performed (no AF)	Expressive dysphasia Left sided weakness and numbness	78
3	M	76	TIA	90	23	2 – AGE	Paroxysmal	Holters/ECG's performed (no AF)	Expressive dysphasia	72
4	F	69	ISCHEMIC GI	92	32	3 – HTN, AGE, FEMALE	Persistent	Holters/ECG's performed (no AF)	Abdominal pain	72
5	M	56	CVA	413	19	2 – HTN, DM	Persistent	PPM – no AF	Left sided weakness	78
6	M	59	CVA	67	19	1 – HTN	Paroxysmal	Holters/ECG's performed (no AF)	Left sided weakness	66
7	M	73	CVA	0	14	2 – HTN, AGE	Paroxysmal	Holters/ECG's performed (no AF)	Nausea, vomiting and vertigo	15
8	F	77	TIA	7	8	4 – HTN, AGE, FEMALE	Paroxysmal	PPM – no AF	Expressive dysphasia	18
9	F	66	CVA	0	40	3 – HTN, AGE, FEMALE	Paroxysmal	Holters/ECG's performed (no AF)	Dysarthric, Left sided weakness, nauseated	40

CVA = Cerebrovascular event; TIA = Transient ischemic event; MCA = Middle cerebral artery GI = Gastrointestinal; HT = Hypertension; AF = Atrial fibrillation; PPM = Permanent pacemaker; OAC = Oral anticoagulation; DM = Diabetes mellitus

TABLE 3. CHARACTERISTICS OF PATIENTS WHO HAD EVENTS WITH AF RECURRENCE

ID	SEX	AGE	EVENT TYPE	DAYS OFF OAC	MONTHS POST ABLATION	CHA2D2-VASc Score	TYPE OF AF	EVIDENCE OF AF	SYMPTOMS	MONTHS AF FREEDOM
EVENTS WITH AF RECURRENCE										
1	M	57	CVA	228	16	0	Persistent	PPM-Brief episode of AF day prior	Dysarthric, Left sided weakness	Recurrent AF
2	F	75	CVA	2	99	4 – HTN, AGE, FEMALE	Paroxysmal	PPM – Brief episode of AF (missed OAC)	Left hemiparesis, Expressive dysphasia, Hemisensory loss	Recurrent AF
3	M	62	TIA	30	23	1 – HTN	Persistent	Recurrent episode of AF	Visual loss, Left sided weakness	Recurrent AF
4	M	56	TIA	897	37	0	Persistent	AF at time of episode (non-compliant)	Expressive dysphasia	Recurrent AF
5	F	74	TIA	0	4	2 – AGE, FEMALE	Paroxysmal	Recurrent episodes of AF	Right sided visual impairment, Double vision	Recurrent AF
6	M	60	TIA	0	0	1 – HTN	Paroxysmal	Immediate post ablation	Diplopia	Immediate post ablation

FIGURE 1. CONSORT DIAGRAM

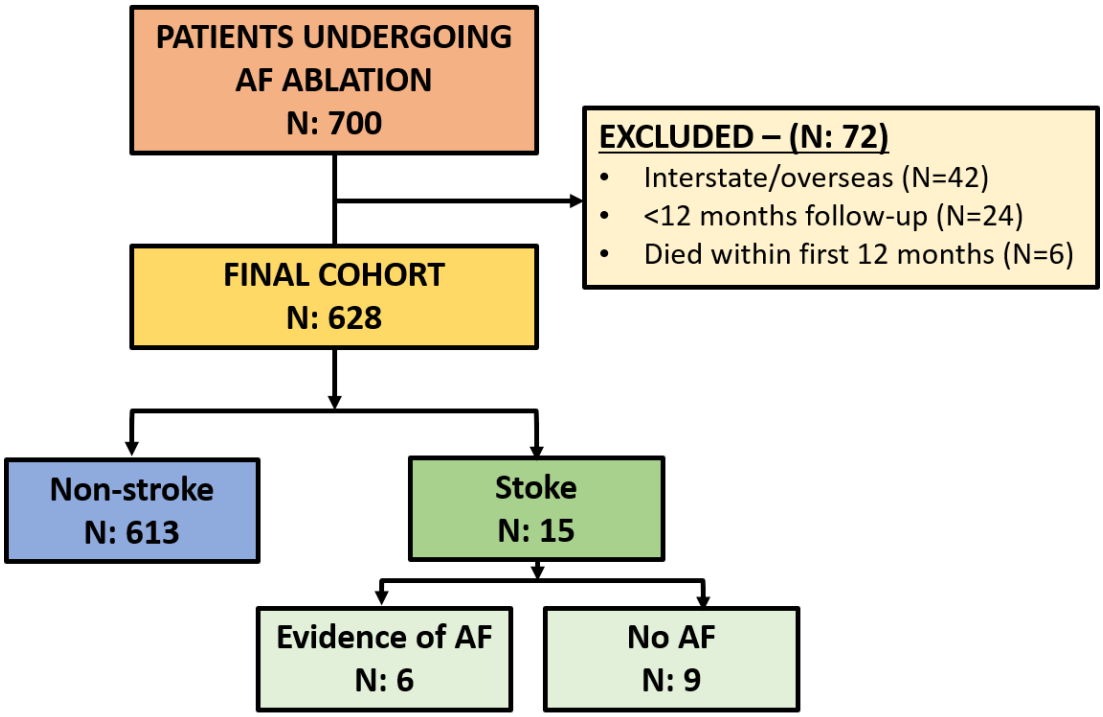


FIGURE 2. TIMING OF EVENTS

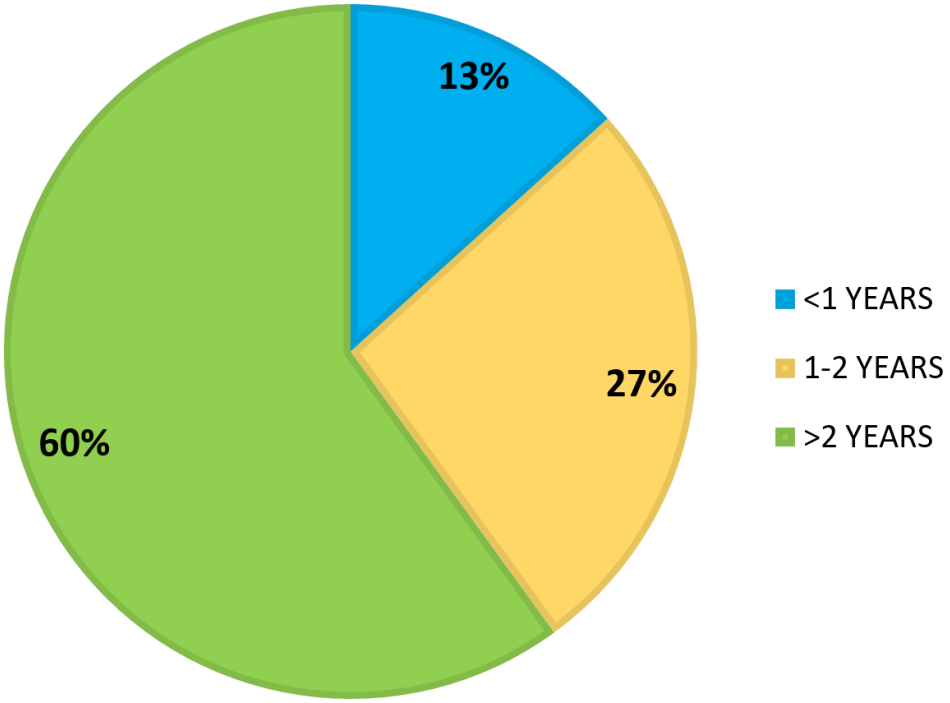


FIGURE 3. ACUTE MANAGEMENT FLOW DIAGRAM

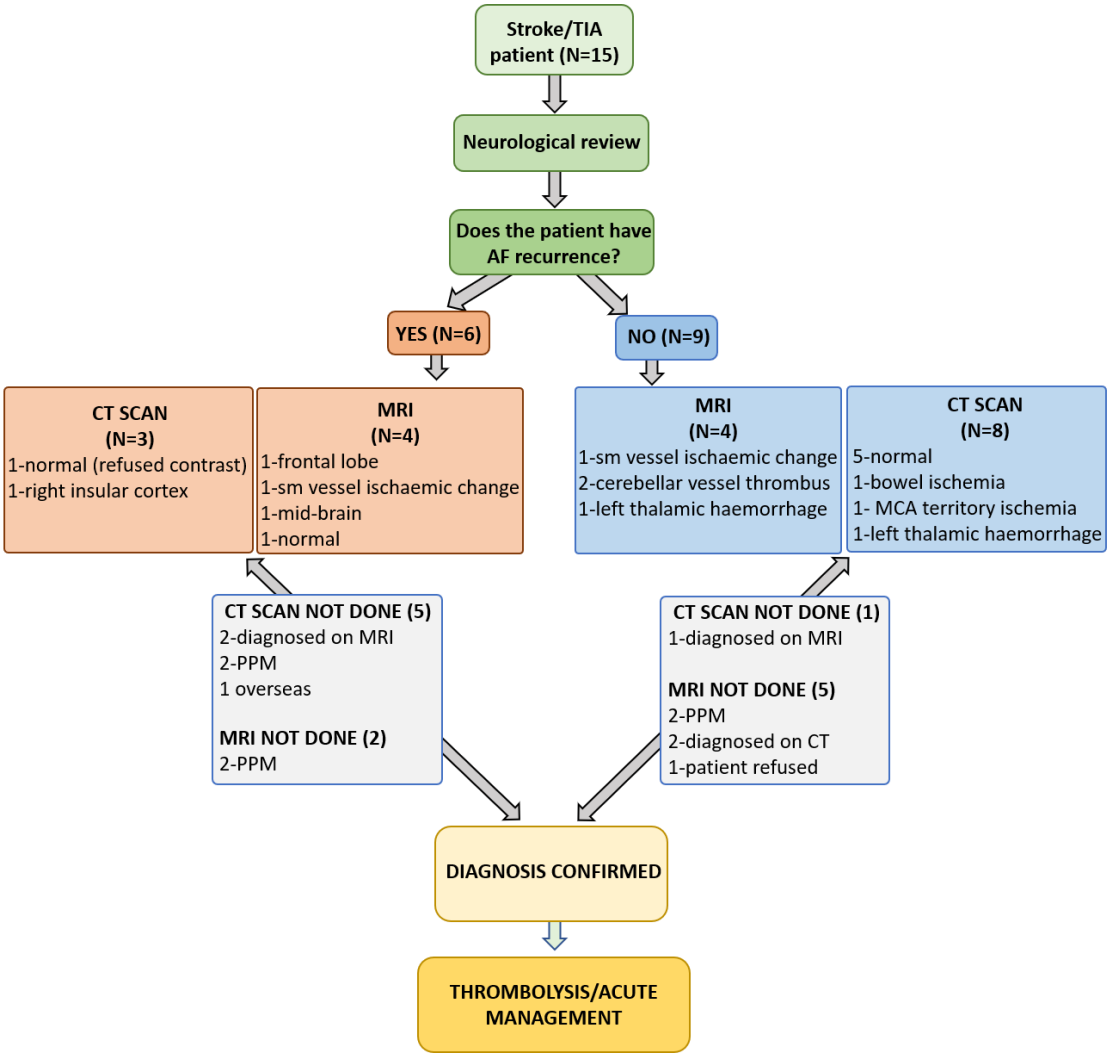
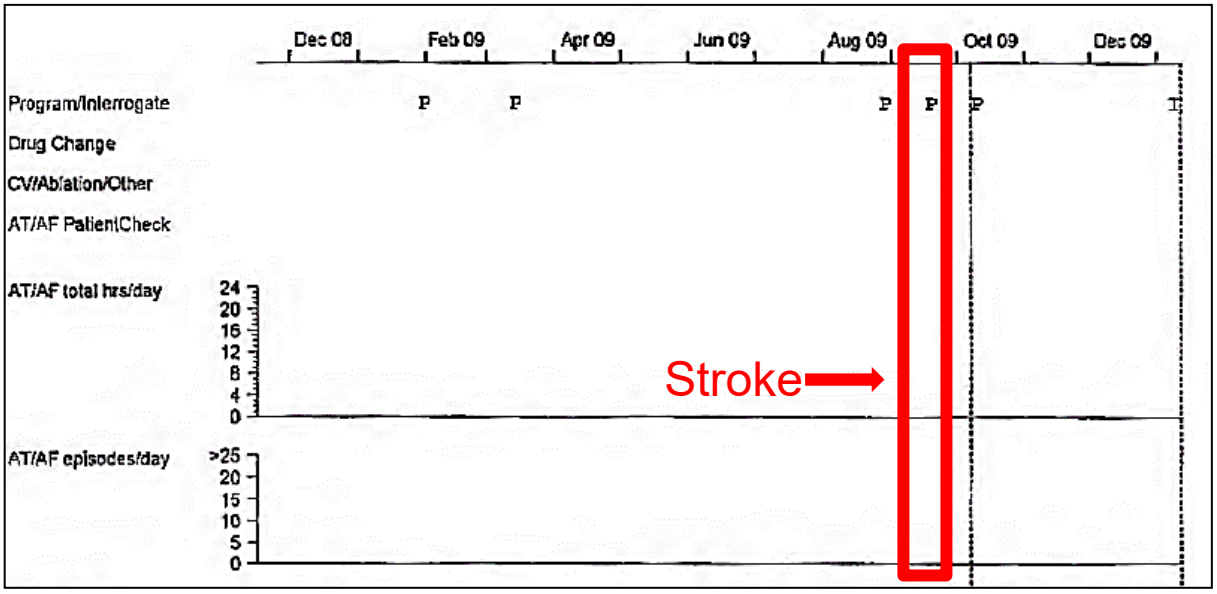


FIGURE 4. PACEMAKER INTERROGATION



Chapter 7: Cessation of Non-vitamin K Antagonist Oral Anticoagulants in Atrial Fibrillation Patients

7.1 INTRODUCTION

The incidence of atrial fibrillation (AF) is growing to epidemic proportions, and set to rise exponentially over the years to come.[1] One of the most devastating AF-related complications is stroke, with 15-40% of all strokes occurring in individuals with a history of AF.[37] This risk increases with age, from 1.5% in 50-59 years up to 23.5% in individuals aged 80-89 years.[440] Anticoagulation is the key management strategy for stroke prevention in individuals with AF. Although vitamin K antagonist (VKA) such as warfarin were for many years the anticoagulant of choice for stroke prevention, the more recent emergence of non-vitamin K antagonist oral anticoagulants (NOAC) has provided an effective alternative. This is largely due to greater ease of prescription with the lack of need for regular blood testing and reduced dietary interactions. The ease of use and efficacy have led to inclusion of NOACs in the recent European Society of Cardiology AF Guidelines as a Class I, level A recommendation in stroke prevention for eligible patients, as a preference over VKA.[109]

However, despite the benefits of NOACs over VKA, recent trials have suggested that there is a large rate of cessation. The cessation rates reported in the Dabigatran versus Warfarin in Patients with Atrial Fibrillation (RE-LY), Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation (ROCKET-AF) and apixaban versus Warfarin in Patients with Atrial Fibrillation (ARISTOTLE) trials were 21% (2 years follow-up), 14.3% (1.9 years follow-up), and 25.3% (1.8 years follow-up) for dabigatran, rivaroxaban and apixaban respectively. The primary cause of cessation was

major bleeding, gastrointestinal bleeding or dyspepsia.[441-443] Indeed, the rates of discontinuation have been used to promote the need for alternative stroke prevention techniques such as left atrial appendage closure devices.[444-446] Despite this, clinical experience suggests that NOAC use is safer than what has been reported by the larger studies.[447]

These strikingly high cessation figures raise the question as to the safety of NOACs in a real-world setting. To assess this, we studied AF patients with an indication for long-term anticoagulation who were prescribed a NOAC in our centre between 2010 and 2017. We aimed to characterise the incidence and causes of NOAC cessation and serious adverse events leading in discontinuation of treatment. Further, we sought to describe the duration of treatment prior to cessation across the three main NOACs and identify predictors of cessation and serious adverse events.

7.2 METHODS

7.2.1 Study Population

This study comprised 1415 consecutive AF patients, from a prospectively collected registry (Clinical Trial Registration: ACTRN12614001123639), at the Centre for Heart Rhythm Disorders, Adelaide, Australia between 2011 and 2017. The study included patients who were prescribed either dabigatran, apixaban or rivaroxaban *(Figure 1A)*. Edoxaban was not included in this cohort as it is not available in Australia. The choice of NOAC prescribed was at the treating physicians' discretion based on the patient's needs, age, and renal function. Prescription in our clinic is an integrated care context, involving a specialist nurse and a pharmacist if required, whereby the patient receives education about AF and the pharmacotherapy.[448] While the NOAC's

were available to limited patients on a physician familiarisation program from 2011, rivaroxaban was listed on the pharmaceutical benefits scheme in August 2013, followed by apixaban and dabigatran which were both listed in September 2013. Patients with a CHA_2DS_2-VASc score of 0 were excluded, as they had no indication for long-term anticoagulation. This included women without other stroke risk factors.[404]

7.2.2 Patient Characteristics

AF was confirmed by at least one 12-lead electrocardiogram (ECG) documentation. Type of AF was defined as per the 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of AF.[401] Baseline characteristics including age, gender and body mass index (BMI) were recorded, and clinical risk factors at the time of NOAC initiation was collected. This included type of AF, hypertension, diabetes mellitus, hyperlipidaemia, smoking status. NOAC type at baseline and at final follow-up, date of commencement and cessation, cause of cessation, and adverse events resulting in cessation were collected for analysis.

The study was approved by the Human Research Ethics Committee of the University of Adelaide and Royal Adelaide Hospital.

7.2.3 Study Outcomes

The main study outcome was the cessation of index NOAC (defined as NOAC type at baseline), either to another form of oral anticoagulation (OAC) or complete OAC cessation. Causes of cessation, duration-to-cessation and predictors of cessation are

reported. Additionally, we characterise the rate and type of serious adverse events resulting in NOAC cessation.

7.2.4 Definitions

Serious adverse events were defined as events leading to discontinuation of treatment. This included major bleeding, minor bleeding, ischaemic stroke and drug-related adverse reaction warranting discontinuation. Bleeding was defined as per the Thrombolysis in Myocardial Infarction bleeding criteria (TIMI)[449]. Major bleeding was defined as: any intracranial bleeding; clinically-overt signs of haemorrhage associated with a decrease in haemoglobin of ≥5 g/dL or a ≥15% absolute decrease in haematocrit; or fatal bleeding (bleeding that directly results in death within 7 days). Minor bleeding was defined as: clinically overt bleeding resulting in haemoglobin drop of 3 to <5 g/dL or ≥10% decrease in haematocrit; no observed blood loss but with ≥4 g/dL decrease in the haemoglobin concentration or ≥12% decrease in haematocrit; or any overt sign of haemorrhage that does not meet the above criteria but is associated with any of the following: requiring medical or surgical intervention, leading to prolonging hospitalization or prompting evaluation. Renal impairment was defined as abnormal estimate glomerular filtration rate (eGFR) <60 mL/min/1.73m^2. Some patients made an informed decision to stop their anticoagulation following a detailed discussion with their treating cardiologist and are represented as a 'patient choice' category in our study, of note no patients decided to stop their NOAC due to cost associated reasons.

7.2.5 Statistical Analysis

Categorical variables are represented as frequencies and percentages. Continuous variables are summarized as mean±SD or median and interquartile range as appropriate. For categorical variables, differences between groups was compared using a Chi-squared test. Continuous variables were compared by independent t-test or Mann-Whitney U test where appropriate. Duration-to-cessation in the population, stratified by NOAC type at baseline, was tested using a log rank test and presented using Kaplan-Meier curves. A multivariable cox regression model was constructed to assess the influence of clinical variables, selected *a priori* based on clinical consensus. Given the relatively low event rate of NOAC reaction, we limited these candidate variables to age, gender, common comorbidities (body mass index, hypertension, type II diabetes) and AF type (paroxysmal, persistent, or permanent). A p-value of $p<0.05$ was considered statistically significant. All statistical analysis was performed with SPSS version 24.0 (SPSS, Inc., Chicago, IL, USA).

7.3 RESULTS

7.3.1 Baseline Characteristics

A total of 503 patients were prescribed a NOAC between 2011 – 2017, of whom 439 (87.3%) patients had a CHA_2DS_2-VASc of ≥1 and were included in the study (Figure 1), the remaining 64 patients with a CHA_2DS_2-VASc <1 received peri-procedural OAC for ablation or cardioversion with cessation planned once sinus rhythm was maintained. The mean age was 71.9 ± 8.7 years and 162 (36.9%) were females. Two-hundred and thirty patients (52.4%) had paroxysmal AF, while 134 (30.5%) had persistent AF and 75 (17.1%) had permanent AF (Table 1). At baseline, 154 (35.1%)

of patients were prescribed dabigatran, 195 (44.4%) were prescribed apixaban and 90 (20.5%) were prescribed rivaroxaban (Figure 2). Follow-up duration ranged from 0.2 to 7 years, with a median follow-up of 3.6 years [IQR 2.7 – 5.3].

7.3.2 Primary Outcomes

Of the 439 patients, 292 (66.5%) remained on their index NOAC while 147 patients (33.5%) ceased their index NOAC. This group was composed of 113 (76.9%) patients who changed to an alternative NOAC or warfarin and 34 (23.1%) who ceased anticoagulation completely, resulting in a total cessation of index NOAC rate of 8.8 events per 100 patient-years of follow-up. Patients who did not change their NOAC were significantly younger than those who changed or stopped OAC (71.2±7.9 versus 73.2±9.9 years, respectively; p=0.02). AF type was different between the groups, with paroxysmal AF being present in 56.2% of those who remained on their index NOAC compared to 44.9% in the NOAC cessation or alteration group (p=0.008). Inversely, persistent AF was less common (25.7%) in the NOAC continuation group compared to 40.1% in the cessation group, with comparable levels of permanent AF (18.2% and 15.0%, respectively; overall p=0.008). No major differences were seen between other risk factors (Table 1).

7.3.3 Causes of Switching of Index NOAC

Of those who switched their OAC patient choice was the most frequent cause (47/113, 41.6%) (Table 2). Serious adverse events resulting in altering OAC type (either to a different NOAC or to warfarin) took place in 28 patients over the follow-up period, resulting in an adverse event rate of 1.6 per 100 patient-years. Event rate per NOAC

were: 1.7 per 100 patient-years for dabigatran; 1.1 per 100 patient-years for apixaban; and 2.3 per 100 patient-years for rivaroxaban.

Overall, 3 patients experienced major bleeding, all in the form of non-fatal intracranial haemorrhages. A further 3 patients experienced cerebrovascular thromboembolic events, and 6 patients experienced minor bleeds. Over the course of the study, 13 (2.9%) patients died of non-NOAC related causes.

Table 2 outlines the causes of altering treatment including alteration by other physicians involved in patient care, alteration due to AF ablation or surgical intervention, as well as alterations due to drug-related adverse reactions.

7.3.4 Complete Cessation of OAC

Complete cessation of OAC occurred in 34 patients. The most frequent reason for complete discontinuation was patient decision (23/34, 67.6%). Indeed, across the complete cessation and the switching groups, patient choice accounted for 78/147 (53.1%) of all causes. In 8 patients (23.5%), age-related anticoagulation risk outweighed the benefits of anticoagulation resulting in cessation of treatment following an informed discussion with the treating cardiologist. Left atrial appendage occlusion (LAAO) took place in 2 patients and one patient discontinued oral anticoagulation due to undergoing treatment for cancer (Table 2).

7.3.5 Duration to Cessation

The mean duration to cessation was 4.9 (95% CI: 4.6-5.1) years. When stratified by NOAC type at baseline, there was a significant difference across the cohort (log-rank p=0.009) (Figure 2). Patients on apixaban had a significantly longer duration-to-

cessation time compared with other NOAC users with a mean duration of 5.1 (95% CI: 4.8-5.4) years compared to rivaroxaban 4.6 (95% CI: 4.2-4.9) years for dabigatran (p=0.002) and 4.5 (95% CI: 3.9-5.1) years (p=0.025) (Figure 3).

7.3.6 NOAC Use at Follow-up

At final follow-up, 361 (82%) patients remained on a NOAC. Of those, 71 patients remained on index dabigatran and 3 patients crossed over from an alternative NOAC resulting in a total of 74 (20.5%) patients on dabigatran at final follow-up. Of the patients originally on apixaban, 162 (44.9%) remained on this without the need for cessation, however at final follow-up a further 56 patients crossed over from an alternative NOAC with a total of 218 patients (60.4%) on Apixaban. Rivaroxaban was prescribed to 69 patients (19.1%) at final follow-up, 59 of whom were on their index NOAC and 10 crossed over from other groups. Warfarin was commenced in 44 patients (12.2%): 40.9% due to patient decision; 13.6% due to decline in renal function; 11.4% undergoing procedures; and the remainder 34.1% were due to drug-related reactions (Figure 2).

7.3.7 Predictors of Outcomes and Adverse Events

In a multivariate cox regression model including BMI, AF type, gender, hypertension, and diabetes, age (HR 1.03, 95% CI: 1.008-1.05; p=0.006) was an independent predictor of cessation of index NOAC. Female gender (HR 2.2, 95% CI: 1.04-4.64; p=0.04) was found to be an independent predictor of serious adverse events.

7.4 DISCUSSION

7.4.1 Major Findings

This “real world” cohort of ambulatory AF patients demonstrate the following about NOAC use:

1. Persistence of NOACs use was found to be high with only 8.8 cessations per 100 patient-years of follow-up;
2. The rate of serious adverse events rate was low at only 1.6 per 100 patient-years of follow-up;
3. Apixaban had the longest duration-to-cessation of all the NOACS of 5.1 (95% CI: 4.8-5.4) years, suggesting that apixaban is potentially better-tolerated in comparison to other NOACs;
4. Age independently predicted cessation of index NOAC and importantly, female gender was an independent predictor of serious adverse events;
5. Involvement of patients in the decision-making process of their care is paramount, with the most common cause of cessation of index NOAC (53.1%) being patient choice.

7.4.2 Adverse Events and Cessation of NOACs

Our study has demonstrated that NOACs are relatively safe and well tolerated, with two-thirds of patients remaining on their index NOAC following a median follow-up of 3.6 years. Additionally, only 28 patients (6.3%) experienced serious adverse events resulting in cessation of their treatment with a low adverse events rate of 1.6 per 100 patient-years. Our data differs from that seen in the major studies with lower cessation and adverse events rates. While the cessation rates in the major NOAC studies were

reported as 21% for those on dabigatran, 25.3% for those on apixaban and 14.3% for rivaroxaban, this was only for the first year of follow-up and may increase if further follow-up is reported. Further, depending on the definition of adverse events, this ranged from 35% to 86.6% across the three major NOAC, possibly reflecting the variability of definition, as well as the differing reporting methods in phase 3 trials versus real-world clinical experience.[441-443]

7.4.3 Duration to Cessation of NOAC

In our study, patients on apixaban had the longest duration-to-cessation in comparison to other NOAC users, in addition to having a trend towards lower serious adverse events. This is in-line with other studies and adds to the growing body of evidence that apixaban may be better tolerated than other NOACs.[450-452]

7.4.4 Factors and predictors of reactions and cessation

Interestingly, we found that whilst there were fewer women in the study, they presented with 2.5-times more adverse reactions, indicating a potentially important gender implication. Additionally, age was found to be a significant predictor of cessation of index-NOAC, either to a different form of OAC or stopping altogether. The predictive value of these factors for NOAC cessation was not reported in the three major studies and to our knowledge have not been shown previously. Further studies are required to better understand the role that gender may play with regards to NOAC complications and whether a more personalized approach to NOAC choice and initiation may improve compliance.

7.4.5 Approach to Management of Anticoagulation

The importance of patient education and adopting an integrated approach to patient care is highlighted in our study, as it may well have had a significant role in the relatively low serious events rates, by facilitating early detection and management of adverse reactions. This echoes the recent 2018 EHRA practical guide[453] for NOAC use, which recommends that at each clinic visit, adherence, thromboembolism, bleeding, other side effects, and co-medications are checked along with close monitoring of haemoglobin, renal and liver function. The monitoring is recommended to intensify from annually to six-monthly for patients aged ≥75 or those with renal complaints.[404] Additionally, patient education and involvement in the decision-making process further empowers them to make informed choices regarding their care, as reflected in patient-choice accounting for over half (53.1%) of all treatment alterations.

7.4.6 Safety of NOACs and Future Role

The use of NOACs has increased in popularity due to the practical advantages compared to warfarin.[454] One of the inherent risks with anticoagulation is that of bleeding which is potentially a major safety concern. NOACs appear to be more effective than warfarin without compromising safety. In a systematic review and meta-analysis of 12 studies with 54875 patients, NOACs significantly reduced the relative risk of stroke and systemic embolism by 23%, and subsequently all-cause and cardiovascular mortality (RR of 0.89 for both), without increasing the risk of major bleeding.[325] The popularity of NOACs is expected to increase given the development of reversal agents which can alleviate some of the concerns regarding major bleeding.[455,456] Randomized-controlled trials directly comparing the efficacy and

safety of the main NOACs are lacking and may have a significant role in NOAC selection in the future.

7.5 LIMITATIONS

While this is a single centre observational study, it reflects real-world experience with NOAC use and achieved statistically-significant findings by virtue of the relatively long duration of follow-up. Due to geographical and medical prescription differences this may influence the outcomes given that cost of medications and prescription is different in other countries. Therefore, this data is representative of Australian prescription only. Data collection takes place prospectively whenever possible in our practice, potentially mitigating some of the inherent limitations of observational studies.

7.6 CONCLUSIONS

Use of NOAC is safe and well-tolerated in this cohort of real-world AF patients. An integrated approach to patient care enables safe use of NOACs through patient education and monitoring and empowers patients to make informed decisions regarding their care. Apixaban may be better tolerated in comparison to other NOACs, but prospective studies directly comparing NOACs are warranted.

7.7 TABLE AND FIGURE LEGEND

TABLE 1: PATIENT CHARACTERISTICS

TABLE 2: CAUSES FOR CHANGE OR STOPPING ANTICOAGULATION

Table highlighting causes for patients to cease their index NOAC and serious adverse events stratified by NOAC type.

FIGURE 1: PATIENT SELECTION

Consort diagram of the patient selection. Atrial fibrillation (AF), oral anticoagulation (OAC).

FIGURE 2: OVERALL CESSATION/CHANGE OF NOAC

Graph demonstrating the baseline prescription and use of oral anticoagulation (OAC) at final follow-up. Baseline use of non-vitamin K antagonist (NOAC): dabigatran 154 (35.1%), apixaban 195 (44.4%) and rivaroxaban 90 (20.5%). At follow-up, 74 (16.9%) patients were on dabigatran, 218 (49.7%) on apixaban, 69 (15.7%) on rivaroxaban, 44 (10%) on warfarin and 34 (7.7%) discontinued all oral anticoagulation.

FIGURE 3: TIME TO EVENT CESSATION

Kaplan-Meier curve demonstrating duration to cessation event. A log rank test was performed to determine if the type of non-vitamin K antagonist (NOAC) at baseline would affect the duration of remaining on the same index NOAC. Patients were stratified to dabigatran, apixaban and rivaroxaban. The mean duration-to-change in years for the entire population was 4.9 (95% CI=4.6-5.1). Apixaban had the longest duration-to-cessation compared to dabigatran (4.6, 95% CI: 4.2–4.9, p=0.002) and rivaroxaban (4.5, 95%CI: 3.9-5.1, p=0.025) years respectively.

TABLE 1: PATIENT CHARACTERISTICS

PATIENT CHARACTERISTICS				
	ALL PATIENTS N: 439	**PATIENTS NO CHANGE N: 292**	**CHANGED OR STOPPED NOAC N: 147**	**P value for CHANGE v NO CHANGE**
Age, years	71.9 ± 8.7	71.2 ± 7.9	73.2 ± 9.9	0.02
Body mass index, kg/m^2	28.4 ± 8	28.7 ± 8.3	28 ± 7.4	0.12
Female gender, n (%)	162 (36.9)	102 (34.9)	60 (40.8)	0.23
CHA_2DS_2-VASc Score				
1	92 (21)	63 (21.6)	29 (19.7)	
2	112 (25.5)	74 (25.3)	38 (25.9)	
3	88 (20)	57 (19.5)	31 (21.1)	
4	75 (17.1)	45 (15.4)	30 (20.4)	NS
5	50 (11.4)	39 (13.4)	11 (7.5)	
6	14 (3.2)	10 (3.4)	4 (2.7)	
7	6 (1.4)	4 (1.4)	2 (1.4)	
8	2 (0.5)	0 (0)	2 (1.4)	
Atrial fibrillation type				
Paroxysmal, n (%)	230 (52.4)	164 (56.2)	66 (44.9)	
Persistent, n (%)	134 (30.5)	75 (25.7)	59 (40.1)	0.008
Permanent, n (%)	75 (17.1)	53 (18.2)	22 (15)	
Hypertension, n (%)	341 (77.7)	230 (78.8)	111 (75.5)	0.44
Diabetes, n (%)	69 (15.7)	46 (15.8)	23 (15.6)	0.84
Sleep apnoea, n (%)	95 (21.6)	66 (22.6)	29 (19.7)	0.49
Hyperlipidaemia (%)	226 (51.5)	161 (55.1)	65 (44.2)	0.031
SMOKING				
Non-smokers	335 (76.5)	220 (75.6)	115 (78.2)	
Smokers	14 (3.2)	7 (2.4)	7 (4.8)	0.223
Ex-smokers	89 (20.3)	64 (22)	25 (17)	

NOAC: Non-vitamin K antagonist

TABLE 2: CAUSES FOR CHANGE OR STOPPING ANTICOAGULATION

	DABIGATRAN	APIXABAN	RIVAROXABAN	TOTAL
Patient decision (%)	27 (43.5)	12 (52.2)	8 (28.6)	47
Renal impairment (%)	13 (21)	1 (4.3)	2 (7.1)	16
AF ablation (%)	5 (8.1)	0 (0)	5 (17.9)	10
Other treating physician (%)	2 (3.2)	4 (17.4)	1 (3.6)	7
Surgery (%)	1 (1.6)	0 (0)	4 (14.3)	5
SERIOUS ADVERSE EVENTS				
Intracranial haemorrhage (%)	1 (1.6)	0 (0)	2 (7.1)	3
Stroke/transient ischaemic attack (%)	2 (3.2)	1 (4.3)	0 (0)	3
Minor bleed (%)	4 (6.5)	0 (0)	2 (7.1)	6
Gastrointestinal upset (%)	4 (6.5)	2 (8.6)	1 (3.6)	7
Rash (%)	0 (0)	2 (8.6)	1 (3.6)	3
Unwell/myalgia (%)	2 (3.2)	1 (4.3)	2 (7.1)	5
Anaphylaxis (%)	1 (1.6)	0 (0)	0 (0)	1
TOTAL	62 (54.9)	23 (20.4)	28 (24.8)	113

FIGURE 1: PATIENT SELECTION

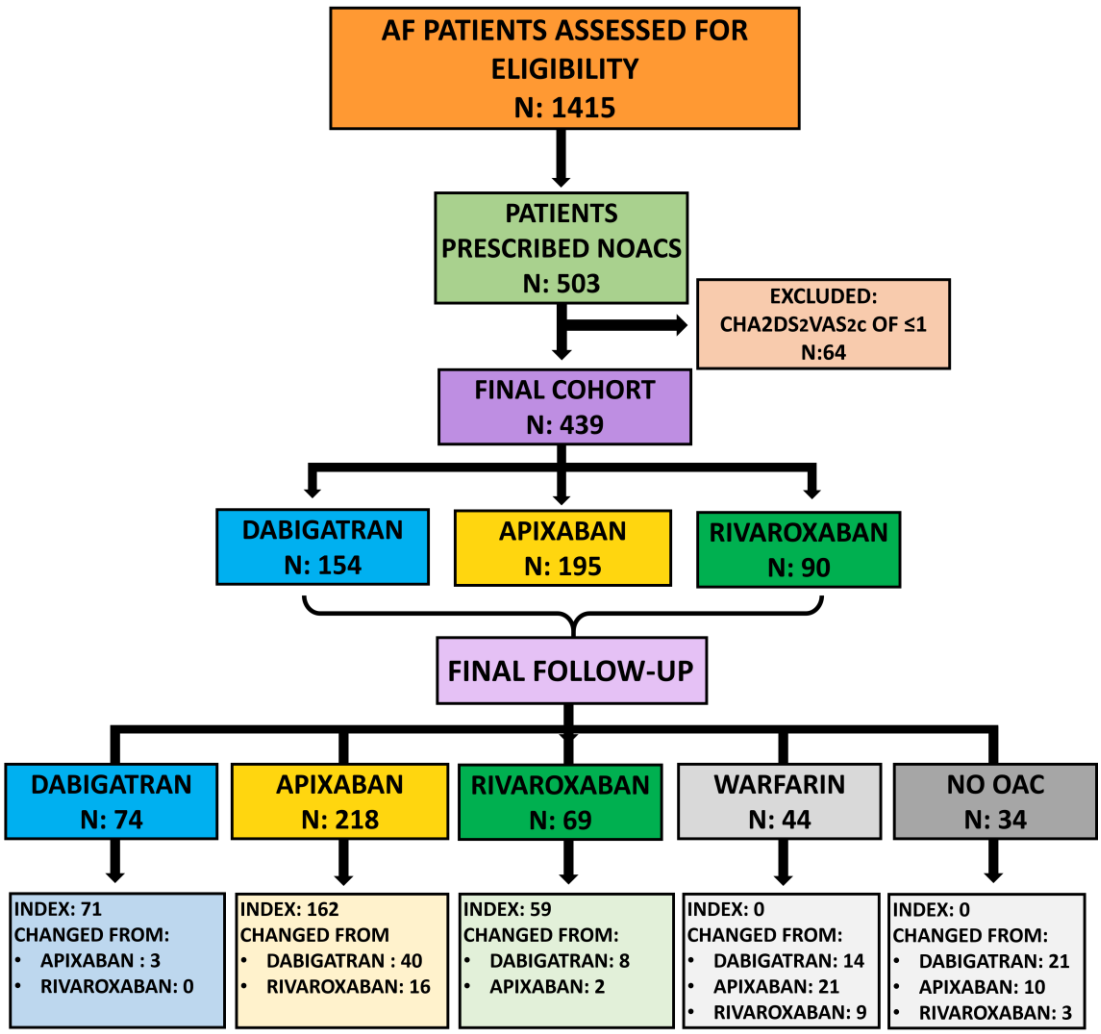


FIGURE 2: OVERALL CESSATION/CHANGE OF NOAC

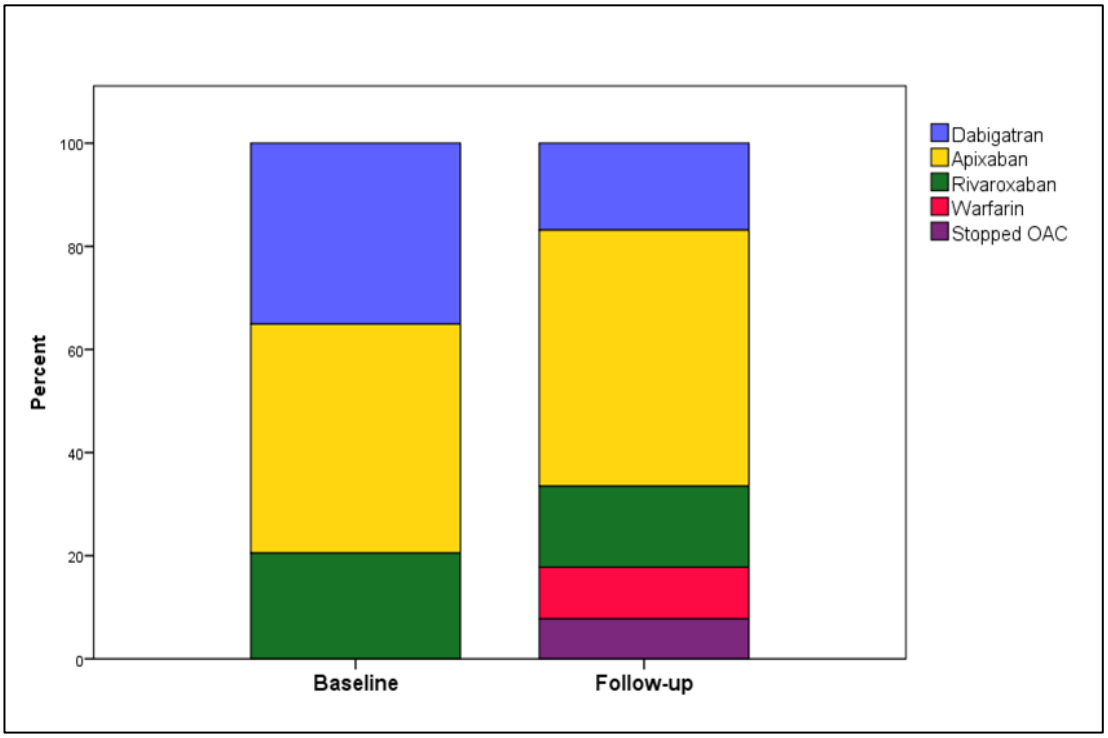
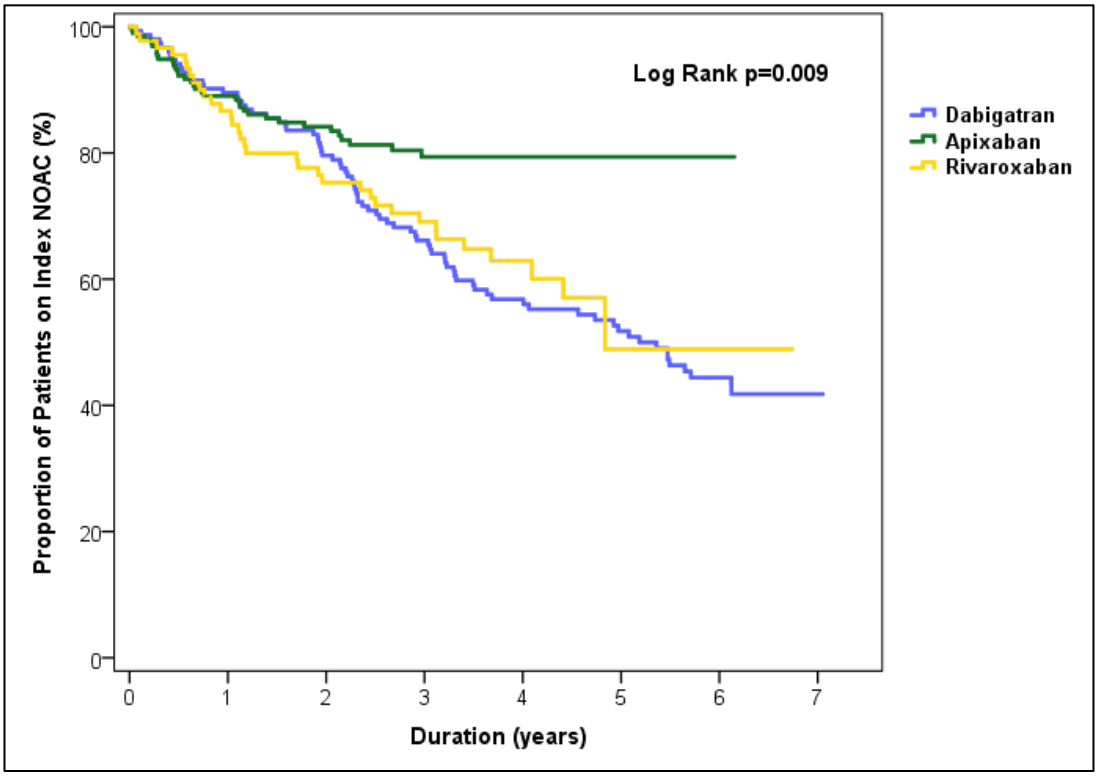


FIGURE 3: TIME TO EVENT CESSATION



Chapter 8: Conclusions

This thesis addresses the identification and management of atrial fibrillation which is the most common heart rhythm disorder. It demonstrates the role of screening for AF and the ability to assess risk of AF in large population screening. Additionally, the importance of treating risk factors and the potential for reversal of the AF substrate for the first time. The role that socioeconomic status plays in risk factor management for AF. Also addressed is the role of gender differences in ablation outcomes. Further, the risk of stroke following ablation providing insight into the implications of a thrombogenic atria despite elimination of the arrhythmia and the use of NOACs regarding adherence, cessation and reactions. These findings help to further the understanding some of the mechanisms of atrial fibrillation and strategies to manage this condition.

Atrial fibrillation is rising in prevalence. Despite this it is a condition that many people in the general public are still unaware of this condition or the risk factors associated with it. The role of screening is one that is becoming clearer with time. In order to undertake screening to assess prevalence this should be done in a targeted cohort. However, screening as part of a National awareness campaign while resulting in a low detection rate did enable the ability to provide the public with a risk of atrial fibrillation based on their individual risk factors. In conjunction with this it enabled education as to the condition and the importance of atrial fibrillation specific risk factors. This method of screening provided individualised 5-year risk prediction on the development of AF based on the participants specific risk factors. This provides a crucial component of education for the individual but also a nationwide risk of AF score. This was lower in Caucasians compared to non-Caucasians.

It has been well established that atrial fibrillation is a condition that progresses with time. In fact, it is demonstrated that progression is determined by the number of risk factors that co-exist in a given individual. In Chapter 2 the findings of a dedicated risk factor and weight loss clinic and the impact on AF progression for the first time. It demonstrates that the better an individual's risk factors are controlled (measured by the degree of weight reduction achieved), the more likely there is to be a reversal of the atrial fibrillation process by a change in the disease profile from persistent to paroxysmal atrial fibrillation. On the other hand, if risk factor control was not achieved there was more risk of progressing the disease to more persistent forms. This reversal in the atrial substrate leads the way in highlighting the importance of risk factors management for individuals with AF. To date there has been no study to demonstrate the potential for the reversal of the atrial substrate by the simple measures of addressing the risk factors of individuals.

The role of socioeconomic status on this risk factor management in patients with atrial fibrillation is not well understood. While those who live in socially disadvantaged areas are seen to have less access to education, employment, and medical treatments. Indeed, lower SES has been attributed to greater risk factors and therefore potentially a greater burden of AF. In Chapter 3 we assessed the socioeconomic impact on individuals who were attending the risk factor clinic and whether this would affect the ability to lose weight or result in more freedom from atrial fibrillation. Interestingly, we did find that individuals who were married were more likely to lose significantly more weight than those who were unmarried. Perhaps this therefore would highlight the importance of family support, motivation and encouragement when it comes to weight-loss and improvement of risk factors. This study showed that being in a middle socioeconomic status was associated with greater

freedom from atrial fibrillation. This suggests that the ability to improve weight and risk factors is not in fact limited to the area you live in, the type of lifestyle you live or the level of education one obtains. This study has provided initial insights into these important potential determinants for risk factor management and needs to be further explored prospectively.

For patients who are highly symptomatic and in which antiarrhythmic therapy has not been successful, ablation has become primary means of therapy. Many studies have shown that women have much different treatment to men, with significantly worse outcomes from ablation. Chapter 4 presents a large cohort of consecutive patients undergoing ablation, over a long-term follow-up, with the aim to assess the difference in outcomes between sexes. This study demonstrated some interesting results. Females presented with more paroxysmal AF, less sleep apnoea, a smaller left atria and coronary artery disease compared to males, there was no other significant difference in baseline comorbidities. There were no significant differences in single procedure outcomes, however women were more likely to have worse outcomes following multiple procedures on and off antiarrhythmic therapies. Similarly, following adjustment for risk factors, women were more likely to have a recurrence following single procedure off AAD and multiple procedure on AAD.

Thromboembolic events remain the most devastating complications of atrial fibrillation. The mechanisms which promote thrombus formation is believed to be due to decreased blood flow in the left atrial appendage, resulting in a thrombus forming, this primarily occurs in the left atrium. While ablation proves to be effective in the elimination of atrial fibrillation the subsequent ability to eliminate the risk of stroke is not well understood. The study in Chapter 6 presents a large cohort of patients undergoing ablation for symptomatic atrial fibrillation A total of fifteen patients had a

stroke following ablation. In this cohort there were no difference in risk factors between the patients who experienced a stroke and those who did not. Importantly, there were nine patients who had a thromboembolic event in the absence of arrhythmia. Interestingly these events occurred quite late following the apparent successful ablation. Seven of these occurred more than 12 months following successful ablation, with two of these occurring after 4 years. This would suggest that perhaps the arrythmia itself is not the cause of the stroke. These may be cryptogenic in nature and this is not well understood.

One of the key management strategies for patients with atrial fibrillation is that of anticoagulation to assist with stroke prevention. In recent years the introduction of non-vitamin K antagonist has led to an ease in the management of anticoagulation. These require less maintenance, with no major food restrictions, avoidance of regular blood testing, and ease in dosing. Large pharmaceutical driven studies have shown that despite the ease of these drugs there is a large cessation rate and similarly many reactions. In Chapter 7, real-world data is presented which addresses the number of cessation rates in three of the popular non-vitamin K antagonists. This study found that majority of the causes for cessation is in fact patient choice. The rate of cessation is low in the real work as is that of the adverse events. Age was an independent predictor of cessation and female gender was an independent predictor of adverse reaction. This perhaps demonstrates that it is the selection of the patient is of importance and more involvement of the patient in the joint decision-making process.

Chapter 9: Future Directions

This thesis has provided some important insights into the risk factors, management strategies, screening for detection and risk of AF, and substrate progression. There are many questions that still require further research some of which are discussed below.

Detection rate of AF in the general population is low. More targeted screening of certain populations may be useful to better assess AF prevalence. AF screening is cumbersome with not much return, better strategies need to be implemented to improve the undertaking of such events. With advancing technology large scale national and potentially international studies with the use of device worn daily such as smart watches may provide some interesting insight into AF prevalence, detection rates, heart rate variability and management strategies. The use of screening to provide 5-year risk prediction scores may assist with targeting individuals at risk of development of AF and provide early preventative education.

This thesis has provided important findings regarding the potential of substrate reversal. Previous studies have shown progression of the AF substrate over time. This has been demonstrated to be due to underlying risk factors. While in chapter 3, the study was able to show potential reversal of the AF substrate, additional studies are required to assess this further. Undertaking mapping studies may help us verify the reversal of the substrate. More studies are required to better understand risk factor management strategies in the treatment of patients with atrial fibrillation. The role of gender and AF remains variable. Greater representation of women in large ablation studies may assist with a better understanding as to the impact of gender and AF. It would be important to perhaps evaluate the potential mechanisms and structural differences to enable better management of females with AF. Studies to evaluate the

difference in triggers and location of drivers in women compared to men may as well as evaluating rate and rhythm control usage, may also assist with knowledge as to ablation outcomes. Furthermore, trials to evaluate the underlying causes of stroke and thromboembolism, genetic associations, mortality outcomes and hormonal influences could provide the insight into ablation outcomes and better targeted management between sexes. While stroke post AF ablation is a reality, it is not well understood as to the mechanisms of cryptogenic stroke. Despite being a common and relatively successful management strategy for patients with AF, it is apparent that 'successful AF ablation does not abolish stroke risk. Larger and randomised trials may assist with the many remaining questions as to the timepoint of anticoagulation cessation safety following apparent successful AF ablation. With the use of cardiac implantable monitors, it is possible some of these questions may be answered. Appropriate anticoagulation needs further evaluation. NOACs use is rising in popularity. Ongoing evaluation is needed to fully understand the complication, cessation and adverse reaction rate. To date this has only been shown in large pharmaceutical driven studies. Our study demonstrated that gender and age were predictors for cessation of the NOACs. Independent studies with larger cohorts will be required to understand the potential predictors for cessation which may assist with more targeted management of patients who are prescribed anticoagulation. Additional studies assessing the differences between NOACs once again independent of pharmaceutical companies may assist with answers on the safety of each NOAC.

There is a role for further evaluation into the substrate, many mechanisms, and risk factors that underly and drive AF. Delivery of AF management and use of dedicated risk factor clinics in other centres both nationally and internationally is pinitol moving forward. Incorporation of risk factor management is an essential

element to assist with reduction of AF and improve outcomes for patients diagnosed with AF to stem the rising epidemic.

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