Aggressive Risk Factor Reduction Study for Atrial Fibrillation  

(ARREST-AF)  

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To my parents Kamalapati and Jayshree,

my parents-in-laws Mahesh and Manju

my soul mate Manina

and

my daughter Rhea
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Abstract

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with evidence from epidemiological data confirming the emergence of AF as a global epidemic. Although population ageing is regarded as an important contributor, several risk factors such as hypertension, diabetes mellitus, obesity, and obstructive sleep apnoea have been epidemiologically linked as promoters of AF.

Cardiac risk factors are associated with structural and electrical remodeling of the atria that form the substrate leading to the development and progression of AF. Evidence from animal studies suggests that management of these risk factors such as obesity can reverse some of these changes. This was associated with reduced vulnerability of AF. However, impact of risk factor management on atrial fibrillation in human has not been evaluated. Furthermore, mechanism and degree of reversibility of substrate in humans, where multiple factors can play a role, with weight and other risk factor management has not been described. This thesis evaluates the reversal of atrial substrate with weight and other risk factor management and its impact on AF freedom and AF ablation outcome.

Chapter 2 assesses the long-term impact of weight-loss and weight-fluctuation on rhythm control in obese individuals with AF. In over-weight and obese individuals with symptomatic AF, progressive weight-loss had a dose-dependent effect on long-term freedom from AF. Additionally, weight-fluctuation of >5% had an adverse effect on overall freedom from AF with a two-fold greater likelihood of recurrent arrhythmia.
Chapter 3 evaluated the impact of cardiorespiratory fitness on long-term freedom from atrial fibrillation (AF). It also looked at the impact of cardiorespiratory fitness gain on AF outcome. This study demonstrates that in overweight and obese individuals with symptomatic AF, preserved baseline cardiorespiratory fitness predicts long-term freedom from AF. Cardiorespiratory fitness gain with a structured exercise program had an additive effect to weight-loss in improving the long-term outcome of AF.

Chapter 4 evaluated the impact of aggressive risk factor management on the outcomes of the catheter ablation. In patients with symptomatic AF undergoing ablation, a structured physician-directed risk factor and weight management program resulted in significant improvement in the long-term outcomes.

Chapter 5 evaluated the impact of risk factor management on the electrophysiological and electroanatomical properties of the atria, cardiac structure and endothelial and platelets function. Aggressive risk factor management was associated with marked structural improvement with a reduction in atrial size, regression of ventricular mass and normalization of bipolar voltages. There was a resultant significant improvement in the electrophysiological properties with marked improvement in conduction properties and tissue refractoriness. Mechanistically, there was a reduction in pericardial fat volumes and serum fibrosis markers. Furthermore, there was improvement in endothelial function, platelet function and inflammatory markers. These changes were associated with significant reduction in the AF vulnerability and clinical burden of AF.
Chapter 6 evaluated the cost effectiveness of a goal dedicated physician led clinic on the outcomes of the catheter ablation. This program is not only clinically effective but also cost-effective in terms of improvement in QALYs and reduction in AF burden.
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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Rajeev Kumar Pathak

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Publications and Communications to Learned Societies

Chapter One


Chapter Two

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   a. **Manuscript**: Letter to Editor: LEGACY: a message not to be lost in translation: Manuscript accepted in *Journal of American college of Cardiology*
   
   b. **Manuscript**: Letter to Editor: LEGACY: More bounce to the ounce, Manuscript accepted in *Journal of American college of Cardiology*
   
   c. **Manuscript**: Implications of LEGACY in US Cardiovascular Practice: An NCDR Rapid Registry Response Project, Manuscript submitted to *Journal of American college of Cardiology*

**Chapter 3**


2. **Late Breaking Clinical Trial Presentation**: Presented at the Annual Scientific Sessions of the *European Heart Rhythm Association*, June 2015, Milan, Italy
Chapter 4


Chapter 5

1. **Presentation**: Presenting in Ralph Reader presentation (Young investigator Award) at the Annual Scientific Sessions of Cardiology Society of Australia and New Zealand, Melbourne, Australia, 2015

Chapter 6


2. **Presentation:** Presenting at the Annual Scientific Session of Cardiology Society of Australia and New Zealand in August, Melbourne, Australia, 2015
Prizes and Awards during Candidature

1. Ralph Reader (Young Investigator award) presentation, Finalist, Cardiology Society of Australia and New Zealand, 15\textsuperscript{th} August 2015.

2. First prize, Nimmo Prize, Royal Adelaide Hospital Research, Adelaide Australia, 2015.


5. Cardiac Society of Australia and New Zealand Travelling Fellowship: 2015


7. Australian Post Graduate Award, University of Adelaide, 2012-2015

8. Leo Maher Electrophysiology Scholarship, University of Adelaide, 2012-2015

9. Lions Medical Research Scholarship, University of Adelaide, 2012-2015
Chapter 1: Literature Review

1.1 Epidemiology of Atrial Fibrillation

Atrial fibrillation (AF) is the most prevalent sustained arrhythmia, with evidence from epidemiological data confirming the emergence of AF as a global epidemic.\(^1\), \(^2\) The lifetime risk of developing AF at age 40 or older is one in four.\(^3\) Current estimated prevalence of AF is approximately 2% in North America and Europe.\(^4\) However, this has been shown to increase with age from 0.1% in those less than 55 years old to 9% in octogenarians, and men are affected more frequently than women.\(^5\), \(^6\) Currently it affects approximately 2.7 million people in the USA alone and its prevalence is expected to rise to between 5.6 and 12 million by 2050.\(^7\)

AF is a major public health problem through its association with an increased risk of stroke, heart failure, reduced quality of life and cognitive dysfunction.\(^8\)-\(^11\) In addition, recent data demonstrates that there has been an exponential rise in hospitalizations due to AF that already exceeds those for congestive heart failure (CHF).\(^12\), \(^13\) Cardioembolic strokes associated with AF are more severe, with greater disability and mortality.\(^14\) AF increases mortality risk by 1.5 - 2.9 fold even after adjusting for other associated cardiovascular factors.\(^8\), \(^15\), \(^16\) Therefore, there is an urgent need for improved primary and secondary AF prevention strategies to reduce the impact of this potentially enormous health burden.
Although population aging is regarded as an important contributor, traditional cardiac risk factors such as hypertension (OR 1.5 for men and 1.4 for women), diabetes (OR 1.4 for men and 1.6 for women), congestive heart failure (OR 4.5 for men and 5.9 for women), myocardial infarction (OR 1.4 for men and 1.2 for women) and valvular heart disease (OR 1.8 for men and 3.4 for women) have been linked as promoters of AF.\textsuperscript{17} Recently, a number of previously unrecognized or underappreciated novel risk factors for AF have been identified including obesity, pericardial fat, obstructive sleep apnea, aortic stiffness, pre-hypertension, inflammation and excessive endurance exercise.\textsuperscript{17-21}\n
Other modifiable risk factors and conditions include cigarette smoking, excessive alcohol consumption (>3 drinks/day)\textsuperscript{22, 23} and thyroid disorder. Studies have also identified atrial septal defects, pericarditis,\textsuperscript{24} myocarditis,\textsuperscript{24} and sinus node disease\textsuperscript{25} associated with AF.

These cardiac risk factors are associated with structural and electrical remodeling of the atria that forms the substrate leading to the development and progression of AF.\textsuperscript{26-28} Indeed, even in the absence of known risk factors, atrial changes consistent with the AF substrate have been observed in ‘lone AF’ patients.\textsuperscript{29, 30} These findings argue in favor of an underlying atrial substrate responsible for AF that is promoted by unrecognized risk factors. With the identification of novel risk factors like obstructive sleep apnoea\textsuperscript{18, 31} and obesity\textsuperscript{18, 32-34} in the last decade, this group of “lone AF” is diminishing.

Current rhythm control pharmacotherapies for AF are limited by poor efficacy and potentially serious adverse effects profile.\textsuperscript{35} Catheter ablation of AF has evolved as an effective therapy for drug-refractory or intolerant AF. Despite recent advances in
ablative techniques, post-ablation freedom from AF has not improved proportionately, especially in those with the more persistent form of the arrhythmia. These limitations of the currently available treatment modalities have stimulated further interest into the mechanisms of genesis and perpetuation of AF, with the hope to find a better and more definitive treatment for the future. As such, specific mechanistic-based therapeutic options are urgently needed to modify the complex interactions maintaining AF in a given individual.

1.2 Initiation of Atrial Fibrillation

Significant advances have been made in our understanding of the fundamental pathophysiological mechanisms underlying AF. AF arises as a result of a complex interaction between triggers, perpetuators, and substrate. Although the complexity of how these interact in the individual patient to initiate and maintain AF remains poorly understood.

1.2.1 Multiple Wavelet Hypothesis

Reports as early as 1907 implicated multiple rapidly firing foci as a mechanism. This hypothesis was challenged in 1913 by Mines with the concept of reentry in cold blooded animal hearts. Subsequently, the notion that a localized source of reentrant activity could maintain AF was first postulated by Lewis in the early part of the 20th century. The “multiple wavelets theory” for AF supported with a computer simulation model was then explored in the 1960s and was proposed as the predominant mechanism for perpetuation of AF. Large atrial mass, dispersion of refractoriness and short refractory period, slow conduction velocity, and anatomical obstacles in different portions of the atria were critical to for AF to sustain itself.
This hypothesis was subsequently confirmed by Allessie et al. during mapping of acetylcholine induced AF. In this study of canine model, the investigators estimated that 4 to 6 wavelets were sufficient to maintain AF in the canine atrium.\textsuperscript{45-48} This concept was further strengthened by anti-arrhythmic studies whereby increased wavelength and decreased number of wavelets preceded the termination of AF.\textsuperscript{49-51} This concept remained the most acceptable explanation for atrial fibrillation until it was demonstrated to be inadequate to explain the complex dynamics of fibrillation.\textsuperscript{52}

\textbf{1.2.2 Role of Triggers}

The seminal observation by Haissaguerre et al that the pulmonary veins (PVs) can initiate and perpetuate AF revolutionized the mechanistic and therapeutic paradigms of AF.\textsuperscript{53} Although, it is still unclear as to why some PVs become arrhythmogenic in some individuals. Genetic predisposition, physical factors such as stretch, metabolic factors such as inflammatory and neurohormonal factors and autonomic factors have all been implicated. Most of these external factors could be as a result of the co-existing cardiac risk factors in an individual.

During embryonic development, the PVs are incorporated into the left atrium (LA). The PV-LA junction with discontinuous myocardial fibers separated by fibrotic tissues is highly anisotropic and therefore it can initiate and sustain micro re-entry. Although, under normal physiological conditions PVs and the PV-LA junction still manifest synchronous electrical activity, acute stretch or autonomic imbalance due to factors such as obesity, sleep apnoea and hypertension or rapid atria rate can lead to altered electrical homeostasis with delayed after depolarizations (DADs), abnormal automacity and triggered activity.\textsuperscript{54-56} Additionally, the PVs of patients with paroxysmal AF
demonstrate differential conduction properties from markedly reduced refractoriness, progressive conduction delay and conduction block at PV-LA junction, providing a substrate for reentry.\textsuperscript{54,57}

Subsequently, several other non-pulmonary vein foci such as superior vena cava, coronary sinus, ligament of Marshall, crista terminalis, and tricuspid/mitral valve annuli, have also been found to be source of triggers in initiating AF.\textsuperscript{58-60} Atrial tachycardia or supraventricular tachycardia’s due to accessory pathways can act as a trigger and degenerate into AF in presence of substrate. Discrete ablation of these extra pathways have been shown to eliminated AF in subset of patients.\textsuperscript{61}

During embryonic development, four pulmonary veins have variable amalgamation with LA. Seemingly uniform, the walls of posterior LA and LA-PV junction are composed of multiple overlapping layers of non-uniformly aligned myocardial fibres, with marked regional variations in orientation and thickness.\textsuperscript{62} Recent studies have also found a variable fat deposition in the posterior LA and asymmetric stretch.\textsuperscript{63} These factors can lead to conduction delay promoting localized reentry.\textsuperscript{64,65} Studies have found a marked anisotropic conduction in posterior LA in patients with mitral regurgitation or heart failure.\textsuperscript{65,66} These distinctive electrophysiological properties of posterior LA may therefore facilitate arrhythmogenesis by harboring source of stable reentrant activity that serves as a periodic background focus, with break-up of emanating waves in atrial tissue spreading in various directions, acting as a trigger or perpetuator.
Overall, it appears that in an individual patient with AF, many of these mechanisms may be operational and we still lack a unifying hypothesis capable of convincingly explaining the mechanisms responsible for initiation of AF.

1.3 Maintenance of AF: Role of substrate

After initiation, AF can be brief and requires perpetuators to maintain the tachycardia. While initiators can be drivers of the tachycardia, AF can also persist in absence of the focal drivers. However, this requires electrical and structural remodeling of the atria for AF to beget more AF.

There are dynamic adaptive electrical changes in the atria in response to AF, enhancing the ability of the AF not only to sustain itself, but also to recur (i.e. “AF begets AF”). In brief, the intra-cellular calcium (Ca\(^{2+}\)) increases due to persistent tachycardia, which eventually leads to down-regulation of L-type Ca\(^{2+}\) channels and a resultant decrease in action potential duration. Electrical remodelling is associated with shortening of atrial refractoriness, reduction in conduction velocity and shortening of re-entry wavelength.\(^{37,39,67-70}\) Moreover, altered calcium homeostasis due to tachycardia along with deranged calcium-handling leads to abnormal automacity.\(^{71-73}\) These electrical changes play pivotal role as a perpetuator during the initiation of AF. These electrical changes correlated strongly with the duration of AF. The electrical remodeling seen after the first few minutes of acutely induced AF could be completely reversed following cardioversion in a goat model. However, the recovery time increased with longer duration of remodeling.\(^{74}\) Similarly atrial electrical remodelling in VVI paced patients due to atrioventricular dysynchrony was restored when atrioventricular synchrony was restored with dual chamber pacing.\(^{75}\) Similar findings were seen in
humans where most of the electrical changes reversed after cardioversion. Based on these finding, it was postulated that early cardioversion would prevent the remodeling due to AF and allow “sinus rhythm to beget sinus rhythm”. However, restoration of sinus rhythm with early repeated cardioversion while reversed electrical remodeling but did not impact the maintenance of sinus rhythm. In summary, the ionic changes underlying electrical remodelling can only in part explain how AF promotes its own maintenance, and failed to account for the substrate that further maintains AF.

Li et al provided the seminal observations of the importance of “structural remodelling” in creating a substrate for arrhythmia in a rapid ventricular pacing model of heart failure to highlight the importance of “additional factors”. Structural remodeling refers to adaptive or maladaptive changes in cardiac architecture in response to “external stressors”. While electrical remodeling can lead to structural remodeling, this can also occur independently. The external stressors or “modulating factors” can directly lead to structural remodeling and help to initiate and maintain AF. Modulating factors can be non-modifiable (age, gender, genetics) or modifiable such as hypertension, obstructive sleep apnea (OSA), obesity, valvular heart disease, congestive heart failure (CHF), ischemia, endocrine abnormalities, inflammation and infective states. The structural changes occur at both macro- and microscopic levels and are time and etiology dependent.

The hallmark of macroscopic change is “atrial dilation”. Most of the comorbidities seen in patients with AF can directly or indirectly cause pressure or volume overload of the atria. The augmented atrial load leads to atrial dilatation and stretch. Indeed,
Acute atrial stretch has been shown to increase the dispersion of atrial refractoriness, slow atrial conduction, increase AF vulnerability and pulmonary vein ectopy.\textsuperscript{83-85} Chronic atrial dilatation or stretch has also been demonstrated to result in direction-dependent conduction block thereby increasing the anisotropic properties of the atrial myocardium leading to increased AF inducibility.\textsuperscript{86, 87} This may be due to activation of ion channels, which are sensitive to increased volume and wall stretch, including Cl\textsuperscript{-}, K\textsuperscript{+}, Na\textsuperscript{+}-Ca\textsuperscript{2+} Exchanger and other non-specific stretch-sensitive channels.\textsuperscript{88-90}

“Atrial Fibrosis” is the hallmark of microscopic structural remodeling.\textsuperscript{91} Other changes include cellular hypertrophy, myolysis, dedifferentiation, apoptosis, mitochondria and sarcoplasmic reticulum disruption.\textsuperscript{92-95} These structural changes have not only been described with different risk factors but also with lone AF.\textsuperscript{96} AF itself can promote atrial fibrosis especially in the epicardial layer.\textsuperscript{97} Atrial Fibrosis is a common feature in cardiac remodeling due to various cardiac risk factors such as hypertension, heart failure, obstructive sleep apnoea and obesity, contributing to the development and progression of AF.\textsuperscript{26-29, 97-107}

1.4 Common clinical substrates

Several conditions have been recognized to be associated with a greater frequency for the development of AF. Detailed below are the various conditions known to be associated with electrical and structural remodeling of atria leading to development and progression of AF.
1.4.1 Age

Early epidemiological data from the Framingham study had found sharp increases in the incidence of AF with aging. The estimated odds ratio for developing AF was 2.1-2.2 with each decade of advancing age.\textsuperscript{108, 109} Many investigators have since studied the substrate for AF with senescent in both experimental and clinical settings. Spach et al. elegantly demonstrated the progressive electrical uncoupling of the side-to-side connections between groups of atrial fibers due to collagen deposition in the aging atria. This resulted in reduced transverse conduction velocities and an environment conducive to the reentry mechanism of AF.\textsuperscript{110} Both increased atrial fibrosis and myocyte hypertrophy had been demonstrated in the aging atria to result in electrical changes of atrial conduction slowing, increased conduction heterogeneity and electrogram fractionation.\textsuperscript{111, 112} Similar changes have also been documented in more recent clinical studies with electroanatomic mapping showing reduced voltage, conduction slowing and increased electrogram fractionation with senescence.\textsuperscript{105, 113} Together, these structural changes are responsible for the increased propensity for AF with increasing age.

1.4.2 Congestive heart failure

CHF is an established risk factor for AF with odds ratio of 4.5 to 5.9 as seen in the Framingham study.\textsuperscript{109} This relationship can be explained by the presence of common risk factors in both conditions.\textsuperscript{114} In addition, the prevalence for AF in CHF is known to increase with increased severity of pump failure.\textsuperscript{115} In the canine rapid ventricular pacing model, Li et al found that 5 weeks of induced heart failure resulted in increased atrial interstitial fibrosis and conduction heterogeneity leading to more sustained AF.\textsuperscript{78} Similar atrial structural changes due to heart failure have since been confirmed in
chronic (4 months) rapid ventricular pacing model in dogs and doxorubicin-induced non-ischemic cardiomyopathy model in sheep.\textsuperscript{116, 117} In patients with both ischemic and non-ischemic cardiomyopathy, Sanders et al demonstrated significant electro-anatomic remodeling with areas of low voltage (scar), conduction slowing, site-specific conduction blocks and increased atrial refractoriness.\textsuperscript{102} Also, significant structural remodeling with atrial interstitial fibrosis has also been demonstrated in autopsied hearts of patients with dilated and hypertrophic cardiomyopathy.\textsuperscript{78}

\textbf{1.4.3 Mitral valve disease}

Valvular heart disease is one of the common causes of AF. In addition, it is well recognized that the risk of stroke due to AF in this population is increased to a greater extent.\textsuperscript{118} The concept of atrial fibrosis, myocyte hypertrophy and degeneration in AF was initially studied by Thiedemann et al in humans with mitral valve disease whereby cellular contractile function was found to be impaired with these structural changes.\textsuperscript{119} In an animal model, Verheule et al demonstrated that volume overload and atrial stretch due to mitral regurgitation was associated with increased atrial volume, interstitial fibrosis, chronic inflammation and glycogen accumulation.\textsuperscript{120} In patients with mitral stenosis, John et al found significant bi-atrial remodeling characterized by atrial enlargement, loss of myocardium, and areas of electrical scarring associated with widespread and site-specific conduction abnormalities. These abnormalities were associated with a heightened vulnerability for AF.\textsuperscript{103} [Fig.2]. Examinations of atrial appendage tissues from patients with valvular heart disease undergoing open-heart surgeries have demonstrated that increased atrial endothelin-1 and decreased matrix metalloproteinases were associated with increased atrial fibrosis.\textsuperscript{121, 122} Furthermore,
increased atrial amyloid deposition has also been seen in biopsies from patients with rheumatic valve disease and long-standing AF.123

1.4.4 Atrial septal defect
AF is one of the well-documented sequelae of atrial septal defects (ASD) that appear to be minimally altered by ASD closure.124, 125 Although the precise pathogenesis of arrhythmias in ASD patients is unclear, both electrical and structural remodeling due to chronic atrial stretch appear to play a major role. Chronic atrial stretch resulting from ASD causes electrical remodeling with anatomically determined conduction delay at the crista terminalis, a trend toward an increase in right atrial ERP, and impaired sinus node function.126 Additionally, significant structural remodeling due to volume overload leads to marked bi-atrial enlargement and left atrial scarring evidenced by regions of low voltage amplitude and electrical silence.127

1.4.5 Coronary artery disease
Coronary artery disease is also recognized as an independent risk factor for AF.114, 128 In contemporarily managed patients with acute coronary syndrome, new onset AF remains commonly encountered to result in increased short and long term complications.129, 130 However, the mechanistic link between myocardial ischemia and the development of AF remains incompletely understood. Detailed assessment of coronary angiography in patients has shown that coronary artery disease affecting the atrial branches is associated with AF in the setting of acute myocardial infarction.131, 132 Experimentally, atrial ischemia due to acute occlusion of atrial arterial branch in dogs resulted in significant conduction slowing which can promote re-entry that can maintain AF.133 In dogs with chronic atrial ischemia, increased atrial fibrosis was seen
in infarct border zone as substrate for increased conduction heterogeneity, sustained re-entry and even increased spontaneous ectopy.\textsuperscript{134} Indeed, recent work by Alasady and co-workers have demonstrated that direct atrial ischemia played a dominant role in the substrate for AF over and above hemodynamic and neurohumoral changes during acute myocardial infarction.\textsuperscript{135}

### 1.4.6 Hypertension

Hypertension (HTN) is the most prevalent, independent, and potentially modifiable risk for atrial fibrillation.\textsuperscript{5, 128} In the Manitoba Follow-up study, prevalence of HTN was 53%, and the risk of AF was 1.42 times higher in hypertensive.\textsuperscript{136} HTN is associated with structural changes in the left atrium that are associated with atrial fibrillation. They include left atrial enlargement, changes in left atrial mechanical function, altered left atrial electrophysiology, and increased atrial ectopic activity.\textsuperscript{137} These changes occur in different time domains making early and aggressive management of HTN prudent. Structural changes such as atrial dilatation and hypertrophy develop early and are an important step in the progression from HTN to AF.\textsuperscript{106, 138} With prolonged HTN these changes worsen and are characterized by increased atrial fibrosis, atrial hypertrophy, scarring and apoptosis.\textsuperscript{26, 139} Indeed, the magnitude of LA enlargement is proportional to the degree of HTN. In the Framingham study, the risk of developing AF increased by 39% for each 5mm increase in left atrial size.\textsuperscript{5} Changes in atrial electrical properties occur early in hypertensive heart disease with higher refractoriness, progressive conduction slowing and anisotropy.\textsuperscript{26, 106} These progressive structural and electrophysiological changes lead to functional impairment with reduced atrial ejection fraction.\textsuperscript{26} This impaired contractile function of the left atrium has also been shown to predict the development of atrial fibrillation.\textsuperscript{140}
1.4.7 Diabetes

Diabetes mellitus (DM) is a recognized risk factor for AF. In the Framingham Heart Study, the presence of diabetes conferred a 1.4-increased risk of AF in men and 1.6 in women. AF commonly coexists with cardiovascular risk factors that may predispose to AF. However in a meta-analysis, after adjusting for multiple risk factors for AF, the RR of AF in patients with DM was still 1.24. DM-related cardiac structural, functional and electrophysiological changes predispose the atria to fibrillate. Possible pathophysiologic mechanisms of these structural changes include oxidative stress, cellular apoptosis, interstitial fibrosis, mitochondrial dysfunction and myocardial hypertrophy. In a DM rat model, widespread fibrotic deposit has been seen in the atria. This was associated with longer intra-atrial activation time due to decreased conduction velocity. Decreased phosphorylation of connexin-43 can also result in impaired intercellular electrical coupling and atrial arrhythmia. Oxidative stress and activation of the AGE-RAGE (advanced glycation end product/AGE—receptor for AGE) system mediate the diffuse interstitial fibrosis of the atrial myocardium via up-regulation of circulating tissue growth factors and by pro-inflammatory response resulting in formation of hyperglycemia associated AF substrate.

1.4.8 Obstructive sleep apnoea

Considerable evidence links AF and sleep apnea with high prevalence of sleep disordered breathing found in AF patients. Gami et al reported that obstructive sleep apnea (OSA) was a strong predictor of incident AF (hazard ratio 2.18) and that the measures of OSA severity were also strong predictors of incident AF. Patients with moderate-to-severe OSA have impaired LV diastolic function and increased LA size independent of obesity. Furthermore, prolonged atrial electromechanical
activation time as measured by tissue Doppler imaging was evident in subjects with severe OSA as compared to controls with similar body mass index. Therefore, OSA itself may induce cardiac changes that could predispose to AF independent of obesity\textsuperscript{147, 148}. Detailed electrophysiological study and electroanatomic mapping by Dimitri and co-workers had found significant atrial remodeling characterized by atrial enlargement, prolonged sinus node recovery time, reduction in voltage, site-specific and widespread conduction abnormalities in patients with OSA. These factors may account for the development and maintenance of AF in patients with OSA\textsuperscript{28}. Further insights into the link between OSA and AF can be gained from various pre-clinical studies. In sheep with induced hypercapnia, lengthening of atrial refractoriness and conduction time was observed. However, AF vulnerability was only documented in the period on return to eucapnia due to differential recovery in atrial refractoriness and conduction\textsuperscript{149}. In a pig model of OSA, negative tracheal pressure during obstructive episodes led to shortened atrial refractoriness and increased AF susceptibility that were prevented by vagotomy or atropine, implicating a mechanistic role of vagal activation in OSA related AF\textsuperscript{150}. Other AF inducing mechanisms include hypoxemia and atrial stretch during apneic episodes as well as sympathetic activation with acute hypertension on arousals\textsuperscript{150-153}. There are acute and chronic changes due to repetitive OSA. Acute OSA promotes arrhythmias via autonomic changes\textsuperscript{154} along with acute cardiac stretch and diastolic dysfunction\textsuperscript{151, 155}. Furthermore, chronic repetitive OSA produces cardiac remodelling, including left and right ventricular (LV) dilation, hypertrophy and systolic and diastolic dysfunction. The intermittent hypoxia, oxidative stress, connexion-43 changes and inflammation are all variably implicated as causes of fibrosis and cardiac remodelling\textsuperscript{156, 157}. 
1.5 Mechanism of atrial structural remodeling

A multitude of signalling pathways are involved in the fibro-proliferative process including underlying cardiac risk factors or AF itself. Pro-fibrotic factors such as inflammatory cytokines, renin–angiotensin–aldosterone system, downstream mediators such as transforming growth factor-β1, connective tissue growth factor, calcium dependent proteases/phosphatases, extracellular matrix regulatory proteins, hypoxia inducible factor-1α and endothelin-1 system are known to be involved.

1.5.1 Neurohormonal factors:

1.5.1.1 Angiotensin II

Renin-angiotensin-aldosterone system is involved in atrial fibrosis in various cardiac pathologies including hypertensive heart disease, myocardial infarction and congestive heart failure. Increased Angiotensin II is associated with cardiomyocyte apoptosis and reactive interstitial fibrosis leading to marked atrial dilatation and AF. Exposure to Angiotensin II dramatically alters cardiac fibroblast function. During structural remodeling process both the production of Angiotensin II and AT1 receptor expression are increased. Mechanical stretch increases the Angiotensin II production and TGFβ1 expression in cardiac fibroblasts. Thus chronic dilatation of atria through the auto feedback mechanism leads to progressive structural remodeling and domestication of AF.

1.5.1.2 Transforming growth factor beta

TGFβ1 is central to signaling cascades implicated in the genesis of cardiac fibrosis. It is the primary downstream mediator of Angiotensin II pro-fibrotic effects. Angiotensin II upregulates TGFβ1 expression through the angiotensin type 1 (AT1)
receptor in cardiac fibroblasts and cardiomyocytes and blockade of the angiotensin II type 1 (AT1) receptor suppresses TGFβ1 expression. Increases in Angiotensin II and activated TGFβ1 concentrations reciprocally enhance each other’s production, creating positive feedback cycles for fibrosis. TGFβ1 acts in a autocrine-paracrine fashion and overexpression can lead to selective atrial fibrosis, conduction heterogeneity and AF. TGFβ1 acts primarily through the SMAD signaling pathway to stimulate collagen production. TGFβ, in addition, induces fibroblasts to differentiate into α-SMA expressing myofibroblasts. In Vitro when applied to fibroblasts, TGFβ directly induces ECM gene expression and promotes collagen deposition by suppressing matrix metalloproteinase gene expression and inducing tissue inhibitors of matrix metalloproteinase gene expression.

1.5.2 Tissue factors

1.5.2.1 Connective tissue growth factor (CTGF)
CTGF (CCN2) is a potent pro-fibrotic factor. In Patients with AF, an increased level of CTGF was associated with increased left atrial fibrosis. Notably, this was in conjunction with increased tissue levels of Angiotensin II levels. CTGF is a downstream mediator of Angiotensin II and TGFβ1. Angiotensin II can directly induces CTGF via activation of Rac1 AND NADPH oxidase. Also, Angiotensin II via TGFβ1 and SMAD signaling can also induce CTGF. CTGF, on its own accord, is not sufficient to promote the development of fibrosis. However, CTGF enhances the ability of TGFβ1 to induce fibrosis. Though direct evidence proving causality between elevated CTGF expression and induction of fibrosis is still lacking, but in vitro and in vivo studies have found enhanced CTGF expression regularly with fibrosis and AF. It is possible that
several factors such as associated risk factors, systemic activation of RAS system and duration of AF may be required to turn CTGF into a pro-fibrotic factor. Diabetes mellitus, an established risk factor of AF is associated with atrial fibrosis and activation of CTGF expression. Studies have shown that angiotensin receptor blockers reduce CTGF levels in diabetics.  

1.5.2.2 Matrix metalloproteinase proteins and tissue inhibitor of MMP

The RAAS system is likely not the only system involved in atrial fibrosis and structural remodeling. Homeostasis of the extracellular matrix is a balance between synthesis and degradation of the tissue. By breaking down the ECM, matrix metalloproteinases (MMP) contribute to matrix turnover, to dilatation and to structural remodeling in general. An increase in MMP activity can induce extracellular matrix remodeling leading to dilatation, while a decrease can reduce the extracellular matrix breakdown and lead to fibrosis. There are twenty-three different MMPs categorized according to expression patterns and functions. Under normal circumstances the expression levels of MMPs are very low, however they are upregulated in case of injury by activation of the precursors, or by tissue inhibitors of metalloproteinase (TIMPs). There are four different TIMPs, each with distinct ability to bind and deactivate MMP molecules. MMPs influence ECM modulation by degrading ECM components such as type IV collagen. Stomelysins (MMP-3) degrades fibronectins, laminin, gelatins I, III, IV and proteoglycans. An abnormal increase in MMP activity results in degradation of the matrix proteins while TIMPs directly inhibit the proteolytic activity of MMPs by binding to them. TNF-a directly via induction of transcription of MMPs or through activation of different proteases in a paracrine manner is capable of activating MMPs. Atrial ECM remodeling in conjunction
with up-regulation of MMP-2 and down-regulation of TIMP-2 have been associated with development of sustained AF in patients with cardiomyopathy and heart failure.

1.5.3 Vascular and Hemostatic Factors

1.5.3.1 Platelet derived growth factor
PDGF, a vascular endothelial growth factor family member, stimulates fibroblast proliferation and migration. PDGF receptor activation stimulates the mitogen-activated protein kinase, JAK/STAT, and phospholipase C pathways, a final common pathway shared by Angiotensin II and TGFβ1. The gene expression of PDGF and its receptors is stronger in the atrial than ventricular rat fibroblasts. This could explain why atria are much more susceptible to fibrotic remodeling than ventricles. PDGF receptor inhibition prevents the electromechanical remodelling of adult atrial myocytes and may serve as a novel potential therapeutic target of AF.

1.5.3.2 Endothelin-1
The endothelial system plays an important role in the development of AF. There are 3 isoforms of Endothelin (ET), the most important being ET1 in humans. It acts through 2 subtypes of receptors (ET receptor subtype A [ETA] and ET receptor subtype B [ETB]). Plasma endothelin levels are elevated in patients with AF as compared to patients with sinus rhythm. Endothelin-1 (ET-1), an endothelium-derived vasoconstrictor peptide, participates in the pathophysiology of AF via membrane ion channels and atrial remodeling. Furthermore, ET-1 modulates of the renin-angiotensin-aldosterone system, stimulating aldosterone release. Studies have shown that ET-1 is released by stretched cardiac cells, such as cardio- myocytes, cardiac fibroblasts, endothelial
cells, and vascular smooth muscle cells. Angiotensin II–induced ET-1 gene expression in cardiac fibroblasts may serve as autocrine/paracrine growth factors for the cardiac fibroblasts. Endothelin system acts downstream to TGFβ1 and activates the procollagen I promoter and collagen synthesis in fibroblasts.\textsuperscript{190} ET1 induces ECM production and in association with TGFβ1 promotes differentiation of fibroblasts to myofibroblasts.\textsuperscript{191} Considering the downstream position of ET1 in the signaling network, ET receptor antagonism represents a potential candidate as an inhibitor of atrial fibrosis.

\subsection*{1.5.4 Oxidative stress and Inflammation}

Inflammation is purported to be among one of the primary causal factors of AF initiation, perpetuation as well as the pro-thrombotic state associated with AF.\textsuperscript{192} This temporal relationship is supported by the fact that AF is frequently associated with inflammatory states such as myocarditis\textsuperscript{193}, pericarditis\textsuperscript{194}, post cardiac surgery\textsuperscript{195} and systemic infections. Raised levels of inflammatory markers such as CRP are associated with increased risk of AF.\textsuperscript{196} Similarly, elevated baseline CRP is associated with increased risk of AF recurrence after successful cardioversion.\textsuperscript{197} Various studies have suggested the central role of oxidative stress on atrial tissue during AF in structural and electrical remodeling of the atrium.\textsuperscript{198-200} The atrial oxidative damage experienced due to high rate activity of AF alters myofibrillar energetics and myocyte calcium overload leading to myocyte necrosis.\textsuperscript{93} The resultant apoptosis and myocardial necrosis induce low-grade inflammation leading to structural remodeling. Additionally, CRP has been shown to act as an opsonin and may participate in the clearance of apoptotic myocytes and a resultant “replacement fibrosis”.\textsuperscript{201} Additionally, studies have revealed central role of RAAS in the inflammatory process.\textsuperscript{192}
1.5.5 Galectin

Galectin-3 (Gal-3) is a member of the β-galactoside-binding lectins family. It is an emerging biomarker in heart failure that is involved in fibrosis and inflammation.\textsuperscript{202} Gal-3 is highly expressed in fibrotic tissues, and upregulated in chronic inflammatory and fibrotic conditions in human. It is mainly produced by activated macrophages, mast cells and eosinophils, and plays a role in cell adhesion, migration and proliferation, increasing fibrosis.\textsuperscript{202} However, the mechanisms by which Gal-3 exerts fibrogenic activity are not completely understood and is a matter of ongoing research. Studies have suggested that Gal-3 may initiate fibrosis by activation of Renin Angiotensin Aldosterone system and up regulation of profibrotic effectors such as TGF-β1.\textsuperscript{203, 204} Gal-3 levels correlate with risk factors of cardiovascular disease such as diabetes, hypertension or obesity.\textsuperscript{205} Recently, Ho et al. demonstrated in a large population based study an association between higher Gal-3 levels and incident AF. However, this association was not significant after adjusting for the coexistent risk factors.\textsuperscript{206} In a more selected population of post myocardial infraction patients, Szadkowska et.al found Gal-3 levels > 16 ng/mL was associated with increases risk of incident AF.\textsuperscript{207} A recent study has found a significant association between higher BMI and baseline Gal-3 levels in AF cohort.\textsuperscript{208} Raised Gal-3 level are also seen in patients with more persistent form of AF.\textsuperscript{208} It is also an independent predictor of AF recurrence post AF ablation.\textsuperscript{208, 209}
1.6 Obesity

1.6.1 Obesity and Atrial Fibrillation - the epidemiologic link

Obesity is a worldwide public health crisis. In the United States, the prevalence of obese individuals has risen by 3-fold since 1960 with 1 in every 3 adults and 1 out of 7 youths affected. If such trends were to continue unabated, it is estimated that 164 million Americans will be obese by 2030, with an additional health care cost of $66 billion. Several population-based studies have demonstrated a robust relationship between obesity and AF. Historically, the propensity for cardiac arrhythmias in obesity was recognized as early as the fourth century BC when Hippocrates observed, “sudden death is more common in those who are naturally fat than in the lean”. Data from the Framingham cohort study has demonstrated a significant dose relationship with increased risk of developing AF with increasing severity of obesity. This relationship holds true even after multivariate adjustment for other known risk factors with 3-7% increased AF risk per unit increment of body mass index. The metabolic consequences of weight gain and the accompanying co-morbid conditions often seen in obese individuals such as hypertension, arterial stiffness, diabetes and sleep apnoea, are also known independent contributors to adverse cardiac remodelling leading to increased arrhythmogenicity. In a meta-analysis by Wanahita et al., there was a graded dose-response relationship between obesity and AF in the general population. This impact of obesity on AF is not only significant for old age individuals but a recent Danish study has identified obesity as an independent predictor of AF in otherwise young and healthy females.
1.6.2 Atrial remodeling in obesity

The mechanisms by which obesity could result in increased cardiac arrhythmias remain incompletely understood. The dilated left atria seen in obese subjects appear to be mechanistically important as the association between body mass index and AF was significantly weakened when adjustments were made for left atrial size in the Framingham study.\textsuperscript{3} Both left atrial dilatation and atrial dysfunction are known consequences of the cardiomyopathy due to obesity.\textsuperscript{219} Indeed, earlier data has demonstrated a hazard ratio of 1.39 for developing AF per 5mm increment in left atrial diameter.\textsuperscript{220} More recently, left atrial dilatation has also been linked to both AF recurrence and progression to chronic AF,\textsuperscript{221, 222} while left atrial dysfunction has been shown to increase the risk of new onset AF.\textsuperscript{223} Further, acute left atrial stretch in the setting of left ventricular diastolic dysfunction has been shown to be pivotal to AF promotion in an obese rat model with acute obstructive sleep apnea.\textsuperscript{151}

The atrial remodeling as a result of obesity encompasses more than the anatomical and functional changes as described above. Significant atrial electrical remodeling has also been identified from recent studies. Obese AF patients had shorter atrial and pulmonary vein effective refractory period as compared to their normal weight counterparts. This was associated with slowed longitudinal conduction velocity from LA to PV.\textsuperscript{224} Increased adiposity as measured by body mass index was found to be significantly associated with larger electrocardiographic P wave indices including P wave duration, PR interval and P wave terminal force, indicative of underlying atrial electrophysiologic remodeling.\textsuperscript{225}
Similarly, in an ovine model of diet-induced obesity, our group has demonstrated widespread electrophysiological changes in the atria. At 4 months there was already significant atrial conduction slowing seen with increased conduction heterogeneity leading to increased AF inducibility. With sustained obesity, Mahajan et al demonstrated there is progressive worsening of electrical properties with reduced atrial conduction velocity, increased conduction heterogeneity, increased fractionated electrogram and decreased posterior LA voltage.

These electrical changes were seen in conjunction with increased atrial interstitial fibrosis, inflammation, and myocardial lipidosis. In an ovine model of sustained obesity, Mahajan et al found significant hemodynamic changes. There was elevated LA pressure, elevated right heart pressure and systemic hypertension. This resulted in a bi-atrial enlargement in the presence of a normal ventricular function. Additionally, there was significant structural remodelling with increased interstitial fibrosis and fatty infiltration of the atrial myocardium. These changes were associated with increased TGFβ1 expression. As a result of these hemodynamic, structural, and electrophysiological changes, obese animals were more vulnerable to AF. The electro-structural abnormalities of increased interstitial fibrosis resulting in increased separation within and between muscle bundles are thought to interfere with electrical conduction thereby promoting atrial reentry and fibrillation. Such changes have been featured in other established AF substrates of congestive heart failure, hypertension, and myocardial ischemia. The complex signaling pathways underlying atrial fibrosis in obese hearts remain incompletely
understood to involve at the very least, the transforming growth factor-β₁, connective tissue growth factor, and endothelin-1 system.²⁷

1.6.3 Mechanism of atrial remodeling

1.6.3.1 Role of Adipose Depots and Adipokines
Recent attention has focused on the increased epicardial adipose tissue in obese hearts and its association with AF. Increased posterior left atrial fat thickness or pericardial fat as detected by computed tomography imaging has been shown to be independently associated with AF burden.²²⁹,²³⁰ Similarly, pericardial fat as determined by magnetic resonance imaging has also been shown to be associated with AF burden, severity and AF recurrence following catheter ablation.²³¹ Of note, the above associations were found to be independent of standard measures of adiposity such as body mass index or body surface area.²²⁹-²³¹ Non-invasive method for quantitation of atrial pericardial adipose tissue has recently been validated and will facilitate further studies.²³² The mechanisms by which pericardial fat leads to atrial remodeling remain incompletely understood. Recent evidence suggests a significant association between pericardial fat and atrial conduction abnormalities determined by electrocardiographic P-wave indices.²³³ Further, epicardial fat are thought to contribute to atrial fibrosis via paracrine effects. Venteclef et al have elegantly demonstrated that secretome from human epicardial adipose tissue could induce atrial fibrosis in a rat organo-culture model.²³⁴ The epicardial adipose tissue was rich in adipo-fibrokines including Activin A, a member of the TGF-β superfamily, that was found to be responsible for the pro-fibrotic effects in a paracrine-dependent fashion.²³⁴ Moreover, infiltration of
adipocytes into the atrial myocardium from the epicardial fat depot has been shown in human samples with increased pericellular fibrosis in its surround. Mahajan et al. in the ovine model found contiguous epicardial fat infiltration in the region demonstrating low voltage. Taken together, the altered 3-dimensional atrial architecture in obese hearts with epicardial adiposity, adipocyte infiltration into the myocardium and the resultant increase in atrial fibrosis may contribute to conduction heterogeneity and anisotropy that promote a pro-fibrillatory substrate of reentry as well as endo-epicardial electrical dissociation and breakthrough.

Both animal and human studies have demonstrated that the expansion of adipose tissue with obesity is accompanied by inadequate capillarization resulting in hypoxia. Hypoxia of the adipose tissue has been shown to result in alteration in gene expression, with hypoxia-inducible factor 1α being the key transcriptional factor mediating adipose tissue fibrosis. Adipocytes encased in fibrous tissue undergo necrosis and prompt infiltration by macrophages, neutrophils and lymphocytes leading to a pro-inflammatory microenvironment, with production and release of pro-inflammatory cytokines as well as alteration in adipokine levels. Obesity is associated with elevated leptin and reduced adiponectin levels. These alterations may also contribute to adverse atrial remodeling with increased atrial fibrogenesis and AF persistence. In addition, in-vitro studies on rabbit left atrial myocytes have demonstrated that leptin could acutely prolong action potential duration in an inhomogeneous manner that can be pro-arrhythmic although a lower incidence of isoproterenol induced delayed afterdepolarization was also seen.
1.6.3.2 Role of Pro-Inflammatory Cytokines and Oxidative Stress

Obesity is associated with a pro-inflammatory state and increased oxidative stress. Increased leucocyte count and various pro-inflammatory cytokines including C-reactive protein, interleukin 6 and tumor necrosis factor-α have been shown in obese subjects. Several markers of systemic inflammation have been shown to be significantly associated with AF development in large cohort studies. While the arrhythmogenic mechanisms as a result of increased inflammation and oxidative stress are not fully understood, they are likely to involve alterations in ion channels properties, calcium handling and homeostasis as well as atrial fibrosis.

1.6.3.3 Role of Autonomic Dysregulation

Obesity is also associated with autonomic nervous system dysfunction. Both increased sympathetic activity and reduced vagal tone have been demonstrated in obese subjects with increased urinary norepinephrine excretion and alterations in heart rate variability measures. The contributory role of the autonomic system has been demonstrated elegantly in an obese rat model with acute obstructive sleep apnea whereby autonomic blockade resulted in reduced AF inducibility.

1.6.4 Primary and secondary prevention of atrial fibrillation

Long-term maintenance of sinus rhythm is difficult to achieve in AF patients. Factors such as underlying etiology and its duration, extent of atrial remodeling and management of risk factors collectively determine the success of AF therapy.

1.6.4.1 Reversal of LA Remodeling: Therapeutic Implications

Although atrial remodeling can be reversible, it is time critical and early intervention is prudent. Electrical remodeling due to AF is completely reversible following
Based on these finding, it was postulated that early cardioversion would prevent the remodeling due to AF and allow “sinus rhythm to beget sinus rhythm”. However, restoration of sinus rhythm with early repeated cardioversion while reversed electrical remodeling but did not impact the maintenance of sinus rhythm. Thus the role of a “second factor” i.e. atrial substrate responsible for propagation of AF, has been implicated. Indeed, abnormal atrial changes have been observed even in ‘lone AF’ patients. In addition, a recent study has observed a progressive atrial substrate even after successful catheter ablation of AF. These findings argue in favor of an underlying atrial substrate responsible for AF.

Li et al was first to highlight the importance of structural changes in maintaining AF. While the electrical remodeling is more “forgiving”, controversies exist regarding reversibility of structural changes on withdrawal of the initiating stimulus. Some changes may be reversible; others such as atrial fibrosis have been suggested to be irreversible. In chronically stretched atria due to ASD, Morton et.al found only modest improvement in RA volume and non-significant changes in the electrophysiological parameters with ASD closure. However, in this study only 4 patients underwent repeat electrophysiological study and the mean follow up was only 8.3±5.6 months. The small numbers at follow up and relatively short follow up time could be responsible for these findings. Similarly, reversal of heart failure by cessation of rapid pacing for 5 weeks was associated with a hemodynamic improvement but persistent atrial fibrosis, conduction heterogeneity and inducibility of AF. The lack of reverse structural remodelling following cessation of rapid pacing may be due to the significantly shorter period of recovery (at 5 weeks).
In contrast, in the established substrate of mitral stenosis, treatment of the primary cause was surprisingly associated with an improvement in atrial voltage and conduction with a reduction in abnormal and fractionated electrograms when studied ≥6 months later.\textsuperscript{260} Recently, our group has presented results from an ovine study, where weight reduction over a prolonged period of 8 months was associated with reversal of hemodynamic abnormalities, atrial fibrosis, and the electrophysiological abnormalities resulting in reduced AF vulnerability.\textsuperscript{261} Various upstream therapies have demonstrated beneficial effects on AF. Antihypertensive therapy has been shown to reduce left atrial size and left ventricular hypertrophy leading to a lower risk of AF in hypertensive individuals.\textsuperscript{262}

1.6.4.2 Role of Upstream Therapy

1.6.4.2.1 Drugs targeting Renin Angiotensin Aldosterone System (RAAS)

Both ACE-inhibitor (ACE-I) and angiotensin receptor blocker (ARB) have been shown to be effective in the prevention of AF in a recent meta-analysis although this effect appears to be most clearly seen in patients with systolic LV dysfunction and left ventricular hypertrophy.\textsuperscript{263} Recently, there has also been increased awareness on the role of aldosterone in atrial ionic remodeling and fibrosis.\textsuperscript{264, 265} Several pre-clinical studies have demonstrated the beneficial role of ACE-I, ARB and aldosterone antagonists in preventing the substrate for AF in pacing models of AF and CHF. For example, in animal models of CHF, ACE-I pre-treatment reduced left atrial dilation, contractile dysfunction, fibrosis and shortening of the atrial effective refractory period to result in shorter induced AF duration.\textsuperscript{98, 266} However, the role of ACE-I/ARB in the secondary prevention of AF is non-conclusive with divergent results. When AF
recurrence was examined in patients with HTN and AF, a randomized study has shown no difference in AF frequency between patients with HT and paroxysmal AF treated with candesartan or amlodipine.\textsuperscript{267} Furthermore, several secondary prevention trials have reported that inhibitors of the RAAS may not reduce the risk of arrhythmia recurrence in AF patients.\textsuperscript{268, 269}

\textbf{1.6.4.2.2 HMG-CoA Reductase Inhibitors:}
The exact mechanisms by which statins may prevent AF are not well established although their anti-inflammatory and antioxidant properties, membrane stabilizing effect and effect on endothelial and neurohormonal activation are thought to be contributory.\textsuperscript{270} In animal experiments with sterile pericarditis, rapid atrial pacing, and ventricular tachypacing AF models, statins have been shown to attenuate electrical and structural atrial remodeling and reduced vulnerability to AF.\textsuperscript{271-273} However, the beneficial effects of statins in human AF have not been convincingly demonstrated in large randomized control trials.\textsuperscript{274}

\textbf{1.6.4.2.3 Omega-3 Polyunsaturated Fatty Acids (n-3 PUFAs):}
Several population-based studies have shown conflicting results regarding the role of n-3 PUFAs in preventing AF.\textsuperscript{275-278} Similarly, its role in AF and in associated conditions such as post open-heart surgery and AF prevention following cardioversion remains uncertain given recent contradictory findings.\textsuperscript{279-283} In contrast, n-3 PUFAs have been associated with reduction in incident CHF, fewer CHF hospitalizations and associated mortality. In animal CHF models, several groups have demonstrated that n-3 PUFAs use was protective against adverse atrial remodeling in CHF by preventing atrial enlargement, fibrosis, and conduction abnormalities to result in shorter induced AF
More importantly, it has been suggested that its protective role can be reduced if n-3 PUFAs was not given prophylactically.\textsuperscript{286} The anti-arrhythmic mechanisms of n-3 PUFAs can include anti-inflammatory, anti-fibrotic, anti-sympathetic, anti-oxidative and pro-autonomic. Specifically, it has been shown to inhibit \( I_{to} \), \( I_{kur} \) and \( I_{Na} \) in human atrial myocytes, modulate Connexin 40 in canine atria and prolong refractoriness in human pulmonary vein and left atria.\textsuperscript{287-289} Perhaps, the beneficial effects of n-3 PUFAs are limited to specific underlying atrial substrate and at the right therapeutic window.

1.6.4.2.4 \textit{Anti-fibrotic Drugs:}
Atrial fibrosis is an important substrate in AF and an attractive therapeutic target. This fibrosis is responsible for conduction abnormalities to favor re-entry and maintenance of AF. Pirfenidone have been shown to have broad anti-fibrotic and anti-inflammatory effects. In canine CHF atria, it reduced atrial conduction heterogeneity, fibrosis and AF vulnerability by inhibiting pro-fibrotic mediators such as TNF-\( \alpha \) and TGF-\( \beta_1 \).\textsuperscript{290} More recently, prevention of adverse atrial remodeling by another anti-fibrotic agent, Tranilast, has been shown in a different canine model of rapid atrial pacing and left ventricular dysfunction.\textsuperscript{291} However, clinical evidence are still lacking with the above-mentioned agents.

1.6.4.2.5 \textit{Anti-inflammatory Agents:}
Inflammation is frequently implicated in different substrates of AF. However, both glucocorticoids and non-steroidal anti-inflammatory agents are also known to be pro-arrhythmic in humans.\textsuperscript{292,293} This is despite solid experimental evidence regarding the beneficial effects of prednisolone in rapid atrial pacing and sterile pericarditis
models. More recently, a randomized control trial has shown that transient corticosteroids treatment after AF ablation procedure could reduce both immediate and mid-term AF recurrences as compared to placebo. Certainly, further work is needed to define the utility of these agents in AF patients.

1.6.4.3 Secondary Prevention of Atrial Fibrillation

1.6.4.3.1 Anti-Arrhythmic Therapy

Most of the anti-arrhythmic drugs work by direct inhibition of ion channels. Amiodarone, in addition to its polypharmacology has been shown to affect atrial electrical remodeling in an experimental animal model. Shinagawa et al. have shown that amiodarone, but not flecainide or dofetilide, prevented tachycardia-induced ERP shortening in canine atria by preventing L-type Ca\(^{2+}\) channel down regulation. Moreover, amiodarone treatment after the induction of atrial tachycardia was able to reverse remodel the electrical changes seen with tachycardia and restored ERP, ERP rate adaptation, and AF duration to their control values, despite concomitant tachypacing. Similar finding were shown by Ashikaga et.al in canine atria. In this study, Amiodarone also suppressed the increases in MMP-2 activity and fibrosis induced by long-term rapid atrial pacing. Amiodarone therefore reversed both electrical and structural remodeling and suppressed the inducibility of sustained atrial fibrillation. Although it is unclear whether amiodarone has similar effects in patients, such effects could potentially contribute to its clinical efficacy.

However, anti-arrhythmic drugs are ineffective in maintaining sinus rhythm in long term. Amiodarone is the most effective anti-arrhythmic drug. However, even in trials with best results, Amiodarone use was associated with a 65% long-term success.
Class 1C drugs have been shown to be suppressing AF recurrence in 30-60% and Sotalol maintained SR in 30-70% cases.\textsuperscript{300,301} Additionally, the clinical values of anti-arrhythmic drugs are limited by its wide range of side effects. Recent studies have found that rhythm control with anti-arrhythmic drugs did not provide any significant benefit. On treatment analysis of AFFRIM study, showed a trend towards increased mortality.\textsuperscript{302} However, post hoc analysis suggested that this mostly likely due to adverse effects of the anti-arrhythmic drugs.\textsuperscript{303} While there are no doubt that restoration and maintenance of sinus rhythm is associated with better quality of life.\textsuperscript{304} Detrimental effects of antiarrhythmic agents offset the benefit from sinus rhythm maintenance.\textsuperscript{305-307} A recent meta-analysis reported that while Class IA, IC, and III drugs are somewhat effective in maintaining sinus rhythm they are associated with significant increase in adverse effects and apart from Amiodarone were generally pro-arrhythmic.\textsuperscript{308}

1.6.4.3.2 **Radiofrequency catheter ablation of AF**

Catheter ablation of AF has evolved as an effective therapy for drug-refractory symptomatic AF.\textsuperscript{309} Studies have demonstrated the advantage of catheter ablation over pharmacological methods of rhythm control.\textsuperscript{310-313} Catheter ablation is effective in drug refractory symptomatic AF patients with regards to maintenance of sinus rhythm and improvement in symptoms, exercise capacity, and quality of life.\textsuperscript{312,314} Although associated with high initial cost, several cost benefit studies have found catheter ablation to be cost effective in long-term.\textsuperscript{315-317} There is paucity of data related to benefit of catheter ablation and hard endpoint such as mortality.\textsuperscript{318} However, there is evidence that catheter ablation of AF is particularly beneficial in heart failure patients. Ablation improves left ventricular function along with restoring sinus rhythm and alleviating heart failure symptoms.\textsuperscript{319,320}
However, reports of the long-term outcomes of AF ablation demonstrate attrition in success with time.\textsuperscript{321-327} The efficacy of catheter ablation in maintaining sinus rhythm has been reported to vary between 60% - 85% in patients with paroxysmal AF and between 30% - 75% in patients with more persistent form of AF.\textsuperscript{36, 328-330} Type of AF, left atrial size, termination of AF during procedure and successful isolation of pulmonary veins during ablation are few key factors associated with long term success of AF ablation.\textsuperscript{326, 327, 331-333} Updates from several centres confirm the need for multiple procedures, which in general have occurred early\textsuperscript{257, 322, 323} and are related to incomplete ablation during previous efforts with residual PV conduction.\textsuperscript{334, 335} More concerning is that despite consolidative ablation and a period without arrhythmia, a progressive attrition in success is observed with time.\textsuperscript{322-324} It has been proposed that this late recurrence is also due to persistent PV conduction.\textsuperscript{334, 335} However, it seems unusual that recovery of PV conduction, that would be expected to occur early, would contribute to delayed recurrence of arrhythmia.

Cardiac risk factors such as hypertension, diabetes mellitus, obesity and OSA have been independently shown to increase incidence of AF.\textsuperscript{17, 18, 32, 33} 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.\textsuperscript{26-28} Studies have also associated these cardiac risk factors with the more frequent recurrence of AF.\textsuperscript{324, 327, 336, 337, 332, 338} In a recent study, raised baseline inflammatory markers and presence of metabolic syndrome was associated with increased risk of AF recurrence post ablation in patients with non-paroxysmal AF.\textsuperscript{337} Elevated BMI, hypertension and sleep apnoea have been independently shown to increase risk of AF recurrence.\textsuperscript{324, 338} In fact, this
risk of AF recurrence increases proportionately with increase in number of risk factors. Presence of metabolic syndrome and sleep apnoea can act synergistically and exert more negative effect on outcome of AF ablation than when they are present independently.

1.6.4.4 Role of Risk Factor Management in Cardiac Disease

In patients who have had a myocardial infarction or revascularization procedure, secondary prevention of coronary artery disease by comprehensive risk factor modification reduces mortality, decreases subsequent cardiac events, and improves quality of life. Smoking cessation reduces overall mortality by 25% to 50% in those who have suffered an MI, and at least 50% of this decline is seen in the first year. Similarly, large body of data have shown benefit of control of hypertension with reduction in morbidity and mortality due to stroke, coronary artery disease and heart failure.

While aggressive management of associated cardiac risk factors have been shown in multiple large randomised studies to be beneficial in primary and secondary prevention of coronary artery disease and has been incorporated into the guidelines. Limited data exist regarding their role in management of atrial fibrillation.

Current evidence suggests that continuous positive airways pressure (CPAP) therapy directed at OSA can lead to a reduction in AF burden. In patients with OSA, Oliveira et al demonstrated that long-term effective CPAP therapy significantly increased LA passive emptying volume and improved left ventricular diastolic dysfunction. Recent studies have also shown that CPAP therapy in OSA patients was associated with higher
success with pulmonary vein ablation and lower subsequent AF recurrences as compared to those not receiving CPAP therapy.\textsuperscript{349, 350}

Antihypertensive therapy has been shown to prevent left atrial dilatation and favorable reverse remodeling. It is associated with reduction in the left atrial size and left ventricular hypertrophy leading to a lower relative risk of AF. \textsuperscript{262, 351} Although current consensus statements have not provided strict guidelines on blood pressure targets and evidence remains lacking regarding usage of specific class of anti-hypertensive agents, close monitoring and titration of anti-hypertensive agents to control this risk factor remain prudent.

There is limited published data available currently regarding impact of weight loss on AF. Recent prospective randomized clinical trial has shown that weight reduction following caloric restriction in obese individuals can result in regression in left ventricular hypertrophy, reduction in left atrial size as well as reduced AF burden and severity.\textsuperscript{352} In an animal study, Mahajan et al demonstrated that weight reduction was associated with reduction in total body fat, atrial size, atrial fibrosis and improved hemodynamics and atrial connexin-43 expression to result in reduced AF vulnerability.\textsuperscript{353}

Purposeful weight loss has been shown to improve the metabolic derangements related to obesity with studies demonstrating improved blood pressure levels, glycemic control and lipid profile.\textsuperscript{354-356} Further, obesity associated conditions such, as sleep apnea and cardiomyopathy are also known to improve with weight reduction.\textsuperscript{357, 358} The improvement of the above parameters that are individual risk factor for AF development will no doubt contribute to reverse remodeling.
In summary, Causal relationship of cardiac risk factors and atrial fibrillation is well established. Given this strong association with development and progression of AF an optimal management strategy for AF should include management of these cardiac risk factors.
Chapter 2: Long-Term Effect of Goal Directed Weight Management in an Atrial Fibrillation Cohort: A Long-term Follow-Up Study (LEGACY)

1.7 Introduction

Recent epidemiological data confirm the emergence of obesity and atrial fibrillation (AF) as global epidemics.\textsuperscript{1,210} In the United States, the prevalence of obese individuals has risen 3-fold since 1960 with one in every three persons being obese.\textsuperscript{211} If such trends continue unabated, it is estimated that 164 million Americans will be obese by 2030, with an additional healthcare cost of $66 billion annually.\textsuperscript{212,359} The prevalence of AF is projected to reach 15.9 million in the United States alone by 2050.\textsuperscript{1,7,360} Given obesity is independently associated with AF these dual epidemics confer an enormous management and economic burden.\textsuperscript{12,32,33,361}

Obesity and its associated cardio-metabolic comorbidities such as hypertension, diabetes mellitus, and sleep apnoea have been proposed as contributors to the expanding epidemic of AF,\textsuperscript{17,18,33} and are thus potential targets for intervention to stem the expanding AF epidemic. Weight-loss in the short-term results in a reduction in symptomatic AF burden.\textsuperscript{352} Recent data demonstrate that aggressive weight and risk factor management improves maintenance of sinus rhythm after AF ablation.\textsuperscript{362}
However, whether a critical weight-loss threshold is required or if benefits conferred by the initial weight-loss are sustained in the long-term is unknown. Furthermore, obese individuals frequently oscillate in weight over time and the impact of such weight fluctuation on arrhythmia burden is not known. We hypothesized that weight-loss, if sustained, will be of incremental benefit in rhythm control. In this study, we assess the long-term impact of weight-loss and weight-fluctuation on rhythm control in obese individuals with AF.

1.8 Methods

1.8.1 Study Population
The study comprised consecutive patients referred for management of symptomatic paroxysmal or persistent AF to the Centre for Heart Rhythm Disorders at the University of Adelaide, Adelaide, Australia. All patients with a body mass index (BMI) ≥27kg/m² were included in this analysis. Exclusion criteria were: permanent AF; history of myocardial infarction or cardiac surgery in the previous 12-months; significant cardiac valvulopathy or ventricular dysfunction, active malignancy; autoimmune or systemic inflammatory diseases; severe renal or hepatic failure; and <24-months follow-up. The study protocol was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital and University of Adelaide.

1.8.2 Study Protocol and Design
All patients were counselled on the importance of weight and risk factor management with optional participation in a dedicated physician-led weight management clinic or self-managed weight-loss program.
1.8.2.1 Weight Management

The weight and other risk factor management protocol have been presented previously and are outlined in the supplement. In brief, a structured motivational and goal-directed program using face-to-face counselling was used for weight reduction. Patients were reviewed regularly (Every 3 months in the initial phase) and encouraged to utilize support counselling and schedule more frequent reviews as required. Initial weight reduction was attempted by a meal plan and behavior modification. Participants were required to maintain a diet and physical activity diary. Meals consisted of high protein and low glycemic index, calorie controlled foods. If patients lost <3% of weight after 3-months they were then prescribed very-low-calorie meal replacement sachets (Prima Health Solutions or Nestle Health Science) for 1-2 meals/day. The initial goal was to reduce body weight by 10%. After patients achieved the initial goal, meal replacement was substituted to high protein and low glycemic index, calorie-controlled foods to achieve a target BMI of $\leq 25\text{kg/m}^2$. Low intensity exercise was prescribed initially for 20-minutes thrice-weekly increasing to at least 200-minutes of moderate-intensity activity/week. Hypertension, glucose intolerance, sleep apnoea, alcohol and tobacco use were screened for and managed individually according to AHA/ACC guidelines. Changes in metabolic (lipid profile and fasting insulin) and inflammatory state (hsCRP) levels were monitored.

1.8.2.2 Weight-loss definition:

A stadiometer and digital weighing machine was used to record height and weight in light clothing without shoes and BMI was calculated. Anthropometric values measured at annual follow-up were utilized for weight-loss and weight-fluctuation assessment. The AHA/ACC guidelines recognise that any weight-loss $\geq 3\%$ is considered a
meaningful reduction.\textsuperscript{363} To determine the dose response effect of weight-loss on AF burden, groups were divided as follows: 10% or greater weight-loss (\textbf{Group-1}); 3-9% weight-loss (\textbf{Group-2}); and <3% weight-loss or weight gain (\textbf{Group-3}).

\textbf{1.8.2.3 Weight trend definition:}\n
Weight trend was determined by percentage change in annual weight over the course of the study. Linear weight-loss was defined by continuous weight-loss at each annual follow-up with no interim weight-gain of \( \geq 1\% \). Linear weight-gain was defined by continuous weight-gain at each annual follow-up with no interim weight-loss of \( \geq 1\% \). Weight-fluctuation was defined by \( \geq 1\% \) weight cycle (“gain-loss” or “loss-gain”) between 2 consecutive annual follow-ups.

\textbf{1.8.2.4 Quantification of weight fluctuation}\n
To assess the effect of the magnitude of weight-fluctuation, patients were divided based on yearly follow-ups: greater than 5% weight-fluctuation (\textbf{wide}); 2-5% weight-fluctuation (\textbf{average}); and <2% weight-fluctuation (\textbf{stable}).

\textbf{1.8.3 Arrhythmia management}\n
Management of AF was undertaken in a dedicated AF clinic independent of the weight management clinic. Usage of rate and rhythm control strategies was at the treating physician’s discretion. The drugs used for rhythm control include Sotalol or Flecaïnide. Amiodarone is not standardly used. Ablation was advocated in patients who remained symptomatic despite use of anti-arrhythmic drugs. The ablation technique utilized at our institution has been previously described and outlined in the supplement.\textsuperscript{29} AF was determined at least annually by clinical review, 12-lead electrocardiogram and 7-day Holter monitoring. In patients undergoing ablation, procedural success was
determined after a 3-month blanking period. AF was taken as any atrial arrhythmia \( \geq 30 \) seconds. The earliest date with documented AF was set as the date of arrhythmia recurrence.

### 1.8.4 Outcomes

Primary outcome was AF burden as determined by symptom burden and AF freedom. AF symptom burden was determined by the AF Severity Scale (AFSS, University of Toronto) that quantitates three domains of AF related symptoms: frequency, duration and severity.\(^\text{10}\) The AFSS has been clinically validated and used for assessment of AF burden.\(^\text{352, 362}\) Additionally, it provides a symptom subscale and global well-being score. The AFSS questionnaire was administered at baseline and final follow-up. AF freedom was determined with 7-day Holter monitoring. Secondary outcomes included structural parameters of left atrial volume and left ventricular wall thickness from echocardiographic studies.

### 1.8.5 Statistical Analysis

Categorical variables are represented by frequencies and percentages. Continuous variables are summarized by 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. Time-to-recurrence and event-free survival curves following the last ablation procedure were estimated by the Kaplan-Meier product-limit method. Differences between curves were tested with the log-rank test. Predictors of recurrent AF were assessed using proportional hazards Cox regression models. Candidate variables with
P<0.1 in univariate analyses were considered in multivariate regression models. Two-tailed P<0.05 was considered statistically significant. Statistical analysis was performed with SPSS version 21.0 (SPSS, Inc., Chicago, IL, USA).

1.9 Results

1.9.1 Baseline Characteristics
Of the 1415 consecutive patients with symptomatic AF, 825 patients had BMI≥27 kg/m2. After screening for exclusion criteria, the final cohort consisted 355 patients (Figure 1): 135 in Group-1 (>10% weight-loss), 103 in Group-2 (3-9% weight-loss) and 117 in Group-3 (<3% weight-loss). Baseline characteristics and follow-up duration (48.4±18.2, 46.0±16.7 and 48.3±18.4 months respectively, p=0.3) were similar for all groups (Table-1).

1.9.2 Weight-loss and maintenance
Weight change was greater in Group-1 than Group-2 and Group-3 (-16.0±3.0 vs. -6.0±0.4 vs. +2.0±1.0Kg respectively, p<0.001). This corresponded with higher participation in the dedicated weight management clinic (84% in Group-1 vs. 57% in Group-2 vs. 30% in Group-3, p<0.001). The weight-loss was largely durable over time with 66% (34 out of 52 patients) who lost >10% body weight in the first year maintaining their weight-loss at 34.5±15.5 months. Importantly, 85% of these patients attended the weight management clinic (p<0.001). In contrast, only 2 of the 18 patients that had regained weight after initial weight-loss >10% in the first year attended weight management clinic.
1.9.3 Effect of weight-loss on risk factor profile

Table-2 shows the impact of weight management on various cardiac risk factors.

**Blood Pressure Control:** There was a stepwise improvement in mean systolic BP with weight-loss (Group-1: -18.0±5.0 vs. Group-2: -10.0±3.0 vs. Group-3: -7.0±2.0 mmHg, p<0.001). This was despite reduced, unchanged and increased anti-hypertensive agents use in Group-1, Group-2 and Group-3 respectively (p=0.037).

**Lipid Management:** A greater reduction in LDL-C, triglyceride, and total cholesterol levels was seen in Group-1 compared to Group-2 and Group-3 (p<0.001) in conjunction with reduced use of lipid-lowering therapy (p=0.04).

**Glycemic Control:** Diabetic patients demonstrated improved glycemic control (HbA1c <7%) from Group-3 to Group-2 to Group-1 (p<0.001). This was in conjunction with a decrease in fasting insulin in Group-1 (p<0.001) and Group-2 (p=0.06) as opposed to an increased insulin level in Group-3 (p=0.03).

**Inflammation:** Patients in Group-1 and Group-2 demonstrated a decrease in mean hsCRP (p<0.001 and p=0.004 respectively) as opposed to increased hsCRP levels in Group-3 (p=0.001).

1.9.4 Effect of weight-loss on cardiac structure

Table-2 shows the effect of weight-loss on cardiac structure. Left atrial volume indexed for body surface area (LAVI) decreased significantly with weight-loss in Group-1 (p<0.001) and Group-2 (p<0.001), yet increased in Group-3 (p=0.02). Likewise, inter-ventricular septal (IVS) thickness decreased significantly with weight-loss in both
Group-1 (p=0.001) and Group-2 (p=0.03) but remained unchanged in Group-3 (p=0.33). A similar trend was seen in LV end-diastolic diameter (LVEDD) and E/E’ for Group-1 and Group-2 with subjects in Group-3 showing increasing E/E’ (p=0.001).

1.9.5 Effect of weight-loss on atrial fibrillation symptom burden
AF frequency, duration, symptom and symptom severity were improved in Group-1 and 2 as compared to Group-3 (p<0.001) (Table 2). The global well-being score improved by 5.9±0.9 in Group-1 and was higher than Group-2 and 3 (p<0.001).

1.9.6 Freedom from AF without the use of rhythm control strategies
Figure-2A demonstrates the “ablation and drug free” AF freedom. At final follow-up, 45.5% of Group-1; 22.2 % of Group-2 and 13.4 % of Group-3 (p<0.001) remained free from arrhythmia without antiarrhythmic drugs or ablation. Univariate predictors of AF recurrence were: Group (Compared to Group-1, Group-2: HR 1.8, 95% CI: 1.3-2.5; Group-3: HR 2.1, 95% CI: 1.6-3.0; p<0.001); inter-ventricular septal thickness (HR 0.44, 95% CI: 0.23-0.86; p=0.01); and E/E’ ratio (HR 1.4, 95% CI: 1.2-1.7; p<0.001). On multivariate analysis, Group (Group-2: HR 2.0, 95% CI: 1.4-2.9 and Group-3: HR 3.0, 95% CI: 2.0-4.3; p<0.001); IVS (HR 0.2, 95% CI: 1.1-2.1; p<0.001) and E/E’ ratio (HR 1.5, 95% CI: 1.2-1.9; p<0.001) remained independent predictors of AF recurrence.

1.9.7 Total Arrhythmia-free Survival
Figure-2B demonstrates the total arrhythmia-free survival with significant attrition in Group-3 compared to Group-1 and 2. At final follow-up, total arrhythmia-free survival rates was 86.2% in Group-1 compared to 65.5% in Group-2 and 39.6% in Group-3 (p<0.001). There was no difference in mean number of ablation procedures between the 3 groups (p=0.8). At final follow up, mean number of anti-arrhythmic drug use was
significantly lower in Group-1 compared to Group-2 and Group-3 (P<0.001). Univariate predictors of AF recurrence were: Group (Compared to Group-1, Group-2: HR 2.8, 95% CI: 1.5-5.2 and Group-3: HR 5.5, 95% CI: 3.1-9.6; p<0.001); diabetes (HR 1.6, 95% CI: 1.1-2.3; p=0.013); and current smoking status (HR 1.4, 95% CI: 1.0-2.1; p=0.048). On multivariate analysis, Group (Group-2: HR 3.1, 95%CI: 1.7-5.6; p<0.001 and Group-3: HR 5.9, 95% CI: 3.4-10.3; p<0.001) and history of diabetes (HR 1.8, 95% CI: 1.2-2.7; p=0.002) remained independent predictors of AF recurrence.

1.9.8 Effect of weight-loss trend
Of 355 patients, 141 had linear weight-loss, 24 linear weight gain and 179 had weight-fluctuation. 11 patients were excluded from analysis, due to missing yearly weight data. Figure-3A demonstrates total arrhythmia-free survival based on weight change trends. At final follow-up, 76% of patients with linear weight-loss remained arrhythmia-free (p<0.001). Weight-fluctuation offset some of the benefit conferred by weight-loss with 59% patients remaining free from AF. However, this remained higher than the no weight-loss or weight gain group where only 38% remained AF free (p<0.001).

1.9.9 Effect of weight fluctuation
Of 179 patients with weight-fluctuation during the annual follow-ups, 54 had ≤2%, 68 had 2-5% and 57 had >5% weight-fluctuation. Patients attending the dedicated weight management clinic had smaller weight-fluctuation: 69% of <2% group, 55% of 2-5% group and 30% of >5% weight-fluctuation group (p<0.001). Table-3 shows the impact of weight-fluctuation on various cardio-metabolic risk factors. More than 5% weight-fluctuation was associated with significantly increased requirement of anti-
hypertensive medication (p=0.04). Significantly lower systolic BP was seen in patients with <2% weight-fluctuation compared to 2-5% weight-fluctuation and >5% weight-fluctuation groups. Mean fasting insulin (p=0.01), hs-CRP level (p=0.05) and serum LDL-C (p<0.001) levels were significantly higher in patients with >5% weight-fluctuation. Similarly, >5% weight-fluctuation was associated with adverse impact on cardiac structural remodeling, with LAVI, IVS and LVEDD remaining largely unchanged compared to patients with <5% weight-fluctuation.

Figure 3B shows total arrhythmia-free survival based on degree of weight-fluctuation with a significant attrition seen with >5% compared to <5% weight-fluctuation. At final follow-up, 85.2% of patients with <2% weight-fluctuation; 59 % with 2-5% weight-fluctuation and 44 % with >5% (p<0.001) remained arrhythmia-free. After adjustment for baseline BMI, the effect of weight-fluctuation remained statistically significant for total AF recurrence (p=0.03). On multivariate analysis, >5% weight-fluctuation was associated with increased risk of AF recurrence when compared to <2% weight-fluctuation (HR 2.06, 95% CI 1.0-4.3; p =0.02).

1.10 Discussion

This study demonstrates that in over-weight and obese individuals with symptomatic AF, progressive weight-loss has a dose-dependent effect on long-term freedom from AF. Long-term weight-loss maintenance is achievable in these patients and associated with a six-fold greater freedom from AF. Notably, weight-fluctuation of >5% has an adverse effect on overall freedom from AF with a two-fold greater likelihood of recurrent arrhythmia. Weight-loss was also associated with beneficial structural remodeling including significant reductions in left atrial volumes and left ventricular
hypertrophy. Importantly, achieving and maintaining weight-loss was facilitated by a dedicated physician-led clinic that was focused on the management of weight and risk factors. These findings underscore the importance of treating underlying causative conditions when attempting to maintain sinus rhythm in obese AF patients.

Epidemiological data have shown an incremental risk of AF with progressive increase in BMI.\textsuperscript{33} Obesity is associated with structural and electrical remodeling of the atria that forms the substrate in the development and progression of AF.\textsuperscript{27,364} Weight-loss results in reversal of atrial dilation, left ventricular hypertrophy along with marked reduction of AF symptoms and arrhythmia burden.\textsuperscript{352} However, controversies exist regarding long-term sustainability of weight-loss.\textsuperscript{365} In the current study, progressive and linear weight-loss of >10% was associated with marked improvement in long-term freedom from AF. Indeed, 45.5% previously symptomatic AF patients no longer required anti-arrhythmic medications or ablation. In this study, 66% of the patients who lost >10% weight maintained the weight-loss at long-term follow-up. Notably, participation in dedicated weight management clinic was associated with higher weight-loss maintenance. These results highlight the central role of a dedicated weight management clinic in treating over-weight and obese patients with AF.

Our data provide a unique opportunity to ascertain the effect of weight-fluctuation during the weight-loss process. Our results revealed that >5% weight-fluctuation dampens the benefit conferred by weight-loss. This effect of weight-fluctuation on AF recurrence risk remained significant despite adjusting for baseline weight and accords with prior studies showing that weight-fluctuation is associated with increased risk of hypertension and diabetes, and elevations in other cardiometabolic traits.\textsuperscript{366-369} It is
pertinent to note that weight-fluctuation was significantly less in patients regularly attending a dedicated weight management clinic. Patient engagement and collaborative involvement improves treatment-plan adherence and persistence and may be “the forgotten piece” in the compliance puzzle.

It is probable that multiple mechanisms contribute to the impact of weight-loss on reduction of AF burden. Obesity clusters with other cardiovascular risk factors including impaired glucose tolerance, dyslipidemia, hypertension, and sleep apnea, all associated with an increased AF risk in the general population. Intentional weight-loss in obese patients systematically reduces these allied risk factors. In this study, we observed beneficial effects of weight-loss on BP, diabetic control, lipid profile and inflammation, all of which may have contributed to reduction in AF burden. Our prior work demonstrated that short-term weight-loss and other risk factor management resulted in reduction in AF burden. The current study demonstrates that these beneficial effects on AF burden persist during long-term follow up, is dose-dependent, but partially offset in the face of significant weight-fluctuation.

1.11 Study Limitation

This study has the potential for bias inherent to observational studies. However, measurement bias has been reduced through standardized processes in our clinic and the evaluation by operators blinded to the patient’s weight management regimen. AF burden assessment using 7 days holter may miss some AF episodes. However, this was utilized for AF freedom assessment in both the groups and was a limitation for all groups. Ascertainment bias was reduced through the routine collection of outcome
data. Importantly, the impact of weight-fluctuation on AF burden cannot be evaluated by a randomized design. Finally, weight loss results in improvement in various associated risk factors such as sleep apnea and BP. This study does not provide insight into the relative contribution of each risk factor.

### 1.12 CONCLUSION

Sustained weight-loss, particularly with avoidance of weight-fluctuation, is associated with a dose-dependent reduction in AF burden and maintenance of sinus rhythm. This occurs in conjunction with favorable changes in cardio-metabolic risk factor profile, inflammatory state and cardiac remodeling.
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<td>Hypertension, n (%)</td>
<td>109 (81%)</td>
<td>75 (73%)</td>
<td>90 (78%)</td>
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<tr>
<td>DM, n (%)</td>
<td>41 (30%)</td>
<td>28 (27%)</td>
<td>34 (29%)</td>
<td>0.35</td>
</tr>
<tr>
<td>IGT, n (%)</td>
<td>18 (13%)</td>
<td>8 (8%)</td>
<td>8 (7%)</td>
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<tr>
<td>Hyperlipidemia, n (%)</td>
<td>66 (49%)</td>
<td>45 (44%)</td>
<td>56 (48%)</td>
<td>0.70</td>
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<tr>
<td>Coronary artery disease, n (%)</td>
<td>21 (16%)</td>
<td>12 (12%)</td>
<td>11 (9%)</td>
<td>0.31</td>
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<tr>
<td>Valvulopathy, n (%)</td>
<td>8 (6%)</td>
<td>3 (3%)</td>
<td>8 (7%)</td>
<td>0.41</td>
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<tr>
<td>AHI&gt;30, n (%)</td>
<td>69 (51%)</td>
<td>52 (50%)</td>
<td>61 (52%)</td>
<td>0.97</td>
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<tr>
<td>Alcohol excess (&gt;30g/week), n (%)</td>
<td>42 (31%)</td>
<td>35 (34%)</td>
<td>34 (29%)</td>
<td>0.73</td>
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<tr>
<td>Smoker, n (%)</td>
<td>50 (37%)</td>
<td>41 (40%)</td>
<td>47 (40%)</td>
<td>0.86</td>
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<tr>
<td><strong>Medication Use</strong></td>
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<tr>
<td>Mean no. of Anti-Arrhythmic (±SD)</td>
<td>1.1±0.7</td>
<td>1.0±0.7</td>
<td>0.9±0.8</td>
<td>0.10</td>
</tr>
<tr>
<td>Mean no. of Anti-HTN (±SD)</td>
<td>1.0±0.9</td>
<td>1.0±0.8</td>
<td>1.1±1.0</td>
<td>0.08</td>
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**Serology and Lipid Profile**

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<tbody>
<tr>
<td>Mean hsCRP (mg/L)</td>
<td>5.1±9.2</td>
<td>4.4±5.8</td>
<td>4.1±2.9</td>
<td>0.70</td>
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<tr>
<td>Mean Fasting Insulin level (mU/L)</td>
<td>18.1±6.7</td>
<td>16.6±6.3</td>
<td>18.1±7.0</td>
<td>0.10</td>
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<tr>
<td>Mean LDL Level (mg/dL)</td>
<td>112±38</td>
<td>116±35</td>
<td>104±35</td>
<td>0.20</td>
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<tr>
<td>Mean HDL Level (mg/dL)</td>
<td>46±15</td>
<td>46±15</td>
<td>42±12</td>
<td>0.11</td>
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<tr>
<td>Mean TG Level (mg/dL)</td>
<td>141±62</td>
<td>141±53</td>
<td>141±62</td>
<td>0.78</td>
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<tr>
<td>Mean Total cholesterol (mg/dL)</td>
<td>189±37</td>
<td>185±42</td>
<td>181±42</td>
<td>0.50</td>
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</table>

**Echocardiographic Measures**

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<tbody>
<tr>
<td>LA Volume Indexed (mls/m²)</td>
<td>37.6±5.4</td>
<td>38.5±6.2</td>
<td>39.0±3.8</td>
<td>0.20</td>
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<tr>
<td>LV IVS (mm)</td>
<td>11.7±2.0</td>
<td>11.5±2.0</td>
<td>11.5±2.0</td>
<td>0.24</td>
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<tr>
<td>LVEDD (cm)</td>
<td>5.0±0.6</td>
<td>5.0±0.6</td>
<td>5.0±0.6</td>
<td>0.92</td>
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<td>E/E' ratio</td>
<td>12.7±4.2</td>
<td>12.0±4.6</td>
<td>11.3±3.7</td>
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**Atrial Fibrillation Severity Scale (AFSS)**

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<tbody>
<tr>
<td>Frequency [1-10]</td>
<td>7.0±1.6</td>
<td>7.0±1.3</td>
<td>7.0±1.7</td>
<td>0.97</td>
</tr>
<tr>
<td>Duration [1-10]</td>
<td>7.1±1.8</td>
<td>6.7±1.8</td>
<td>6.9±1.7</td>
<td>0.21</td>
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<td>Severity [1-10]</td>
<td>7.0±1.9</td>
<td>7.1±1.5</td>
<td>6.8±1.5</td>
<td>0.50</td>
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<tr>
<td>Symptom [0-35]</td>
<td>19.0±5.9</td>
<td>18.1±4.9</td>
<td>17.7±5.6</td>
<td>0.19</td>
</tr>
<tr>
<td>Global well-being (1-10)</td>
<td>2.7±0.8</td>
<td>2.4±0.9</td>
<td>2.5±0.9</td>
<td>0.4</td>
</tr>
</tbody>
</table>

WL: Weight-loss; BMI: Body Mass Index; SBP: Systolic Blood Pressure; DM: Diabetes Mellitus; IGT: Impaired glucose tolerance; AHI: Apnea Hypopnea Index; hsCRP: High sensitive C reactive Protein; TG: Triglyceride; LA Left atrium; LV IVS: Left Ventricular Inter ventricular septum; LVEDD: Left Ventricular End Diastolic Diameter.
Table 2-2: Impact of weight loss on cardiac risk factors, cardiac structure and AF severity

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>&gt;10%WL Group; N = 135</th>
<th>3-9% WL Group; N = 103</th>
<th>&lt;3%WL Group; N = 117</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow Up‡</td>
<td>P value*</td>
<td>Baseline</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>101±17</td>
<td>85±14</td>
<td>&lt;0.001</td>
<td>99±16</td>
</tr>
<tr>
<td>BMI (Kgm⁻²)</td>
<td>33.7±4.7</td>
<td>28.4±4.0</td>
<td>&lt;0.001</td>
<td>32.7±4.4</td>
</tr>
<tr>
<td>Mean SBP (mmHg)</td>
<td>147±17</td>
<td>129±12</td>
<td>&lt;0.001</td>
<td>144±17</td>
</tr>
<tr>
<td>DM with HbA1c≥7, n (%)</td>
<td>40 (30)</td>
<td>5 (4)</td>
<td>-</td>
<td>28 (27%)</td>
</tr>
</tbody>
</table>

Medication Use

| Mean no. of Anti-HTN, n  | 1.0±0.9  | 0.5±0.6  | <0.001   | 0.7±0.8  | 0.7±0.6   | 0.74     | 0.8±1.0  | 1.0±0.7    | 0.01     | <0.001   |
| N on Lipid Rx n (%)      | 66 (49)  | 37 (27)  | -        | 45 (44)  | 38 (37)   | -        | 56 (48)  | 54 (46)    | -        | <0.001   |
| Mean no. of AAD, n       | 1.1±0.7  | 0.1±0.4  | <0.001   | 1.0±0.7  | 0.5±0.6   | <0.001   | 0.8±0.8  | 0.4±0.6    | <0.001   | <0.001   |

Serology and Lipid Profile

<p>| Mean hsCRP (mg/L)        | 5.1±9.2  | 1.2±2.4  | &lt;0.001   | 4.4±5.8  | 2.7±3.2   | 0.004    | 4.1±2.9  | 4.9±5.0    | 0.001    | &lt;0.001   |
| Mean Fasting Insulin (mU/L) | 18.3±6.6 | 8.4±3.9  | &lt;0.001   | 16.9±6.1 | 14.8±9.4  | 0.06     | 14.5±6.9 | 17.3±9.6   | 0.03     | &lt;0.001   |
| Mean LDL Level (mg/dL)   | 116±37   | 89±31    | &lt;0.001   | 116±35   | 93±23     | &lt;0.001   | 104±35   | 108±31     | 0.05     | &lt;0.001   |</p>
<table>
<thead>
<tr>
<th></th>
<th>Mean HDL Level (mg/dL)</th>
<th>Mean TG Level (mg/dL)</th>
<th>Mean Total cholesterol (mg/dL)</th>
<th>Echocardiogram</th>
<th>AF symptom Score</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>50±15</td>
<td>141±62</td>
<td>189±38</td>
<td>Indexed LA Volume (ml/m²)</td>
<td>AF frequency [1-10]</td>
</tr>
<tr>
<td></td>
<td>58±15</td>
<td>97±35</td>
<td>158±35</td>
<td>37.6±5.4</td>
<td>7.0±1.5</td>
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<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>30.9±6.4</td>
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<td>46±11</td>
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<td>50±11</td>
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<td>46±11</td>
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<td>178±35</td>
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<td>AF duration [1.25-10]</td>
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<td>10.1±0.7</td>
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<td>LVEDD (cm)</td>
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<td>11.1±4.9</td>
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<td>18.2±5.1</td>
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<td>13.6±4.4</td>
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<td>Global well-being (1-10)</td>
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<td>2.7±0.8</td>
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<td>8.1±1.2</td>
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<td>2.5±0.9</td>
<td>5.7±2.0</td>
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<td></td>
<td>0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>
*P value refers to within group difference (baseline to follow-up); †P value refers to between group differences over time (group-time interaction). ‡Median follow-up: 48.4±18.2 months for Group-1 and 46.0±16.7 months for Group-2 and 48.3±18.4 months for Group-3.

WL: Weight-loss; BMI: Body Mass Index; SBP: Systolic Blood Pressure; DM: Diabetes Mellitus; IGT: Impaired glucose tolerance; AHI: Apnea Hypopnea Index; hsCRP: High sensitive C reactive Protein; TG: Triglyceride; LA Left atrium; LV IVS: Left Ventricular Inter ventricular septum; LVEDD: Left Ventricular End Diastolic Diameter.
Table 2-3: Impact of weight fluctuation on cardiac risk factors and cardiac structure

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>&lt;2%WF Group; N = 54</th>
<th>2-5% WF Group; N = 68</th>
<th>&gt;5%WF Group; N = 57</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow Up‡</td>
<td>P value*</td>
<td>Baseline</td>
</tr>
<tr>
<td><strong>BMI (Kgm⁻²)</strong></td>
<td>32.6±4.7</td>
<td>29.2±4.8</td>
<td>&lt;0.001</td>
<td>33.3±3.9</td>
</tr>
<tr>
<td>Mean SBP (mmHg)</td>
<td>147±21</td>
<td>130±14</td>
<td>&lt;0.001</td>
<td>146±17</td>
</tr>
<tr>
<td>DM with HbA1c≥7, N (%)</td>
<td>16 (29)</td>
<td>4 (7)</td>
<td>-</td>
<td>18 (26)</td>
</tr>
<tr>
<td></td>
<td>32.3±4.0</td>
<td>31.8±4.8</td>
<td>0.10</td>
<td>146±16</td>
</tr>
<tr>
<td></td>
<td>33.3±3.9</td>
<td>30.9±4.5</td>
<td>&lt;0.001</td>
<td>146±17</td>
</tr>
<tr>
<td></td>
<td>29.3±3.9</td>
<td>26.9±4.5</td>
<td>&lt;0.001</td>
<td>146±16</td>
</tr>
<tr>
<td></td>
<td>32.3±4.0</td>
<td>31.8±4.8</td>
<td>0.10</td>
<td>146±17</td>
</tr>
<tr>
<td></td>
<td>33.3±3.9</td>
<td>30.9±4.5</td>
<td>&lt;0.001</td>
<td>146±17</td>
</tr>
<tr>
<td><strong>Medication Use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean no of Anti-HTN ± SD</td>
<td>1.0±0.8</td>
<td>0.6±0.6</td>
<td>0.04</td>
<td>1.0±0.9</td>
</tr>
<tr>
<td>Mean no. of AA ± SD</td>
<td>1.0±0.8</td>
<td>0.4±0.6</td>
<td>&lt;0.001</td>
<td>1.2±0.7</td>
</tr>
<tr>
<td>Mean HsCRP (mg/L)</td>
<td>3.4±3.5</td>
<td>1.6±2.3</td>
<td>0.001</td>
<td>5.5±11.6</td>
</tr>
<tr>
<td>Mean Fasting Insulin level(mU/L)</td>
<td>17.7±7.7</td>
<td>12.5±9.5</td>
<td>0.08</td>
<td>17.4±5.6</td>
</tr>
<tr>
<td>Mean LDL Level (mg/dL)</td>
<td>108±31</td>
<td>89±23</td>
<td>&lt;0.001</td>
<td>116±35</td>
</tr>
<tr>
<td>Mean HDL Level (mg/dL)</td>
<td>46±11</td>
<td>54±15</td>
<td>&lt;0.001</td>
<td>46±15</td>
</tr>
<tr>
<td>Mean TG Level (mg/dL)</td>
<td>133±53</td>
<td>106±44</td>
<td>&lt;0.001</td>
<td>141±53</td>
</tr>
<tr>
<td>Mean Total cholesterol (mg/dL)</td>
<td>185±35</td>
<td>162±31</td>
<td>&lt;0.001</td>
<td>189±35</td>
</tr>
<tr>
<td></td>
<td>178±46</td>
<td>174±35</td>
<td>0.21</td>
<td>178±46</td>
</tr>
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</table>
### Echocardiogram

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
<th>Group 6</th>
<th>Group 7</th>
<th>Group 8</th>
<th>Group 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indexed LA Volume (ml/m^3)</td>
<td>37.4±4.9</td>
<td>32.2±7.2</td>
<td>&lt;0.001</td>
<td>38.4±4.3</td>
<td>33.8±8.0</td>
<td>&lt;0.001</td>
<td>39.2±4.2</td>
<td>39.8±6.5</td>
<td>0.55</td>
</tr>
<tr>
<td>IV Septum (mm)</td>
<td>12.0±2.0</td>
<td>11.1±1.2</td>
<td>&lt;0.001</td>
<td>11.5±2.0</td>
<td>11.0±2.0</td>
<td>0.01</td>
<td>11.4±2.0</td>
<td>11.2±2.0</td>
<td>0.59</td>
</tr>
<tr>
<td>LVEDD (cm)</td>
<td>4.9±0.6</td>
<td>4.7±0.7</td>
<td>0.05</td>
<td>4.9±0.5</td>
<td>4.7±0.7</td>
<td>0.05</td>
<td>5.0±0.6</td>
<td>5.0±0.6</td>
<td>0.71</td>
</tr>
<tr>
<td>Lateral E/E' ratio</td>
<td>11.9±3.5</td>
<td>9.4±3.8</td>
<td>&lt;0.001</td>
<td>12.5±4.0</td>
<td>10.4±4.8</td>
<td>0.01</td>
<td>12.1±3.9</td>
<td>12.7±5.2</td>
<td>0.42</td>
</tr>
</tbody>
</table>

*P value refers to within group difference (baseline to follow-up); †P value refers to between group differences over time (group-time interaction). ‡ Median follow-up: 48.4±18.2 months for Group-1 and 46.0±16.7 months for Group-2 and 48.3±18.4 months for Group-3.

WF: Weight-Fluctuation; BMI: Body Mass Index; SBP: Systolic Blood Pressure; DM: Diabetes Mellitus; IGT: Impaired glucose tolerance; AHI: Apnea Hypopnea Index; hsCRP: High sensitive C reactive Protein; TG: Triglyceride; LA Left atrium; LV IVS: Left Ventricular Inter ventricular septum; LVEDD: Left Ventricular End Diastolic Diameter
Figure 2-1: Flow diagram demonstrating patient recruitment and attrition

Assessed for Eligibility N=1415

Patients with BMI ≥ 27 N=825

Final Cohort N=355

Met Exclusion Criteria (N=293)
Terminal Cancer (N=10)
Inflammatory Dx (N=20)
Permanent AF (N=84)
AV Node ablation (N=12)
AF ablation (N=90)
Severe Medical Illness (N=77)

Patients from other states (N=177)

Total Weight at Final Follow up

<3%WL or WG N=117
3-9%WL N=103
10%WL N=135

Yearly Weight Trend

Linear Weight Loss N=141
Weight Fluctuation N=179
No Loss or Linear Gain N=24

<2%WF N=54
2-5%WF N=68
>5%WF N=57

Patients

N=1415

N=825

N=355

<3%WL or WG

3-9%WL

10%WL

<2%WF

2-5%WF

>5%WF

Terminal Cancer
Inflammatory Dx
Permanent AF
AV Node ablation
AF ablation
Severe Medical Illness

Patients from other states

N=177

N=293

N=293

N=355

N=117

N=103

N=135

N=24

N=141

N=179

N=24

N=57

N=54

N=68

N=57
Figure 2-2: AF Freedom outcome according to group

A: Kaplan-Meier Curve for AF free survival without the use of rhythm control strategies.

B: Kaplan-Meier Curve for AF free survival for total AF free survival (Multiple ablation procedures ± drugs; right).
Figure 2-3: Outcomes of AF freedom according to weight trend and weight fluctuation

A: Kaplan-Meier Curve for total AF free survival (Multiple ablation procedures ± drugs) according to weight trend.

B: Kaplan-Meier Curve for total AF free survival (Multiple ablation procedures ± drugs) according to weight fluctuation.
Figure 2-4: Schematic of the process

**Substrate Modification**

**Weight Loss (WL)**
- Dose Effect
- Improved metabolic profile
- Improved structural remodelling

**Progressive Atrial Substrate**

**AF**

**Substrate Progression**

**Weight Fluctuation (WF)**
- Dose Effect
- Worsen metabolic profile
- Retrogress structural remodelling

Impact of weight loss on 5-years AF freedom without any rhythm control strategies:
- <3% WL: 13%
- 3-9% WL: 23%
- ≥10% WL: 46%

Impact of weight fluctuation on 5-years total AF freedom:
- Weight Gain: 38%
- Weight Fluctuation: 50%
- Linear WL Loss: 76%
Chapter 3: Impact of CARDIOrespiratory FITness on Arrhythmia Recurrence in Obese Individuals with Atrial Fibrillation: The CARDIO-FIT Study

1.13 Background

Atrial fibrillation (AF) is a growing epidemic affecting approximately 33.5 million individuals worldwide.\textsuperscript{1,378} Cardiac risk factors such as obesity are associated with increased risk of AF and could explain this rising epidemic.\textsuperscript{32} A variety of lifestyle factors, including the lack of physical activity, are associated with increased incidence of obesity.\textsuperscript{379}

Lifestyle modification with weight-loss has been shown to reduce the burden of AF.\textsuperscript{352} In LEGACY study, progressive weight loss had a dose dependent effect on long-term freedom from AF.\textsuperscript{380} Increased physical activity to enhance cardiorespiratory fitness is an integral component of the lifestyle modification. Cardiorespiratory fitness is an independent predictor of cardiovascular outcome and mortality.\textsuperscript{381} Recent studies have found an inverse relationship between increased physical activity and the risk of incident AF.\textsuperscript{382,383} The impact of cardiorespiratory fitness on risk of AF recurrence has not been examined previously. Furthermore, longitudinal improvement in cardiorespiratory fitness is associated with a lower risk of both all-cause and cardiovascular mortality.\textsuperscript{384} However, the impact of cardiorespiratory fitness gain with a graded exercise program along with weight-loss on AF outcome remains unclear and is largely neglected as a therapeutic target.
We hypothesize that preserved cardiorespiratory fitness at baseline in obese AF patients, offsets some of the detrimental effects of obesity and that gain in cardiorespiratory fitness through a structured exercise program has synergistic effect with weight-loss on overall freedom from AF (Clinical Trial Registration: ACTRN12614001123639).

1.14 Methods

1.14.1 Study Population
The study comprised patients referred for management of symptomatic paroxysmal or persistent AF to the Centre for Heart Rhythm Disorders at the University of Adelaide, Adelaide, Australia. All patients with a body mass index (BMI) ≥27kg/m² and undergoing an exercise stress test at baseline were included in this analysis. Exclusion criteria were: permanent AF; history of myocardial infarction or cardiac surgery in the previous 12-months; active malignancy; autoimmune or systemic inflammatory diseases; severe renal or hepatic failure; left ventricular ejection fraction <40%; pacemaker in-situ and <24-months follow-up. In addition, patients who were in AF or could not perform exercise stress test due to neuromuscular or musculoskeletal problems were excluded.

All patients provided written informed consent. The Human Research Ethics Committee of the Royal Adelaide Hospital and University of Adelaide approved the study protocol.
1.14.2 Study Protocol and Design

1.14.2.1 Weight and Risk Factor Management
All patients were offered attendance at a dedicated physician led risk factor management clinic at the time of initial assessment. The weight and risk factor management protocol used in our service have been presented previously. In brief, a structured motivational, individualized, goal-directed program using face-to-face counselling was used for initiating and reinforcing graded exercise therapy along with weight reduction. Initial weight-loss was attempted by a meal plan and behaviour modification. Meals consisted of high protein and low glycemic index, calorie controlled foods. Hypertension, glucose intolerance, dyslipidaemia, sleep apnoea, alcohol and tobacco use were screened for and managed individually according to AHA/ACC guidelines. Changes in metabolic (lipid profile and fasting insulin) and inflammatory state (hsCRP) levels were monitored.

1.14.2.2 Exercise Program
Patients were recommended structured physical activity according to AHA guidelines. Baseline exercise stress test was utilized to ascertain their cardiorespiratory fitness. Subsequently, a tailored exercise program was designed in which consideration for age and physical ability was made so that targets were achievable without risking injuries. F.I.T.T principle (Frequency, Intensity, Time (duration) and Type of exercise) was utilized to design combination of aerobic and resistance/strength exercises for progressive fitness gain to avoid weight plateaus. Low intensity exercise was prescribed initially for 20-minutes thrice-weekly increasing to at least 200-minutes of moderate-intensity exercise per week. For patients with decreased mobility due to weight and or musculoskeletal problems, hydrotherapy,
aqua aerobics, upper body training and physiotherapy sessions were initially utilized. Participants were advised to use wearable heart rate monitor and required to maintain a diet and physical activity diary to log exercise type, frequency, intensity and duration. Calculated maximum heart rate (220-Age), patients were advised to avoid reaching heart rate higher than 85% of the maximum predicted heart rate.

1.14.2.3 Assessment of Cardiorespiratory Fitness
Cardiorespiratory fitness was evaluated in gender-specific metabolic equivalents (METs), estimated from a symptom-limited maximal treadmill exercise test using the standard Bruce protocol at baseline and final follow up. The test time using this protocol on the treadmill was recorded. If patients only achieved a fraction of the stage of exercise, credit for exercise capacity was “pro-rated”. Test time was then utilized to calculate METs. Age and gender predicted peak METs were calculated using St. James model (METs = 14.7 - [0.13 x age]) for women and Veterans Affairs referral model (METs = 18 - [0.15 x age]) for men.

1.14.3 Definitions
Baseline Cardiorespiratory Fitness Definition: Study patients were subsequently categorized according to baseline cardiorespiratory fitness into low (<85% Predicted METs), adequate (86-100% Predicted METs), and high (>100% Predicted METs) cardiorespiratory fitness groups.
**Cardiorespiratory Fitness Gain Definition:** To investigate the change in cardiorespiratory fitness on AF outcome we dichotomized fitness gain into METs Gain ≥2 and METs gain <2 at final follow up.

**Weight Loss and Cardiorespiratory Fitness Gain Interaction:** We have previously demonstrated effect of weight-loss on AF outcome.\(^{380}\) As previously presented, no weight-loss was defined as <3% weight-loss and significant weight-loss as ≥10% weight-loss. To investigate the interaction between weight-loss and METs gain we divided patients into Group-1 (<10% weight-loss & <2 METs gain), Group-2 (<10% weight-loss and ≥2 METs gain), Group-3 (≥10% weight-loss and <2 METs gain) and Group-4 (≥10% weight-loss and ≥2 METs gain).

### 1.14.4 Arrhythmia Management

Management of AF was undertaken in a separate arrhythmia clinic. The use of rate and rhythm control strategies was at the discretion of the treating physician. In patients who remained symptomatic despite the use of anti-arrhythmic agents, AF ablation was offered. The ablation technique utilized at our institution has been previously described and is outlined in the supplement.\(^{29}\) AF was determined at least annually by clinical review, 12-lead electrocardiogram and 7-day Holter monitoring. In patients undergoing ablation, procedural success was determined after a 3-month blanking period. AF was taken as any atrial arrhythmia ≥30 seconds. If patients developed recurrent arrhythmia after the blanking period (3-months), repeat ablation was offered. The earliest date with documented AF was set as the date of arrhythmia recurrence. Only confirmed events were included in the analyses. All patients were anticoagulated if the CHADS\(_2\) score >1.
Cardiac structural parameters were monitored by serial echocardiographic examinations. All echocardiographic and rhythm evaluations are detailed in the supplement and were performed by operators blinded to the patient’s weight and fitness management regimen.

1.14.5 Outcomes
The primary outcome was AF burden as determined by symptom burden and freedom from AF. AF symptom burden was determined by the AF Severity Scale (AFSS, University of Toronto) that quantitates three domains of AF related symptoms: frequency, duration and severity. The AFSS has been clinically validated and used for assessment of AF burden.

In addition, it provides a symptom subscale and global well-being score. The AFSS questionnaire was administered at baseline and final follow-up. Freedom from AF was ascertained with 7-day Holter monitoring. Secondary outcomes included structural parameters of left atrial volume, left ventricular wall thickness and diastolic function from echocardiographic studies.

1.14.6 Statistical Analysis
Categorical variables are represented by frequencies and percentages. Continuous variables are summarized by mean±SD. The differences in baseline characteristics between groups were assessed using ANOVA procedures for continuous variables and chi-squared for categorical variables. 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. Time-to-recurrence and event-free survival curves following the last ablation procedure were estimated by the Kaplan-Meier product-limit method. Differences between curves were tested with the
log-rank test. Predictors of recurrent AF were assessed using proportional hazards Cox regression models. Candidate variables with P<0.1 in univariate analyses were considered in multivariate regression models. Two-tailed P<0.05 was considered statistically significant. Statistical analysis was performed with SPSS version 21.0 (SPSS, Inc., Chicago, IL, USA).

1.15 Results

Of 1415 patients with symptomatic AF, 825 had a BMI ≥27 Kg/m². Only patients who did not meet exclusion criteria, had regular follow up and underwent stress testing were included in the analysis. Patients were excluded for: pre-defined criteria (n=303); interstate patients (n=177); premature termination of test due to musculoskeletal problem (n=8); beta-blocker or calcium channel blocker use on the day of procedure (n=16); or those with AF on the exercise stress test (n=13) (Figure 1). The final cohort included 308 patients with a mean follow-up of 49±19 months.

1.15.1 Baseline Cardiorespiratory Fitness

The characteristics of each group are shown in Table-1. 95 patients had low, 134 had adequate and 79 had high cardiorespiratory fitness at baseline. Mean MET achieved in low cardiorespiratory fitness was 5.2±1.6, adequate cardiorespiratory fitness 7.9±1.6 and high cardiorespiratory fitness group was 8.8±1.7 (p=0.008). Mean duration of follow up was 47±18.3, 48±17 and 48.2±18 months respectively (p=0.8).
1.15.2 Effect of Baseline Cardiorespiratory Fitness on AF outcomes

1.15.2.1 Freedom from AF without the use of rhythm control strategies

Figure-2A demonstrates the “ablation and drug free” AF freedom. At final follow-up, 12% of low; 35 % of adequate and 66% of high cardiorespiratory fitness group (p<0.001) remained free from arrhythmia without antiarrhythmic drugs or ablation. Univariate predictors of AF recurrence were: cardiorespiratory fitness group (p<0.001), no weight-loss (p=0.001) and left ventricular hypertrophy (p=0.05). On multivariable analysis, cardiorespiratory fitness group (Compared to high cardiorespiratory fitness group, low cardiorespiratory fitness: HR 2.75, 95% CI: 1.61-4.68 and adequate cardiorespiratory fitness: HR 1.89, 95% CI: 1.14-3.12; p=0.001), no weight-loss (HR 2.95, 95% CI: 1.8-4.8) remained an independent predictor of AF recurrence. Each unit increase in MET of baseline cardiorespiratory fitness, was associated with a 13% decline in the risk of AF recurrence (HR 0.87, 95% CI: 0.80-0.94; p<0.001) even after adjusting for weight-loss during follow-up.

1.15.2.2 Total Arrhythmia-free Survival

Figure-2B demonstrates the total arrhythmia-free survival with significant attrition in the low cardiorespiratory fitness group compared to adequate and high cardiorespiratory fitness groups. At final follow-up, total arrhythmia-free survival rates was 17% in low; 76 % in adequate and 84% in high cardiorespiratory fitness groups (p<0.001). Univariate predictors of AF recurrence were: cardiorespiratory fitness group (p<0.001), no weight-loss (p<0.001), diabetes mellitus (p=0.01) and smoking status (p=0.04). On multivariable analysis, low cardiorespiratory fitness, but not adequate
cardiorespiratory fitness (Compared to high cardiorespiratory fitness Group, low cardiorespiratory fitness: HR 5.94, 95% CI: 3.15-11.23; p<0.001 and adequate cardiorespiratory fitness: HR 1.17, 95% CI: 0.60-2.26; p<0.65) and no weight-loss (HR 3.64, 95% CI: 1.95-6.76) remained an independent predictor of AF recurrence. For cardiorespiratory fitness expressed as a continuous variable, even after adjusting for weight-loss during follow-up, there was a 20% reduction in total arrhythmia recurrence for each additional MET achieved during baseline cardiorespiratory fitness assessment (HR 0.80, 95% CI: 0.74-0.87; P<0.001).

1.15.3 Cardiorespiratory Fitness Gain
Cardiorespiratory fitness gain was 2.9±0.9 versus 0.5±1.4 MET in the ≥2 MET and <2 MET gain groups, respectively (p<0.001). This corresponded with higher participation in the dedicated risk factor management clinic (83% in ≥2 MET gain versus 39% in < 2 MET gain group p<0.001). The characteristics of both groups are shown in Table-2.

1.15.3.1 Effect of Cardiorespiratory Fitness Gain on risk factor profile
Table-3 shows the impact of cardiorespiratory fitness gain on various cardiac risk factors.

Weight Loss: Weight decreased in both groups, but significantly more in patients who gained ≥2 METs compared to those with <2 MET gain (-12±8.8 versus -3±7.6 kg; p=0.001). Additionally, ≥2 METs gain group had more sustained weight-loss compared to <2 MET gain group (54% versus 46%, p=0.006) and less patients fluctuated >5% in their weight during the yearly follow up (37% versus 63% p=0.001).
Blood Pressure Control: There was a greater decline in systolic BP in patients who gained ≥2 METs compared to those with a <2 MET gain (14±16.4 versus 10±18mmHg; p=0.05). Number of anti-hypertensive agents used for BP control decreased in patients with ≥2 MET gain (0.8±0.8 to 0.5±0.5; p=0.01) and remained unchanged in those with <2 MET gain (0.8±1.0 to 0.9±0.7; p=0.2).

Lipid Profile: At baseline, 46% of the ≥2 MET and 48% of the <2 MET gain groups had dyslipidaemia (p=0.7). Drug therapy was required in 29% and 35% of patients in each group, respectively (p<0.001). Both LDL-C and plasma triglycerides declined significantly in patients who gained ≥2 METs (p<0.001) but did not differ in those with <2 MET gain.

Glycemic Control: At baseline, 29% of ≥2 MET and 25% of <2 MET gain groups had history of DM (p=0.8). At final follow up, DM patients in ≥2 MET had significantly better glycemic control compared to <2 MET gain group (HbA1c < 7% in 12% versus 3%, respectively; p=0.001).

Inflammation: Patients with ≥2 MET gain demonstrated a decrease in mean hsCRP (p<0.001) from baseline to follow-up. There was no change in hsCRP in patients with <2 MET gain (p=0.8).

1.15.3.2 Effect of Cardiorespiratory Fitness Gain on Cardiac Structure
Table-3 shows the effect of cardiorespiratory fitness Gain on cardiac structure. Left atrial volume indexed for body surface area (LAVI) decreased significantly in both groups. There was a greater decline in LAVI with ≥2 MET gain (p<0.001). A similar trend
was seen in left ventricular end-diastolic diameter (LVEDD), where ≥2 MET gain corresponded to greater reductions in LVEDD. Lateral E/E’ declined in patients with ≥2 MET gain but did not change in the <2 MET gain group.

1.15.3.3 Effect of Cardiorespiratory Fitness Gain on Atrial Fibrillation Symptom Burden

At baseline, both groups had comparable and high AFSS subscale scores (Table-3). AF frequency, duration, symptom and symptom severity were reduced at final follow up in both groups with a significantly greater reduction seen in the ≥2 MET gain group (p<0.001).

1.15.3.4 Freedom from AF without the use of rhythm control strategies

Figure-3A demonstrates the “ablation and drug free” AF freedom based on MET gain groups. At final follow-up, 61% of patients who gained ≥2 METs remained free from arrhythmia without antiarrhythmic drugs or ablation, compared to 18% of patients in <2 MET gain group. Change in cardiorespiratory fitness was a significant univariate predictor of AF recurrence (p<0.001). On multivariable analysis, <2 METs gain (HR 2.1, 95% CI: 1.3-3.3; p=0.001); no weight-loss (HR 1.7, 95% CI: 1.0-3.1; p=0.005) and low baseline cardiorespiratory fitness (HR 2.7, 95% CI: 1.57-4.52; P<0.001) remained independent predictors of AF recurrence. As a continuous variable, every METs gained from baseline to follow-up was associated with a 9% decline in the risk of arrhythmia recurrence even after adjustment for weight-loss and baseline cardiorespiratory fitness (HR per 1-MET change 0.90, 95% CI: 0.83-1.00; p=0.036).
1.15.3.5 Total Arrhythmia-free Survival

Figure-3B demonstrates the total arrhythmia-free survival for the two groups. At final follow-up, patients who gained ≥2 METs had higher arrhythmia-free survival rates compared to patients who gained <2 METs (89% versus 40%; p<0.001). Change in cardiorespiratory fitness was a significant univariate predictor of AF recurrence (p<0.001). On multivariable analysis, <2 MET gain (HR 3.9, 95% CI: 2.1-7.3 P<0.001); no weight-loss (HR 1.9, 95% CI: 1.1-3.70; P=0.008); low baseline cardiorespiratory fitness (HR 5.12, 95% CI: 2.67-9.84; p<0.001) and diabetes mellitus (HR 1.77, 95% CI: 1.2-2.6; p=0.003) remained independent predictors of AF recurrence. As a continuous variable, every METs gained from baseline to follow-up was associated with a 12% decline in the risk of total arrhythmia recurrence after multivariate adjustment (HR: 1-MET change 0.88, 95% CI: 0.80-0.96; p=0.005).

1.15.4 Weight-Loss and Cardiorespiratory Fitness Gain Interaction: Synergistic Effect

152 patients had <10% weight-loss and <2 MET Gain (Group-1), 49 had <10% weight-loss and ≥2 MET Gain (Group-2), 29 had ≥10 % weight-loss with <2 MET gain (Group-3) and 78 Patients had ≥10% weight-loss with ≥2 MET Gain (Group-4). Cardiorespiratory fitness gain provides additional benefit above that conferred by weight-loss alone. Figure 4A demonstrates the “ablation and drug free” AF freedom for the 4 groups. At final follow-up, 13.2% in Group-1, 36.7 % of Group 2, 44.8 % of Group 3 and 75.6% of Group 4 (p<0.001) remained free from arrhythmia without antiarrhythmic drugs or ablation. Figure 4B demonstrates the total arrhythmia-free survival for the 4 groups. At
final follow-up, 34% in Group-1, 69% of Group 2, 81% of Group 3 and 94% of Group 4 (p<0.001) remained free from arrhythmia.

1.16 DISCUSSION

This study demonstrates that in overweight and obese individuals with symptomatic AF, preserved baseline cardiorespiratory fitness predicts long-term freedom from AF. We found a significant dose-response relationship between baseline cardiorespiratory fitness with a 20% reduction in the risk of AF recurrence for each MET increase in baseline cardiorespiratory fitness. Cardiorespiratory fitness gain with a structured exercise program has an additive effect to weight-loss in improving the long-term outcome of AF. MET gain in cardiorespiratory fitness ≥2 on top of weight-loss was associated with 2-fold greater freedom from AF. Specifically, participation in a dedicated risk factor management clinic was associated with increased cardiorespiratory fitness gain. These findings highlight the prescriptive role of exercise in managing patients with AF, particularly as a strategy for rhythm control.

Several population-based studies have demonstrated a robust relationship between obesity and AF.32 Modifiers of this association such as weight-loss have been shown to reduce AF recurrence.362, 380 Physical activity has previously been suggested to mitigate some of the cardiovascular hazards associated with excess body weight.388, 389 However, the relationship between physical activity and AF is highly contentious.389, 390 This is mostly based on the results from population based longitudinal studies with self-reported data.389, 391 Recent studies have suggested that increased leisure time
physical activity may be protective against AF even in the presence of obesity.\textsuperscript{382, 392} In the current study, we used objective measures of cardiorespiratory fitness to demonstrate the prognostic benefits in patients with symptomatic AF. This remains significant even after adjustment for change in BMI observed throughout the follow-up. Our results suggest that cardiorespiratory fitness may partially offset the adverse effects of obesity.

Few studies have examined the role of exercise training per se on arrhythmia burden in those with symptomatic AF. Short-term exercise intervention has been shown to improve health-related quality of life and exercise capacity in patients with permanent AF.\textsuperscript{393, 394} In the present study, gain in cardiorespiratory fitness (≥2 MET) was associated with reduction in AF burden marked improvement in long-term freedom from AF. Indeed, 61% previously symptomatic AF patients no longer required anti-arrhythmic medications or ablation. We observed a 9% gain in long-term freedom from AF for each unit gain in MET. This gain is independent from the benefit conferred by the weight-loss alone in these patients. The seminal finding that the change in cardiorespiratory fitness over a follow-up period reduces AF recurrence supports a possible role for the prescription of exercise in this cohort. Notably, participation in dedicated risk factor management clinic was associated with greater increase in cardiorespiratory fitness.

Obesity is associated with various electrical and structural remodeling leading to genesis and perpetuation of AF.\textsuperscript{27, 395, 396} Our prior work demonstrated that weight-loss has a beneficial effect on cardiac risk factors and structural remodeling.\textsuperscript{380} In this study, we have found an additive effect of cardiorespiratory fitness over weight-loss. It
is probable that common mechanisms contribute to this synergistic effect of cardiorespiratory fitness on reduction of AF burden. Regular exercise has been shown to improve autonomic function,\textsuperscript{397} blood pressure (BP),\textsuperscript{398} insulin sensitivity,\textsuperscript{399} vascular function,\textsuperscript{400} and inflammation.\textsuperscript{401} In this study, we observed beneficial effects of cardiorespiratory fitness gain on BP, diabetic control, lipid profile and inflammation, all of which may have contributed to reduction in AF burden. This results into a better outcome and freedom from AF.

The strength of this study is that cardiorespiratory fitness was measured by a commonly performed, highly reproducible and well-validated test. The relative and combined contributions of fitness and fatness to AF remain controversial, but our results suggest that fitness may partially offset the adverse effects of body fatness. Evidently, the compounded benefit of “alliance of cardiorespiratory fitness with weight-loss” is over and above the strategic gain provided by each individually. This data highlights the prognostic role for exercise testing in predicting AF outcomes and importance of interventions to improve physical activity and cardiorespiratory fitness in overweight and/or obese symptomatic AF patients.

1.17 Study Limitations

This study has the potential for bias inherent to observational studies. However, measurement bias has been reduced through standardized processes in our clinic and the evaluation by operators blinded to the patient’s risk factor management regimen. AF burden assessment using 7 day Holter may miss some AF episodes. However, this was utilized for AF freedom assessment in both the groups and was a limitation for all. Ascertainment bias was reduced through the routine collection of outcome data.
While there are clinical limitations of using BMI as a surrogate measure of body fatness, this was utilized due to its wide applicability, non-invasive and simple measure. Improvement in individual risk factor for AF such as obesity, hypertension and diabetes mellitus is likely to vary between patients, but the specific contribution of these risk factors in AF-related outcomes is beyond the scope of this study.

1.18 CONCLUSION

Increased cardiorespiratory fitness was associated with dose-dependent reduction in AF burden and maintenance of sinus rhythm. Cardiorespiratory fitness gain provides a 12% incremental gain over weight-loss in long-term freedom from total AF burden. This occurs in conjunction with favourable changes in cardio-metabolic risk factor profile, inflammatory state and cardiac remodeling.
Table 3-1: Baseline Characteristics for baseline cardiorespiratory fitness groups

<table>
<thead>
<tr>
<th></th>
<th>Low CRF (&lt;85%) N=95</th>
<th>Adequate CRF (86-100%) N=134</th>
<th>High CRF (&gt;100%) N=79</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58±13</td>
<td>56±10</td>
<td>69±9</td>
<td>0.10</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>46 (49%)</td>
<td>64 (48%)</td>
<td>40 (51%)</td>
<td>0.20</td>
</tr>
<tr>
<td>Follow Up Duration, months</td>
<td>47±18.3</td>
<td>48±17.0</td>
<td>48.2±18.0</td>
<td>0.80</td>
</tr>
<tr>
<td>Anthropometric Measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (Kgm⁻²)</td>
<td>34.0±4.8</td>
<td>32.7±4.5</td>
<td>32.8±5.1</td>
<td>0.08</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>145±16</td>
<td>144±18</td>
<td>149±18</td>
<td>0.10</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxysmal AF, n (%)</td>
<td>46 (48%)</td>
<td>69 (52%)</td>
<td>49 (62%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Non-Paroxysmal, n (%)</td>
<td>49 (52%)</td>
<td>65 (48%)</td>
<td>30 (38%)</td>
<td></td>
</tr>
<tr>
<td>Metabolic Risk Factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>73 (77%)</td>
<td>98 (73%)</td>
<td>61 (78%)</td>
<td>0.67</td>
</tr>
<tr>
<td>DM, n (%)</td>
<td>32 (34%)</td>
<td>34 (25%)</td>
<td>18 (23%)</td>
<td>0.28</td>
</tr>
<tr>
<td>IGT, n (%)</td>
<td>5 (5%)</td>
<td>13 (10%)</td>
<td>10 (13%)</td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>38 (41%)</td>
<td>51 (38%)</td>
<td>31 (40%)</td>
<td>0.40</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>17 (18%)</td>
<td>12 (9%)</td>
<td>10 (13%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Valvulopathy, n (%)</td>
<td>5 (5%)</td>
<td>5 (4%)</td>
<td>5 (6%)</td>
<td>0.68</td>
</tr>
<tr>
<td>AHI&gt;30, n (%)</td>
<td>47 (49%)</td>
<td>76 (57%)</td>
<td>40 (51%)</td>
<td>0.50</td>
</tr>
<tr>
<td>Alcohol excess (&gt;30g/week),</td>
<td>27 (28%)</td>
<td>48 (36%)</td>
<td>21 (27%)</td>
<td>0.29</td>
</tr>
<tr>
<td>Smoker, n (%)</td>
<td>8 (8%)</td>
<td>47 (35%)</td>
<td>20 (25%)</td>
<td>0.06</td>
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<tr>
<td>Medication Use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean no. of AAD (±SD)</td>
<td>1.0±0.7</td>
<td>0.9±0.7</td>
<td>0.9±0.7</td>
<td>0.34</td>
</tr>
<tr>
<td>Mean no. of Anti-HTN (±SD)</td>
<td>0.9±1.1</td>
<td>0.7±0.7</td>
<td>0.8±0.9</td>
<td>0.19</td>
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</table>
### Serology and Lipid Profile

<table>
<thead>
<tr>
<th></th>
<th>Mean hsCRP (mg/L)</th>
<th>Mean Fasting Insulin level (U)</th>
<th>Mean LDL Level (mmol/L)</th>
<th>Mean TG Level (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4.4±6.0</td>
<td>14.9±6.6</td>
<td>2.7±1.0</td>
<td>1.6±0.5</td>
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<tr>
<td></td>
<td>4.9±11.9</td>
<td>16.4±6.9</td>
<td>2.9±0.8</td>
<td>1.7±0.8</td>
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<tr>
<td></td>
<td>4.8±7.6</td>
<td>16.0±6.0</td>
<td>3.0±1.0</td>
<td>1.5±0.7</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>Mean hsCRP (mg/L)</td>
<td>4.4±6.0</td>
<td>4.9±11.9</td>
<td>4.8±7.6</td>
<td>0.95</td>
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<tr>
<td>Mean Fasting Insulin level (U)</td>
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<td>16.4±6.9</td>
<td>16.0±6.0</td>
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<tr>
<td>Mean LDL Level (mmol/L)</td>
<td>2.7±1.0</td>
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<tr>
<td>Mean TG Level (mmol/L)</td>
<td>1.6±0.5</td>
<td>1.7±0.8</td>
<td>1.5±0.7</td>
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### Echocardiographic Measures

<table>
<thead>
<tr>
<th></th>
<th>LA Volume Indexed (mls/m²)</th>
<th>IVS (mm)</th>
<th>LVEDD (cm)</th>
<th>E/E’ ratio</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>38.9±3.8</td>
<td>1.2±0.2</td>
<td>5.0±0.6</td>
<td>11.9±3.5</td>
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<tr>
<td></td>
<td>38.1±5.4</td>
<td>1.2±0.2</td>
<td>5.0±0.5</td>
<td>11.4±4.1</td>
</tr>
<tr>
<td></td>
<td>39.4±6.4</td>
<td>1.1±0.2</td>
<td>4.9±0.6</td>
<td>13.0±4.8</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>LA Volume Indexed (mls/m²)</td>
<td>38.9±3.8</td>
<td>38.1±5.4</td>
<td>39.4±6.4</td>
<td>0.21</td>
</tr>
<tr>
<td>IVS (mm)</td>
<td>1.2±0.2</td>
<td>1.2±0.2</td>
<td>1.1±0.2</td>
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</tr>
<tr>
<td>LVEDD (cm)</td>
<td>5.0±0.6</td>
<td>5.0±0.5</td>
<td>4.9±0.6</td>
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<tr>
<td>E/E’ ratio</td>
<td>11.9±3.5</td>
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<td>13.0±4.8</td>
<td>0.06</td>
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</tbody>
</table>

### Atrial Fibrillation Severity Scale (AFSS)

<table>
<thead>
<tr>
<th></th>
<th>Frequency [1-10] 6.9±1.8</th>
<th>Duration [1-10] 6.8±1.9</th>
<th>Severity [1-10] 6.7±1.4</th>
<th>Symptom [0-35] 17.6±5.5</th>
<th>Global well-being (1-10) 2.7 ± 0.8</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency [1-10]</td>
<td>6.9±1.8</td>
<td>7.0±1.6</td>
<td>7.3±1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration [1-10]</td>
<td>6.8±1.9</td>
<td>7.1±1.8</td>
<td>6.6±1.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity [1-10]</td>
<td>6.7±1.4</td>
<td>6.9±1.9</td>
<td>7.1±1.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptom [0-35]</td>
<td>17.6±5.5</td>
<td>18.0±5.5</td>
<td>19.6±5.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global well-being (1-10)</td>
<td>2.7 ± 0.8</td>
<td>2.4 ± 0.9</td>
<td>2.5 ± 0.9</td>
<td>0.4</td>
<td></td>
</tr>
</tbody>
</table>

CRF: Cardiorespiratory Fitness; BMI: Body Mass Index; SBP: Systolic Blood Pressure; AF: Atrial Fibrillation; DM: Diabetes Mellitus; IGT: Impaired glucose tolerance; AHI: Apnea Hypopnea Index; AAD: Anti-Arrhythmic Drugs; Anti-HTN: Anti-hypertensive medication; hsCRP: High sensitive C reactive Protein; LDL: Low density Lipoprotein; TG: Triglyceride; LA Left atrium; LV IVS: Left Ventricular Inter ventricular septum; LVEDD: Left Ventricular End Diastolic Diameter.
Table 3-2: Baseline Characteristics for cardiorespiratory fitness gain groups

<table>
<thead>
<tr>
<th></th>
<th>&lt;2 METs Gain N=181</th>
<th>≥2 METs Gain N=127</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58±11</td>
<td>59±12</td>
<td>0.40</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>118</td>
<td>87 (69)</td>
<td>0.54</td>
</tr>
<tr>
<td>Follow Up Duration, months</td>
<td>48.0±18</td>
<td>47.6±17</td>
<td>0.72</td>
</tr>
<tr>
<td>CRF Gained, MET</td>
<td>0.5±1.4</td>
<td>2.9±0.9</td>
<td>&lt;0.0</td>
</tr>
<tr>
<td><strong>Anthropometric Measures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>101±17</td>
<td>99±16</td>
<td>0.36</td>
</tr>
<tr>
<td>BMI (Kgm⁻²)</td>
<td>33.4±5.0</td>
<td>32.7±4.5</td>
<td>0.20</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>146±18</td>
<td>145±17</td>
<td>0.71</td>
</tr>
<tr>
<td><strong>Atrial Fibrillation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxysmal AF, n (%)</td>
<td>99 (54)</td>
<td>66 (52)</td>
<td>0.67</td>
</tr>
<tr>
<td>Non-Paroxysmal, n (%)</td>
<td>82 (46)</td>
<td>61 (48)</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolic Risk Factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>140</td>
<td>92 (72)</td>
<td>0.28</td>
</tr>
<tr>
<td>DM, n (%)</td>
<td>52 (29)</td>
<td>32 (25)</td>
<td>0.79</td>
</tr>
<tr>
<td>IGT, n (%)</td>
<td>16 (9)</td>
<td>12 (9)</td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>87 (48)</td>
<td>58 (46)</td>
<td>0.65</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>25 (14)</td>
<td>14 (11)</td>
<td>0.49</td>
</tr>
<tr>
<td>Valvulopathy, n (%)</td>
<td>8 (4)</td>
<td>7 (6)</td>
<td>0.66</td>
</tr>
<tr>
<td>AHI&gt;30, n (%)</td>
<td>90 (50)</td>
<td>73 (57)</td>
<td>0.18</td>
</tr>
<tr>
<td>Alcohol excess (&gt;30g/week), n (%)</td>
<td>90 (50)</td>
<td>73 (57)</td>
<td>0.55</td>
</tr>
<tr>
<td>Smoker, n (%)</td>
<td>12 (7)</td>
<td>3 (2)</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>Medication Use</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>% on beta-blocker or CCB</td>
<td>72(40)</td>
<td>54(43)</td>
<td>0.82</td>
</tr>
<tr>
<td>Mean no. of AAD (±SD)</td>
<td>0.9±0.7</td>
<td>0.9±0.6</td>
<td>0.90</td>
</tr>
<tr>
<td>Mean no. of Anti-HTN (±SD)</td>
<td>0.8±1.0</td>
<td>0.8±0.8</td>
<td>0.88</td>
</tr>
<tr>
<td><strong>Serology and Lipid Profile</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean hsCRP (mg/L)</td>
<td>4.8±9.7</td>
<td>4.6±9.0</td>
<td>0.91</td>
</tr>
<tr>
<td></td>
<td>Value 1</td>
<td>Value 2</td>
<td>p-value</td>
</tr>
<tr>
<td>------------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Mean Fasting Insulin level (U)</td>
<td>15.7±6.</td>
<td>16.2±6.</td>
<td>0.67</td>
</tr>
<tr>
<td>Mean LDL Level (mmol/L)</td>
<td>2.8±1.0</td>
<td>2.9±0.9</td>
<td>0.38</td>
</tr>
<tr>
<td>Mean TG Level (mmol/L)</td>
<td>1.6±0.7</td>
<td>1.6±0.6</td>
<td>0.90</td>
</tr>
</tbody>
</table>

**Echocardiographic Measures**

<table>
<thead>
<tr>
<th></th>
<th>Value 1</th>
<th>Value 2</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA Volume Indexed (mls/m²)</td>
<td>39.2±4.</td>
<td>38.0±6.</td>
<td>0.08</td>
</tr>
<tr>
<td>IVS (mm)</td>
<td>1.1±0.3</td>
<td>1.0±0.2</td>
<td>0.90</td>
</tr>
<tr>
<td>LVEDD (cm)</td>
<td>5.1±0.6</td>
<td>5.0±0.4</td>
<td>0.50</td>
</tr>
<tr>
<td>Lateral E/E' ratio</td>
<td>11.7±3.</td>
<td>12.5±4.</td>
<td>0.10</td>
</tr>
</tbody>
</table>

**Atrial Fibrillation Severity Scale (AFSS)**

<table>
<thead>
<tr>
<th></th>
<th>Value 1</th>
<th>Value 2</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency [1-10]</td>
<td>7.2±1.5</td>
<td>6.8±1.6</td>
<td>0.50</td>
</tr>
<tr>
<td>Duration [1-10]</td>
<td>6.8±1.8</td>
<td>7.0±1.8</td>
<td>0.48</td>
</tr>
<tr>
<td>Severity [1-10]</td>
<td>6.8±1.6</td>
<td>7.0±1.8</td>
<td>0.51</td>
</tr>
<tr>
<td>Symptom [0-35]</td>
<td>17.9±5.</td>
<td>18.7±5.</td>
<td>0.25</td>
</tr>
<tr>
<td>Global well-being (1-10)</td>
<td>2.5±0.9</td>
<td>2.4±0.9</td>
<td>0.90</td>
</tr>
</tbody>
</table>

MET: Metabolic equivalent; CRF: Cardiorespiratory Fitness; BMI: Body Mass Index; SBP: Systolic Blood Pressure; AF: Atrial Fibrillation; DM: Diabetes Mellitus; IGT: Impaired glucose tolerance; AHI: Apnea Hypopnea Index; AAD: Anti-Arrhythmic Drugs; Anti-HTN: Anti-hypertensive medication; CCB: Calcium Channel blocker; hsCRP: High sensitive C reactive Protein; LDL: Low density Lipoprotein; TG: Triglyceride; LA Left atrium; LV IVS: Left Ventricular Inter ventricular septum; LVEDD: Left Ventricular End Diastolic Diameter.
Table 3-3: Impact of cardiorespiratory fitness gain on cardiac risk factors, cardiac structure and AF severity

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>&lt;2 MET Gain Group; N = 181</th>
<th>≥2 MET Gain Group; N = 127</th>
<th>P value†</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow Up‡</td>
<td>P value*</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>101±17</td>
<td>98±19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (Kgm⁻²)</td>
<td>33.5±5.0</td>
<td>32.5±5.3</td>
<td>&lt;0.001</td>
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<tr>
<td>Mean SBP (mmHg)</td>
<td>146±18</td>
<td>136±14</td>
<td>&lt;0.001</td>
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<tr>
<td>DM with HbA1c≥7, n (%)</td>
<td>40 (22)</td>
<td>21 (12)</td>
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</table>

Medication Use

<table>
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<tr>
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<th>Baseline</th>
<th>Follow Up‡</th>
<th>P value*</th>
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<tbody>
<tr>
<td>Mean no. of Anti-HTN, n</td>
<td>0.8±1.0</td>
<td>0.9±0.7</td>
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</tr>
<tr>
<td>N on Lipid Rx n (%)</td>
<td>68 (38)</td>
<td>63 (35)</td>
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<tr>
<td>Mean no. of AAD, n</td>
<td>0.9±0.7</td>
<td>0.4±0.6</td>
<td>&lt;0.001</td>
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Serology and Lipid Profile

<table>
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<tr>
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<th>Baseline</th>
<th>Follow Up‡</th>
<th>P value*</th>
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<tbody>
<tr>
<td>Mean hsCRP (mg/L)</td>
<td>4.1±5.9</td>
<td>3.9±4.5</td>
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<tr>
<td>Mean Fasting Insulin level (U)</td>
<td>15.9±6.8</td>
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<td>Mean LDL Level (mmol/L)</td>
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</tr>
<tr>
<td></td>
<td>1.6±0.7</td>
<td>1.5±0.7</td>
<td>0.22</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------</td>
<td>---------</td>
<td>------</td>
</tr>
<tr>
<td><strong>Mean TG Level (mmol/L)</strong></td>
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<tr>
<td><strong>Echocardiogram</strong></td>
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<tr>
<td>Indexed LA Volume (ml/m²)</td>
<td>39.1±4.6</td>
<td>37.9±6.8</td>
<td>0.03</td>
</tr>
<tr>
<td>IV Septum (mm)</td>
<td>1.1±0.3</td>
<td>1.1±0.2</td>
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</tr>
<tr>
<td>LVEDD (cm)</td>
<td>5.1±0.6</td>
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<tr>
<td>Lateral E/E' ratio</td>
<td>11.7±3.5</td>
<td>11.4±5.0</td>
<td>0.55</td>
</tr>
</tbody>
</table>

|                          | 7.2±1.4 | 4.3±1.8 | <0.001 | 6.8±1.6 | 2.8±1.6 | <0.001 | <0.001 |
| **AF symptom Score**     |         |         |        |         |         |        |        |
| AF frequency [1-10]       |         |         |        |         |         |        |        |
| AF duration [1.25-10]     | 6.8±1.8 | 5.4±2.3 | <0.001 | 7.0±1.8 | 3.9±2.2 | <0.001 | <0.001 |
| AF episode severity [1-10]| 6.9±1.6 | 4.7±2.0 | <0.001 | 6.9±1.7 | 3.6±1.7 | <0.001 | <0.001 |
| AF symptom subscale [0-35]| 18.2±5.1| 12.2±5.1| <0.001 | 18.8±5.9| 9.1±4.6 | <0.001 | <0.001 |
| Global well-being (1-10)  | 2.5±0.9 | 5.7±2.0 | <0.001 | 2.4±0.9 | 7.6±1.7 | <0.001 | <0.001 |

* P value refers to within group difference (baseline to follow-up); †P value refers to between group differences over time (group-time interaction). ‡Median follow-up: 48.0±18.0 months for <2 MET Gain group and 47.6±17.1 months for ≥2 MET Gain group. MET: Metabolic equivalent; CRF: Cardiorespiratory Fitness;
BMI: Body Mass Index; SBP: Systolic Blood Pressure; AF: Atrial Fibrillation; DM: Diabetes Mellitus; IGT: Impaired glucose tolerance; AHI: Apnea Hypopnea Index; AAD: Anti-Arrhythmic Drugs; Anti-HTN: Anti-hypertensive medication; CCB: Calcium Channel blocker; hsCRP: High sensitive C reactive Protein; LDL: Low density Lipoprotein; TG: Triglyceride; LA Left atrium; LV IVS: Left Ventricular Inter ventricular septum; LVEDD: Left Ventricular End Diastolic Diameter.
Figure 3-1: Flow diagram demonstrating patient recruitment and attrition

- Assessed for Eligibility N=1415
- Patients with BMI ≥ 27 N=825
- Final Cohort N=308

Met Exclusion Criteria (N=303)
- Terminal Cancer (N=10)
- Inflammatory Dx (N=20)
- Permanent AF (N=84)
- AV Node ablation (N=12)
- AF ablation (N=90)
- Severe Medical Illness (N=77)
- Pacemaker in-situ (N=10)

Musculoskeletal Problem (N=8)
- Negative chronotropic drug (N=16)
- AF on the day of EST (N=13)
- Patients from other states (N=177)

Baseline CRF N=308
- Low <85% Predicted N=95
- Adequate 86-100% Predicted N=134
- High >100% Predicted N=79

CRF Gain N=308
- <2 MET Gain N=181
- ≥2 MET Gain N=127
**Figure 3-2: AF Freedom outcome according to baseline cardiorespiratory fitness**

**A:** Kaplan-Meier Curve for AF free survival without the use of rhythm control strategies.

**B:** Kaplan-Meier Curve for AF free survival for total AF free survival (Multiple ablation procedures ± drugs; right).
Figure 3-3: Outcomes of AF freedom according to cardiorespiratory fitness gain

A: Kaplan-Meier Curve for total AF free survival (Multiple ablation procedures ± drugs) according to weight trend.

B: Kaplan-Meier Curve for total AF free survival (Multiple ablation procedures ± drugs) according to weight fluctuation.
Figure 3-4: Outcomes of AF Freedom according to cardiorespiratory fitness gain and weight loss

A: Kaplan-Meier Curve for total AF free survival (Multiple ablation procedures ± drugs) according to weight trend.

B: Kaplan-Meier Curve for total AF free survival (Multiple ablation procedures ± drugs) according to weight fluctuation.
Figure 3-5: Schematic of the Process

- Structured: age and ability matched
- Frequency: three days to five days
- Intensity: Low to Moderate
- Time: 60 to 200 Minutes /Week
- Type: Aerobic & strength training
- Heart Rate: Monitor, 85% of 220-age

Incremental effect of CRF Gain with <10% weight loss on 5-years AF freedom without rhythm control strategies:
- <2MET gain: 13%
- ≥2MET gain: 37%

Incremental effect of CRF Gain with ≥ 10% weight loss on 5-years AF freedom without rhythm control strategies:
- <2MET gain: 44%
- ≥2MET gain: 76%
Chapter 4 - Aggressive Risk factor REDuction STUDy for Atrial Fibrillation (ARREST-AF Cohort Study): implications for the outcome of ablation

1.19 Introduction

Atrial fibrillation (AF) affects approximately 2.7 million people in the USA alone and its prevalence is expected to rise to 15.9 million by 2050 with significant impact on health care.\textsuperscript{2, 7, 12} Although population ageing is regarded as an important contributor, several risk factors such as hypertension, diabetes mellitus (DM), obesity, and obstructive sleep apnea (OSA) have been linked as promoters of AF.\textsuperscript{17, 18, 32, 402}

Catheter ablation of AF has evolved as an effective therapy for drug-refractory symptomatic AF.\textsuperscript{309} Studies have demonstrated the advantage of catheter ablation over pharmacological methods of rhythm control.\textsuperscript{310, 312, 313, 403} However, reports of the long-term outcomes of AF ablation demonstrate attrition in success with time.\textsuperscript{321, 322, 325, 327, 404} Studies have associated some cardiac risk factors with the more frequent recurrence of AF.\textsuperscript{324, 336, 337} We hypothesise that the attrition in the success of AF ablation is due to progression of the disease process that promoted the development of AF. This study aims to evaluate the impact of aggressive cardiac risk factor and weight management on the outcomes of the catheter ablation.
1.20 Methods

1.20.1 Study Population
The study comprised consecutive patients with body mass index (BMI) ≥27kg/m² and
≥1 risk factor (hypertension, glucose intolerance/DM, hyperlipidemia, OSA, smoking or
alcohol excess) undergoing initial catheter ablation for symptomatic AF despite the use
of antiarrhythmic medication.

All patients provided written informed consent for the ablation procedure and
collection of their clinical data. The study protocol was approved by the Human
Research Ethics Committee of the Royal Adelaide Hospital and University of Adelaide.

1.20.2 Study Protocol
All suitable patients were offered risk factor management (RFM) in a dedicated
physician-directed clinic at the time of initial assessment. Patients who accepted this
strategy formed the intervention group (RFM) while those who declined formed the
control group. Only patients with ongoing significant symptoms despite the use of
antiarrhythmic medications and risk factor management underwent AF ablation.
Exclusion criteria were: history of myocardial infarction or cardiac surgery in the
previous 12-months; previous AF ablation; active malignancy; autoimmune or systemic
inflammatory diseases; severe renal or hepatic failure; and <12-months follow-up after
their procedure.
1.20.3 Risk Factor Management Group

Patients participating in RFM attended a physician-directed RFM clinic (in addition to their arrhythmia follow up) every 3-months and were managed according to ACC/AHA guidelines. 405

**Blood Pressure Control:** Blood pressure (BP) was measured thrice-daily using home-based automated monitor and an appropriate-sized cuff. In addition, exercise stress testing was performed to determine the presence of exercise-induced hypertension with BP>200/100mmHg considered as evidence to optimise therapy. Lifestyle advice constituted dietary salt restriction. Pharmacotherapy was initiated using renin-angiotensin-aldosterone system antagonists with other agents used where necessary to achieve a target BP of <130/80mmHg at least 80% of the time. These were corroborated by in-office and 24-hour ambulatory BP measurements, as required. Echocardiography was monitored to ensure resolution of left ventricular hypertrophy.

**Weight Management:** A structured motivational and goal-directed program using face-to-face counseling was used for weight reduction. Patients were encouraged to utilize support counseling and schedule more frequent reviews as required. Initial weight reduction was attempted by a meal plan and behavior modification. Participants were required to maintain a diet and physical activity diary. Meals consisted of high protein and low glycemic index, calorie controlled foods. If patients lost <3% of weight after 3-months they were then prescribed very-low-calorie meal replacement sachets (Prima Health Solutions or Nestle Health Science) for 1-2 meals/day. The initial goal was to reduce body weight by 10%. After patients achieved the initial goal, meal replacement was substituted to high protein and low glycemic
index, calorie-controlled foods to achieve a target BMI of ≤25kg/m². Low intensity exercise was prescribed initially for 20-minutes thrice-weekly increasing to at least 200-minutes of moderate-intensity activity/week.

**Lipid Management:** Initially managed with lifestyle measures. If patients were unable to achieve LDL-Cholesterol <100mg/dL after 3-months then a HMG-CoA reductase inhibitor was initiated. Fibrates were used for isolated hypertriglyceridemia (TG>500mg/dL) or added to statin therapy if TG>200mg/dL and non-HDL cholesterol was >130mg/dL.

**Glycemic Control:** If fasting glucose was 100-125mg/dL, a glucose tolerance test was performed. Impaired glucose tolerance (IGT) or DM was initially managed with lifestyle measures. If patients were unable to maintain glycosylated hemoglobin ≤6.5% after 3-months, metformin was started. Patients in both groups with suboptimal glycemic control (HbA1c>7%) were referred to a specialized diabetes clinic.

**Sleep Disordered Breathing Management:** In-laboratory overnight polysomnography (PSG) was scored by qualified sleep technicians and reviewed with follow-up by a sleep physician. PSG scoring was according to the AASM alternate PSG scoring criteria. Patients were offered therapy if the Apnea-Hypopnea Index (AHI) was ≥30/hour or if it was >20/hour with resistant hypertension or problematic daytime sleepiness. Treatment included positional therapy and continuous positive airway pressure (CPAP).
**Smoking:** The “5A” (Ask, Advice, Assess, Assist and Arrange follow-up) structured smoking cessation framework was adopted. Smokers were offered behavioral support through a multidisciplinary clinic with the aim of cessation.

**Alcohol:** Written and verbal counseling was provided with regular supportive follow-up for alcohol reduction to ≤30 gm/week.

### 1.20.4 Control Group

The control group was given information on management of risk factors. However, they continued risk factor management under the direction of their treating physician.

### 1.20.5 Catheter Ablation

The ablation procedure was performed with the operator blinded to the patient’s study group. The ablation technique utilized at our institution has been previously described.²⁹ The ablation strategy included wide-encircling pulmonary vein ablation with an endpoint of electrical isolation (PVI) in all patients. Further substrate modification was performed for patients with AF episodes ≥48-hours or if the largest left atrial dimension exceeded 57mm. This included linear ablation (roofline and/or mitral isthmus) with an endpoint of bidirectional block and/or electrogram-guided ablation of fractionated sites.

If patients developed recurrent arrhythmia after the blanking period (3-months), repeat ablation was offered. Individual operators decided on the extent of additional ablation undertaken beyond re-isolation of the pulmonary veins.
1.20.6 Follow-Up

Patients were reviewed for arrhythmia recurrence by physicians blinded to the patient’s study group. Reviews were 3-monthly for the first year and 6-monthly thereafter. At each review, AF recurrence was ascertained from patients’ symptoms, electrocardiogram and ambulatory 7-day monitoring. The ambulatory recordings were analyzed by 2 independent observers blinded to patient group. In the absence of any arrhythmia, antiarrhythmic drugs were stopped at 4-6 weeks. No patient continued on amiodarone after ablation. All patients were anticoagulated using warfarin for ≥3-months following ablation.

Procedural success was determined as the absence of any atrial arrhythmia ≥30-second after a 3-month blanking period.

1.20.7 AF Symptom Burden

AF symptom burden and severity was quantified using the validated AF Severity Scale (AFSS, University of Toronto), that aims to quantitate three domains of AF related symptoms: frequency, duration and severity. In addition, a symptom subscale is determined. The AFSS questionnaire was administered at baseline and follow-up after ablation.

1.20.8 Cardiac Structure

Transthoracic echocardiography was performed by an operator, blinded to the study group, with a 3.5 MHz probe at baseline and yearly with measures performed according to American Society of Echocardiography guidelines.
1.20.9 Statistical Analysis
Categorical variables are represented by frequencies and percentages. Continuous variables are summarized by mean±SD. Repeated measure ANOVA was used to assess the interaction between the groups over time. The “significance of the interaction” in the ANOVA was used to assess these changes. Comparisons of variables for both the Control and RFMx groups were done using paired samples t-tests. For nominal variables such as Diabetes and sleep apnoea (AHI>30), the changes were only assessed for patients who were positive at baseline. The change in the status at final follow up was compared between the two groups using Chi-Square test. Time to recurrence and event-free survival curves following the last ablation procedure were estimated by the Kaplan-Meier product-limit method. Requirement of a repeat procedure was considered an endpoint. Predictors of recurrent AF were assessed in Cox regression models, after verifying proportionality assumptions. Candidate variables with P<0.1 in univariate analyses were considered in multivariate stepwise regression models. Two-tailed P<0.05 were considered statistically significant. Statistical analysis was performed with SPSS version 21.0 (SPSS, Inc., Chicago, IL, USA).

1.21 RESULTS

1.21.1 Baseline Characteristics
Of 281 consecutive patients referred for catheter ablation of symptomatic AF, 165 had both BMI≥27 and ≥1 risk factor. Of these, 3 patients were excluded on the basis of predefined exclusions (1 with terminal cancer and 2 with systemic inflammatory conditions) and a further 13 on the basis of the lack of regular follow-up (from other
States). The final cohort included 149 patients; 61 RFM and 88 controls [Figure-1]. Mean follow-up in the RFM and control groups were 41.6±12.5 and 42.1±14.2 months, respectively (P=0.8). Mean duration before the procedure was 9.8±7.1 months in RFM group and 10.2±9.2 months in control group (p=0.8). Baseline characteristics were similar in the two groups (Table-1).

1.21.2 Risk Factor Modification
Table-2 shows the impact of RFM on various cardiac risk factors.

**Blood Pressure Control:** There was a greater decline in systolic BP with RFM compared to controls (34.1±7.5 versus 20.6±3.2mmHg; P=0.003). Number of anti-hypertensive agents used for BP control decreased with RFM (1.5±1.1 to 1.2±0.9; P=0.04) and increased in controls (1.6±1.2 to 1.9±1.3; P=0.2).

**Weight Management:** Weight and BMI decreased in both groups, but significantly more with RFM compared to controls (-13.2±5.4 vs.-1.5±5.1 kg; P=0.002; Table-2).

**Lipid Management:** At baseline, 64% of RFM and 53% of controls had dyslipidemia (P=0.2). With diet and life style modification, LDL-C and non-HDL-C were well controlled in 46.2% of RFM and 17% of controls (P=0.01). Drug therapy was required in 43.6% of RFM and 68.1% of control group (P=0.01). At final follow up, 10.2% (n=4) with RFM and 15% (n=7) of controls still had dyslipidemia.

**Glycemic Control:** At baseline, 15% of RFM and 19% of controls had history of DM (P=0.5). A further 13% of RFM and 10% of controls were found to have IGT. At final
follow up, DM patients in the RFM had significantly better glycemic control compared to controls; HbA1c< 7% in 100% vs. 29%, respectively (P=0.001).

**Sleep Apnea Management:** At baseline, 52% of RFM and 61% of controls had severe OSA (AHI≥30; P=0.2). Of these, 16 (50%) of RFM had an AHI<15 which we regarded as mild or no OSA when re-tested at follow-up compared to 8 (15%) of controls (P<0.001). Of patients requiring CPAP, compliance with CPAP use was significantly higher in RFM compared to controls (77% vs. 32%; P=0.001).

**Smoking and Alcohol Use:** Most patients successfully stopped smoking: 19 (95%) RFM and 28 (90.3%) of controls (P=0.5). In RFM, 9 (81.8%) patients successfully managed to reduce alcohol consumption to below 30gm/week, while 15 (62.5%) controls achieved this (P=0.2).

**1.21.3 Ablation**
Groups underwent a similar rate of ablation procedures (RFM 1.6±0.7 per patient and controls 1.5±0.7; P=0.3). Table-3 provides the procedural details for each group.

**1.21.4 Cardiac Structure**
Table-2 shows the effect of RFM on cardiac structure. LA volume indexed for body surface area (ml/m²) decreased with RFM from 42.5±12.0 to 30.4±8.3 (P<0.001) and in controls from 42.1±10.4 to 39.5±12.1 (P=0.07); this reduction was significantly greater with RFM compared to controls (P=0.001). Septal (IVS) thickness (mm) decreased with RFM from 11.6±1.7 to 9.6±1.7 (P<0.001) and controls from 11.3±1.6 to 10.9±1.9 (P=0.04); a greater reduction with RFM compared to controls (P<0.001).
1.21.5 Atrial Fibrillation

1.21.5.1 Symptom Burden
At baseline, both groups had comparable and high AFSS subscale scores (Table-2). Figure-2 shows changes from baseline to final follow up for AFSS subscale pertaining to total AF burden and symptom severity. AF frequency, duration, symptom and symptom severity were less at final follow up in both groups with a significantly greater reduction seen with RFM group (P<0.001). The global well-being score improved by >2-fold after ablation; with RFM improving from 2.4±0.9 to 7.6±1.7 (P<0.001) and in controls from 2.5±0.9 to 5.7±2.0 (P<0.001; Figure-2). However, improvement was markedly better with RFM than in controls (P<0.001).

1.21.5.2 Single Procedure Arrhythmia-Free Survival
Figure-3 and Figure-4 demonstrates the single procedure outcomes according to group and type of AF. At final follow up, 32.9% with RFM versus 9.7% of controls (P<0.001) remained free from arrhythmia. After single procedure, univariate predictors of AF recurrence were: control group (HR 2.6, 95% CI: 1.7 to 4.0; P<0.001) and type of AF (Non-paroxysmal AF: HR 1.8, 95% CI: 1.2 to 2.7; P=0.004). Both remained independent predictors of recurrent AF in multivariate analyses: control group, HR: 2.3, 95% CI: 1.5 to 3.6 (P<0.001) and non-paroxysmal AF, HR: 1.7, 95% CI: 1.1 to 2.5 (P=0.01).

1.21.5.3 Multiple Interventions Arrhythmia-Free Survival
Figure-3 demonstrates the arrhythmia-free survival after multiple procedures with a significant attrition in controls compared to RFM. Figure-4 shows arrhythmia-free survival after multiple procedures based on type of AF. At final follow up, arrhythmia-free survival rates following the last catheter ablation procedure was 87% with RFM.
compared to 17.8% for controls (P<0.001). Univariate predictors of AF recurrence after multiple procedures were: control group (HR 6.2, 95% CI: 2.6 to 14.5, P<0.001); type of AF (Non-paroxysmal AF: HR 3.3, 95% CI: 1.8 to 5.9, P<0.001); and poor BP control evidenced by number of anti-hypertensive medication (HR 1.3, 95% CI: 1.03 to 1.64, P=0.02). Patient group (HR: 4.8, 95% CI: 2.04 to 11.4; p<0.001) remained the most significant predictor of recurrent AF in multivariate analyses.

1.22 DISCUSSION

This study demonstrates that in patients with highly symptomatic AF undergoing ablation, a structured physician-directed risk factor and weight management program resulted in significant improvement in the long-term outcomes. These effects were associated with structural remodeling with significant improvement in left atrial volumes and left ventricular hypertrophy. These findings underscore the importance of treating the underlying causes of AF to achieve rhythm control and maintenance of sinus rhythm.

Catheter ablation is an effective therapy for rhythm control in patients with drug-refractory or intolerant AF. Despite recent advances in ablative techniques, the long-term outcomes post-ablation have not improved proportionately, especially in those with more persistent form of the arrhythmia. Updates from several centers confirm the need for multiple procedures which in general have occurred early and are related to incomplete ablation during previous efforts with residual PV
conduction. More concerning is that despite further ablation and a period without arrhythmia, a progressive attrition in success is observed with time. It has been proposed that this late recurrence is also due to persistent PV conduction. However, it seems unusual that recovery of PV conduction, that would be expected to occur early, would contribute to delayed recurrence of arrhythmia. Several single centre experiences have identified a variety of cardiac risk factors that were more frequently present in patients with late recurrence of AF.

Cardiac risk factors such as hypertension, diabetes mellitus, obesity and OSA have been independently shown to increase incidence of AF. 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. Indeed, even in the absence of known risk factors, atrial changes consistent with the AF substrate have been observed in ‘lone AF’ patients. Further evidence of the importance of an underlying substrate to the progression of AF is alluded to by several studies. It was postulated that early cardioversion would prevent the remodeling due to AF and allow “sinus rhythm to beget sinus rhythm”; however, restoration of sinus rhythm reversed electrical remodeling but did not impact the maintenance of sinus rhythm. Finally, a recent study has observed a progressive atrial substrate even after successful catheter ablation of AF. These findings argue in favor of an underlying atrial substrate responsible for AF that is promoted by inadequately treated or unrecognized risk factors.

Upstream therapy has demonstrated a reduction in AF. Antihypertensive therapy has been shown to reduce left atrial size and left ventricular hypertrophy leading to a
lower risk of AF. Angiotensin-receptor blockade used in conjunction with cardioversion has been demonstrated to reduce AF recurrence. In mitral stenosis, treatment of the primary cause has been observed to reverse the abnormal atrial substrate. A recent study observed that weight and cardio-metabolic risk factor management in overweight individuals with AF resulted in a reduction of AF symptom burden. In the setting of AF ablation, emerging data has shown that CPAP for OSA was associated with higher ablation success.

The current study extends these observations by demonstrating markedly improved outcomes of maintaining sinus rhythm by addressing each of the risk factors that potentially contributed to the development of AF and therefore the underlying atrial substrate. The results are so striking that concurrent risk factor treatment seems an essential component of strategies for rhythm control in patients with AF.

1.23 Study Limitation

This study was a single centre observational study and requires confirmation in a randomized controlled trial to minimize the potential for selection bias and better control of confounders. Finally, we targeted each risk factor treating to recommended targets. As a result, this study does not provide insight into the relative contribution of each risk factor or variable treatment targets.
1.24 CONCLUSION

Risk factor management significantly improves the outcomes of AF ablation by reducing AF burden and severity in conjunction with favorable changes in cardiac remodeling. These findings underscore the importance of therapy directed at the primary promoters of the AF substrate to facilitate a rhythm control strategy in patients with AF.
Table 4-1: Baseline Characteristics

<table>
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<th>Control Group (N=88)</th>
<th>RFM Group (N=61)</th>
<th>P Value</th>
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<td>Age (years)</td>
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<td>58.4 ± 10.8</td>
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<td>Male gender, n (%)</td>
<td>61 (69.3)</td>
<td>34 (56)</td>
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</tr>
<tr>
<td>Weight (Kg)</td>
<td>96.6±16.8</td>
<td>100.7±17.6</td>
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</tr>
<tr>
<td>BMI (Kgm⁻²)</td>
<td>32.1±4.7</td>
<td>33.5±4.6</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>Atrial Fibrillation</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Paroxysmal AF, n (%)</td>
<td>49 (56)</td>
<td>40 (65)</td>
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</tr>
<tr>
<td>Non-Paroxysmal, n (%)</td>
<td>39(44)</td>
<td>21(35)</td>
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</tr>
<tr>
<td><strong>Metabolic Risk Factors</strong></td>
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</tr>
<tr>
<td>Hypertension</td>
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</tr>
<tr>
<td>DM n (%)</td>
<td>17 (19)</td>
<td>9 (15)</td>
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<tr>
<td>Hyperlipidemia, n (%)</td>
<td>47 (53)</td>
<td>39 (64)</td>
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<tr>
<td>Coronary artery disease, n (%)</td>
<td>10 (11)</td>
<td>10 (16)</td>
<td>0.4</td>
</tr>
<tr>
<td>AHI&gt;30, n (%)</td>
<td>55 (62)</td>
<td>32 (53)</td>
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</tr>
<tr>
<td>Alcohol excess (&gt;30g/week), n (%)</td>
<td>24 (27)</td>
<td>11 (18)</td>
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<tr>
<td>Smoker, n (%)</td>
<td>31 (35)</td>
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<tr>
<td><strong>Medication Use</strong></td>
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<tr>
<td>Mean no. of Anti-Arrhythmic (±SD)</td>
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<td>Mean no. of Anti-Hypertensive</td>
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<td>1.5±1.1</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Echocardiographic Measures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LA Volume Indexed (mls/m²)</td>
<td>42.4±10.4</td>
<td>42.5±12</td>
<td>0.9</td>
</tr>
<tr>
<td>LV septum (mm)</td>
<td>11.0±2</td>
<td>12.0±2</td>
<td>0.1</td>
</tr>
<tr>
<td>------------------------</td>
<td>--------</td>
<td>--------</td>
<td>-----</td>
</tr>
<tr>
<td>LVIDd (cm)</td>
<td>5.1±0.7</td>
<td>5.3±0.5</td>
<td>0.2</td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>60±10.1</td>
<td>61.1±8</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Atrial Fibrillation Severity Scale (AFSS)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency [1-10]</td>
<td>6.6 ±1.1</td>
<td>6.8±1.2</td>
<td>0.5</td>
</tr>
<tr>
<td>Duration [1-10]</td>
<td>6.7 ±1.3</td>
<td>6.4 ±1.6</td>
<td>0.3</td>
</tr>
<tr>
<td>Severity [1-10]</td>
<td>6.9 ±1.3</td>
<td>6.6±1.5</td>
<td>0.2</td>
</tr>
<tr>
<td>Symptom [0-35]</td>
<td>23.1±3.7</td>
<td>22±5.2</td>
<td>0.1</td>
</tr>
<tr>
<td>Global Well Being [1-10]</td>
<td>2.5±0.9</td>
<td>2.4±0.9</td>
<td>0.4</td>
</tr>
</tbody>
</table>
Table 4-2: Risk Factor, echocardiographic and AF severity changes

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Control Group (N=88)</th>
<th>RF Mx Group (N=61)</th>
<th>P value*</th>
<th>Control Group (N=88)</th>
<th>RF Mx Group (N=61)</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow-up‡</td>
<td></td>
<td>Baseline</td>
<td>Follow-up‡</td>
<td></td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>96.6±16.8</td>
<td>95.8±17.6</td>
<td>0.13</td>
<td>100.7±17.6</td>
<td>87.5±14.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (Kgm⁻²)</td>
<td>32.1±4.7</td>
<td>31.8±4.9</td>
<td>0.12</td>
<td>33.5±4.6</td>
<td>29.1±3.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean SBP (mmHg)</td>
<td>158.7±21.3</td>
<td>138.2±18</td>
<td>&lt;0.001</td>
<td>160.8±20.3</td>
<td>126.8±12.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DM with HbA1c≥7%, n</td>
<td>17</td>
<td>5</td>
<td></td>
<td>9</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>N with AHI&gt;30, n</td>
<td>54</td>
<td>46</td>
<td></td>
<td>32</td>
<td>16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medication Use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean no. of AA ± SD</td>
<td>1.0±0.2</td>
<td>0.7±0.7</td>
<td>&lt;0.001</td>
<td>1.1±0.3</td>
<td>0.3±0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean no of Anti-HTN ± SD</td>
<td>1.6±1.2</td>
<td>1.9±1.3</td>
<td>0.2</td>
<td>1.5±1.1</td>
<td>1.2±0.9</td>
<td>0.04</td>
</tr>
<tr>
<td>Echocardiographic Measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LA Volume Indexed (mls/m²)</td>
<td>42.4±10.4</td>
<td>39.5±12.1</td>
<td>0.07</td>
<td>42.5±12</td>
<td>30.4±8.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV septum (mm)</td>
<td>11.0±2</td>
<td>10.9±0.19</td>
<td>0.047</td>
<td>12.0±2</td>
<td>9.6±0.17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVIDd (cm)</td>
<td>5.1±0.7</td>
<td>5.1±0.6</td>
<td>0.204</td>
<td>5.3±0.5</td>
<td>4.9±0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>60±10.1</td>
<td>61.1±8</td>
<td>0.538</td>
<td>61.3±10</td>
<td>62.6±5.5</td>
<td>0.524</td>
</tr>
<tr>
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</tr>
<tr>
<td><strong>Atrial Fibrillation Severity Score (AFSS)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AF frequency</td>
<td>6.6 ±1.1</td>
<td>3.2±1.1</td>
<td>&lt;0.001</td>
<td>6.8±1.2</td>
<td>2.0±0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AF duration</td>
<td>6.7 ±1.3</td>
<td>3.3±1.3</td>
<td>&lt;0.001</td>
<td>6.4 ±1.6</td>
<td>2.1±0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AF episode severity</td>
<td>6.9 ±1.3</td>
<td>5.2±1.9</td>
<td>&lt;0.001</td>
<td>6.6±1.5</td>
<td>3.3±1.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AF symptom subscale</td>
<td>23.1±3.7</td>
<td>13.3±6.2</td>
<td>&lt;0.001</td>
<td>22±5.2</td>
<td>7.1±4.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Global Well Being [1-10]</td>
<td>2.5±0.9</td>
<td>5.7±2.0</td>
<td>&lt;0.001</td>
<td>2.4±0.9</td>
<td>7.6±1.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Risk Factor and AF severity changes from baseline to follow-up. *P value refers to within group difference (baseline to follow-up), †P value refers to between group difference over time (group-time interaction). ‡Median follow-up: 42.8 months for RF Mx group and 42.4 months for control group.
Table 4-3: Details of procedure

<table>
<thead>
<tr>
<th></th>
<th>Control Group (N=88)</th>
<th>RFM Group (N=61)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First Procedure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary Vein Isolation, n</td>
<td>88 (100)</td>
<td>61 (100)</td>
<td>0.2</td>
</tr>
<tr>
<td>Line Ablation, n (%)</td>
<td>60 (68%)</td>
<td>40 (66%)</td>
<td>0.7</td>
</tr>
<tr>
<td>CAFÉ, n (%)</td>
<td>23 (27.1%)</td>
<td>21 (34%)</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Second Procedure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PV consolidative ablation, n</td>
<td>46(52%)</td>
<td>28(46%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Line Ablation, n (%)</td>
<td>36(41%)</td>
<td>21(34%)</td>
<td>0.3</td>
</tr>
<tr>
<td>CAFÉ, n (%)</td>
<td>15(17%)</td>
<td>6(10%)</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Third Procedure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PV consolidative ablation, n</td>
<td>13(28%)</td>
<td>6(21%)</td>
<td>0.6</td>
</tr>
<tr>
<td>Line Ablation, n (%)</td>
<td>6(6.8%)</td>
<td>5(8.2%)</td>
<td>0.5</td>
</tr>
<tr>
<td>CAFÉ, n (%)</td>
<td>0</td>
<td>1</td>
<td>0.8</td>
</tr>
</tbody>
</table>
Of the 165 patients (69 in RFM and 96 in control), 16 were excluded from the analysis due to absence of regular follow up in 13 as they were from another State (7 RFM and 6 Control) or systemic illness in 3 (1 with malignancy and 2 with systemic inflammatory diseases).
Figure 4-2: Changes in AF Burden using the AFSS questionnaire at baseline and at final follow up.
Figure 4-3: Outcomes of AF ablation according to group

Kaplan-Meier Curve for single procedure drug-free AF free survival (left) and for total AF free survival (Multiple procedures ± drugs; right). The curves have been provided for 2 years after which <20% have completed follow up. Note the data is provided after the last procedure using a 3-month blanking period.
Figure 4-4: Outcomes of AF ablation according to type of AF

Kaplan-Meier Curve for single procedure drug-free AF free survival (left) and for total AF free survival (Multiple procedures ± drugs; right). The curves have been provided for 2 years after which <20% have completed follow up. Note the data is provided after the last procedure using a 3-month blanking period.
Figure 4-5: Schematic of Pathogenic Process

HTN  
DM  
OSA  
OBESITY  
SMOKING  
ETOH  

ATRIAL REMODELLING  
Structural  
Electrical  
Autonomic  

ATRIAL SUBSTRATE  

AF  

AF ablation  

Less AF Recurrence  

Substrate Modification  

Less Incident AF  

RISK FACTOR MANAGEMENT  
Anti-HTN  
DM Management  
CPAP  
Weight Loss  
Smoking Cessation  
Reduced ETOH  

Substrate Modification  

SUBSTRATE PROGRESSION
Chapter 5: Aggressive Risk factor REduction STudy: implications for the substrate for Atrial Fibrillation (The ARREST-AF Substrate Study)

1.25 Background

Atrial fibrillation (AF) is the most prevalent sustained arrhythmia, with evidence from epidemiological data confirming the emergence of AF as a global epidemic.\textsuperscript{1} Various cardiac risk factors such as hypertension, DM, obesity and OSA have been independently shown to increase incidence of AF with the risk of AF increasing exponentially with each additional risk factor.\textsuperscript{17, 18, 104, 409, 410} These have been associated with structural and electrical remodeling of the atria that forms the substrate leading to the development and progression of AF.\textsuperscript{26-28, 411} A dominant feature of this substrate has been the development of atrial fibrosis and the resultant conduction abnormalities; factors that have been considered irreversible.\textsuperscript{26, 258} Indeed, such changes due to remodeling have been described to directly impair the outcomes of attempts to maintain rhythm control.\textsuperscript{412}

Aggressive weight and risk factor management (RFM) has been associated with a reduction in AF burden,\textsuperscript{352} and improved maintenance of sinus rhythm (SR) after AF ablation.\textsuperscript{362} The mechanisms by which RFM results in improved rhythm control with a reduction in AF burden are not known. Additionally, AF confers an increased risk of stroke. This risk is potentiated by the presence of cardiovascular risk factors. Whether aggressive risk factor management has an impact on thrombogenic risk is not known.
Here we hypothesized that aggressive risk factor management, to treat the primary cause of AF, results in reversal of the substrate for AF and improves thrombogenic risk. In this prospective randomized clinical study, we evaluated the impact of RFM on the electrophysiological and electroanatomical properties of the atria, cardiac structure, endothelial and platelets function.

1.26 Methods

1.26.1 Study Population
Patients were recruited from the Centre for Heart Rhythm Disorders at the University of Adelaide, Australia. Consecutive patients with body mass index (BMI) ≥27kg/m² and ≥1 risk factor (hypertension, glucose intolerance/DM, hyperlipidemia, OSA, smoking or alcohol excess) referred for management of symptomatic AF were included. Exclusion criteria included: history of myocardial infarction or cardiac surgery in the previous 12 months; previous AF ablation; permanent AF; amiodarone use in the previous 6 months; active malignancy; autoimmune or systemic inflammatory diseases; severe renal or hepatic failure. All patients provided written informed consent to the study protocol that was approved by the Research Ethics Committees of the Royal Adelaide Hospital and University of Adelaide.

1.26.2 Study Design and Blinding
This was a single center, prospective, randomized controlled study in which patients were randomized in a 1:1 ratio to either a dedicated physician-directed clinic for risk factor management (RFM) at the time of initial assessment or usual care (Control). All
treating physicians, study and clinical personal with the exception of the physician managing RFM were blinded to patient randomization. In addition, blinding of the patient was maintained by having the identical appointment schedule in the RFM clinic but by providing general discussion and advice for the control group.

1.26.3 Sample Size and Power Calculations
Based on our previous work on reverse electrical remodeling by John et al., expected bipolar voltage improvement post RFM of 20%, SD of 0.6, power of 0.8, 2-sided α of 0.05 and 12% attrition, we required n=28 per group.

1.26.4 Risk Factor Management Group
Patients in RFM attended a physician-directed RFM clinic (in addition to their arrhythmia follow up) every 3-months and were managed according to ACC/AHA guidelines. The details of our RFM have been previously presented. A brief outline is presented below with details in the supplement.

1.26.4.1 Risk Factor Management Strategies
Patients participating in RFM attended a physician-directed RFM clinic (in addition to their arrhythmia follow up) every 3-months and were managed according to ACC/AHA guidelines.

**Blood Pressure Control:** Blood pressure (BP) was measured thrice-daily using home-based automated monitor and an appropriate-sized cuff. Patients maintained a BP dairy, which was utilized to monitor the BP control. In addition, exercise stress testing was performed to determine the presence of exercise-induced hypertension with BP>200/100mmHg considered as evidence to optimise therapy. Lifestyle advice constituted dietary salt restriction. Pharmacotherapy was initiated using renin-
angiotensin-aldosterone system antagonists with other agents used where necessary to achieve a target BP of <130/80mmHg at least 80% of the time. These were corroborated by in-office and 24-hour ambulatory BP measurements, as required. Echocardiography was monitored to ensure resolution of left ventricular hypertrophy.

**Weight Management:** A structured motivational and goal-directed program using face-to-face counseling was used for weight reduction. Patients were encouraged to utilize support counseling and schedule more frequent reviews as required. Initial weight reduction was attempted by a meal plan and behavior modification. Participants were required to maintain a diet and physical activity diary. Meals consisted of high protein and low glycemic index, calorie controlled foods. If patients lost <3% of weight after 3-months they were then prescribed very-low-calorie meal replacement sachets (Nestle Health Science) for 1-2 meals/day. The initial goal was to reduce body weight by 10%. After patients achieved the initial goal, meal replacement was substituted to high protein and low glycemic index, calorie-controlled foods to achieve a target BMI of ≤25kg/m². Low intensity exercise was prescribed initially for 20-minutes thrice-weekly increasing to at least 200-minutes of moderate-intensity activity/week.

**Lipid Management:** Initially managed with lifestyle measures. If patients were unable to achieve LDL-Cholesterol <100mg/dL after 3-months then a HMG-CoA reductase inhibitor was initiated. Fibrates were used for isolated hypertriglyceridemia (TG>500mg/dL) or added to statin therapy if TG>200mg/dL and non-HDL cholesterol was >130mg/dL.
**Glycemic Control:** If fasting glucose was 100-125mg/dL, a glucose tolerance test was performed. Impaired glucose tolerance (IGT) or DM was initially managed with lifestyle measures. If patients were unable to maintain glycosylated hemoglobin ≤6.5% after 3-months, metformin was started. Patients in both groups with suboptimal glycemic control (HbA1c>7%) were referred to a specialized diabetes clinic.

**Sleep Disordered Breathing Management:** In-laboratory overnight polysomnography (PSG) was scored by qualified sleep technicians and reviewed with follow-up by a sleep physician. PSG scoring was according to the AASM alternate PSG scoring criteria. Patients were offered therapy if the Apnea-Hypopnea Index (AHI) was ≥30/hour or if it was >20/hour with resistant hypertension or problematic daytime sleepiness. Treatment included positional therapy and continuous positive airway pressure (CPAP).

**Smoking:** The “5A” (Ask, Advice, Assess, Assist and Arrange follow-up) structured smoking cessation framework was adopted. Smokers were offered behavioral support through a multidisciplinary clinic with the aim of cessation.

**Alcohol:** Written and verbal counseling was provided with regular supportive follow-up for alcohol reduction to ≤30 gm/week.

**Control Group**

The control group was given information on management of risk factors. However, risk factor management was under the direction of their treating physician.
1.26.5 Study Protocol

Both the groups had baseline investigations, which included electrophysiological (EP) study, echocardiography, cardiac MRI, and blood investigation for markers of fibrosis, platelet and endothelial function. These tests were repeated after mean of 13.0±1.0 months. Subjects in RFM group had ≥10% weight loss and at least 6 months of optimal RFM before repeat study. All data collection and analyses were performed by investigators blinded to the study randomization.

1.26.5.1 Electrophysiology Study

The details of electrophysiological study used in our laboratory have been previously presented. Electrophysiological study was performed using: 1) a 10-pole catheter (2-5-2 mm interelectrode spacing, Daig Electrophysiology, Minnetonka, Minnesota) within the coronary sinus with the proximal bipole at the coronary sinus ostium; 2) a 20-pole “crista” catheter (1-3-1 mm interelectrode spacing, Biosense-Webster) placed along the crista terminalis, stabilized by a long sheath (CSTA, Daig Electrophysiology); 3) a 20-pole catheter (2-5-2 mm interelectrode spacing, Daig Electrophysiology) placed along the lateral Right Atrium (RA). Electrophysiological evaluation included:

Effective refractoriness: Atrial ERP was evaluated at twice diastolic threshold at cycle lengths of 600 and 450 ms using an 8-beat drive followed by an extra stimulus, starting with a coupling interval of 150 ms increasing in 10-ms increments. ERP was defined as the longest coupling interval failing to propagate to the atrium. At each site the ERP was measured 3 times at each cycle length and averaged. ERP was measured from the following sites: 1) proximal coronary sinus; 2) distal coronary sinus; 3) low-lateral RA;
4) high-lateral RA. Heterogeneity of ERP was determined by the coefficient of variation of ERP at each cycle length (SD/mean x 100%). AF induced by ERP testing lasting >5 min was considered sustained; when this occurred, no further data were acquired.

**Atrial conduction:** Atrial conduction time was assessed along linearly placed catheters by pacing the distal bipole and determining the conduction time to a proximal bipole at coronary sinus and lateral RA. Conduction time at each site was averaged over 10 beats during stable capture at 600 and 450 ms cycle lengths.

**Site-specific conduction abnormalities at the crista terminalis:** The number of bipoles on the crista terminalis catheter with discrete double potentials separated by an isoelectric interval or complex fractionated activity of >50 ms duration and the maximum electrogram duration were determined during sinus rhythm, constant pacing and for the shortest-coupled captured extra-stimulus from the proximal coronary sinus and low-lateral RA.

**Sinus node function:** Sinus node function was evaluated as follows: 1) baseline sinus cycle length was determined over 10 consecutive sinus cycles; 2) corrected sinus node recovery time (CSNRT) was determined after a 30-s drive train at cycle lengths of 600 and 450 ms, correcting for the baseline cycle length. At each cycle length, CSNRT was determined 3 times and averaged.

**1.26.5.2 Electro anatomical Mapping**

The details of electro anatomical mapping used in our laboratory have been previously published and detailed in the supplement. Electro anatomic maps were
created of RA during sinus rhythm using the CARTO mapping system and a 3.5-mm tip catheter (Navistar, Biosense-Webster). Mapping was performed with an equal distribution of points using a fill-threshold of 15 mm. Editing of points was performed offline. Local activation time was manually annotated to the peak of the largest amplitude deflection on bipolar electrograms; in the presence of double potentials, this was annotated at the largest potential. If the bipolar electrogram displayed equivalent maximum positive and negative deflections, the maximum negative deflection on the simultaneously acquired unipolar electrogram was used to annotate the local activation time. Points not conforming to the surface ECG P-wave morphology or <75% of the maximum voltage of the preceding electrogram were excluded. Regional atrial bipolar voltage and conduction velocity were analyzed. For the purposes of evaluating regional voltage and conduction differences, RA was segmented as the high- and low-lateral RA, high- and low- posterior RA, high- and low-septal RA, and anterior RA.

**Voltage analysis:** Low voltage points were defined as point with a bipolar voltage<0.5 mV and electrically silent points (scar) as the absence of recordable activity or a bipolar voltage amplitude ≤0.05 mV (the noise level of the system).

**Conduction velocity analysis:** Isochronal activation maps (5-ms intervals) of the atria were created and regional conduction velocity determined in the direction of the wave-front propagation (least isochronal crowding). An approximation of conduction velocity was determined by expressing the distance between 2 points as a function of the difference in local activation time. Mean conduction velocity for each region was determined by averaging the conduction velocity between 5 pairs of points.
**Complex electrograms:** The proportion of points demonstrating complex electrograms was determined using the following definitions: 1) fractionated signals: complex activity of ≥50 ms duration; and 2) double potentials: potentials separated by an isoelectric interval where the total electrogram duration was ≥50 ms.

### 1.26.5.3 Cardiac Magnetic Resonance Imaging

**CMR acquisition:** Cardiovascular magnetic resonance imaging was performed on supine subjects using a 1.5T scanner (Siemens Avanto) and a standard phased array surface coil. For the ventricular image set, 8 to 12 ventricular short-axis slices (slice thickness 6mm, 4mm intersection gaps) from the level of the mitral valve to LV apex were acquired. Images were obtained during breath-hold with retrospectively ECG-gated free-progression sequences: image matrix 256 x 150, FOV 380mm, repetition time 52.05ms, echo time 1.74ms, flip angle 70°. For the atrial image set, contiguous slices in both short (bi-atrial) and horizontal long axis views (four chamber) were obtained (slice thickness of 6 mm, no intersection gap).

**Ventricular analysis:** LV and RV chambers were manually traced at end-diastole and end-systole with the most basal slice determined by at least 50% of ventricular myocardium surrounding the blood pool.

**Atrial analysis:** Atrial chambers were manually traced utilizing a disc summation method at ventricular end-systole and end-diastole. The borders of the LA were defined as the plane of the mitral valve and the visually apparent juncture of LA with
pulmonary veins. The borders of the RA were defined as the plane of the tricuspid valve and the juncture with the caval veins.

**Pericardial adipose tissue quantification:** Pericardial adipose tissue was traced at end-diastole from the ventricular short-axis stack. Traces were made around the myo-epicardial border and outermost border of adipose tissue, subtending an area of PF. Traces were undertaken on contiguous ventricular slices and PF volume subsequently derived using a disc summation method.

**1.26.5.4 Echocardiography**
Transthoracic echocardiography was performed according to American Society of Echocardiography guidelines by an operator, blinded to the study group. Volumetric parameters including Indexed LA volume (Indexed LAV) and indexed LV end diastolic diameter (Indexed LVEDd), interventricular septal thickness (IVS) and LV diastolic function were determined.

**1.26.5.5 Platelet and Endothelial Function**
The techniques used for evaluating platelet and endothelial function in our laboratory have been previously described and are detailed in the supplement. The following were determined by an investigator blinded to the study randomization.

**Platelet function:** Blood samples were obtained via venipuncture of an antecubital vein and collected into tubes containing 3.8% sodium citrate at 9:1 ratio. Whole blood flow cytometry was performed. The surface expression of the platelet activation
receptor, CD62P (P-selectin) was determined by flow cytometry using the CD62P monoclonal antibody as previously described [ref]. Platelet aggregometry was performed using the whole blood Multiplate Analyzer (Roche Diagnostics International LDT, Rotkreuz, Switzerland). The Multiplate Analyzer is an impedance aggregometer. Aggregation arbitrary aggregation units was determined using adenosine diphosphate (1.6 and 6.5 mmol/L), collagen (3.2µg), arachidonic acid (0.5 mmol/L) or thrombin (32µg) Roche Diagnostics International LDT, Rotkreuz, Switzerland).

**Enzyme-linked immunosorbent assay:** Whole blood from each patient was centrifuged at 2,500g for 15 minutes at 4°C to obtain plasma and then stored at -80°C for batch analysis. ELISAS were completed for levels of Asymmetric dimethylarginine (ADMA, Immunodiagnostic AG) measured as marker of endothelial damage/dysfunction. Vascular function was assessed by measuring levels of Endothelin-1 (ET-1; R&D Systems). Tissue specific inflammatory markers included interleukin-6 (IL-6; R&D Systems), myeloperoxidase (MPO; R&D Systems) and transforming growth factor (TGF-β1; R&D Systems). Extracellular matrix remodeling was evaluated by determining levels of matrix metalloproteinase-9 (MMP-9), tissue inhibitors of matrix metalloproteinase (TIMP-1) (R&D Systems) and B-type natriuretic peptide (BNP) (RayBiotech).

### 1.2.6 Statistical Analysis

Differences in outcomes were determined within each group and between the 2 study groups on an intention-to-treat basis. Categorical variables are represented by frequencies and percentages, and continuous variables are summarized by mean±SD. Repeated measure analysis of variance was used to assess the interaction between the
groups over time. The significance of the interaction in the analysis of variance was used to assess these changes. Comparisons of variables for both the control and RFM groups were performed by using paired-sample Student’s t tests. For nominal variables, changes were only assessed for patients who were positive at baseline. The changes in the status at final follow-up were compared using chi-square tests. Two-tailed p values <0.05 were considered statistically significant. Statistical analysis was performed using SPSS version 21.

1.27 RESULTS

1.27.1 Baseline Characteristics
Of 67 consecutive patients referred for management of symptomatic AF, 60 patients consented and were randomized for the study. Of these, 3 patients subsequently moved out of the region and did not have any follow up investigations, and 7 (4 RFM, 3 Control) declined further participation. The final cohort included 50 patients; 24 RFM and 26 controls [Figure-1]. Mean follow-up in the RFM and control groups were 15.7±2.5 and 15.6±3.4 months, respectively (P=0.8). Mean duration between the baseline and follow up procedure was 13.0±1.0 months in RFM group and 12.3±2 months in control group (P=0.1). Baseline characteristics were similar in the two groups (Table-1).

1.27.2 Risk Factor Modification
Table-2 shows the impact of RFM on various cardiac risk factors.

Blood Pressure Control: There was a greater decline in systolic BP with RFM compared to controls (14.1±3.5 versus 1.6±1.2mmHg; P=0.004).
**Weight Management:** Weight and BMI decreased in both groups, but significantly more with RFM compared to controls (both $P<0.001$).

**Lipid Management:** With diet and lifestyle modification, LDL-C and non-HDL-C were well controlled in 60% of RFM and 24% of controls ($P=0.001$). Drug therapy was required in 40% of RFM and 68.1% of control group ($P=0.02$).

**Glycemic Control:** At baseline, 9% of RFM and 11% of controls had history of DM ($P=0.5$). At final follow-up, DM patients in the RFM had significantly better glycemic control compared to controls; HbA1c < 7% in 100% vs. 33%, respectively ($P=0.003$).

**Sleep Apnea Management:** At baseline, 33% of RFM and 30% of controls had severe OSA ($AHI \geq 30; P=0.1$). This improved significantly in RFM group at final follow-up ($P=0.001$)

**Smoking and Alcohol Use:** Most patients successfully stopped smoking: 9 (90%) RFM and 10 (78%) of controls ($P=0.04$). In RFM, 9 (91%) patients successfully reduced alcohol consumption to below 30g/week, while only 7 (58%) controls achieved this ($P=0.01$).

**1.27.3 Electrophysiological Remodeling**
Table 3 summarizes the electrophysiological changes.

**Atrial refractoriness:** Figure 2 demonstrates the ERP at all sites (600 and 450 ms drive trains) in both groups at baseline and final follow-up. Patients in RFM group demonstrated significant overall increase in ERP ($P=0.01$) with reduced ERP heterogeneity ($P=0.02$) when compared to controls.
**Atrial conduction:** The conduction times along the CS and lateral RA were similar in both groups at baseline (p=0.2). However, at final follow up, the conduction time across both sites reduced significantly in the RFM but not the control group (all P<0.05).

**Site-specific conduction abnormalities:** Site-specific conduction abnormalities at the crista terminalis during SR were similar in both groups at baseline. At final follow up, the RFM group demonstrated significant reduction in bipoles with double potentials (P=0.004) although the maximum electrogram duration was unchanged (P=0.08).

**1.27.4 Atrial Fibrillation**

**Vulnerability for AF:** Table 3 shows the incidence of inducible and sustained AF episodes. Patients in both groups had similar incidence of inducible and sustained AF episodes at baseline (P >0.05). At final follow-up, incidence of inducible (P=0.02) and sustained AF episodes (P=0.001) decreased in RFM group and did not change significantly in controls.

**AF burden:** Table 2 shows the total AF burden. The mean number of AF episodes and total AF burden was similar in both the groups at baseline (P>0.05). At final follow-up, both number of episodes (P=0.001) and total AF burden (P<0.001) decreased in RFM and did not change significantly in controls.

**1.27.5 Electroanatomical mapping**

Table 3 summarizes the electroanatomical changes.

**Bipolar Voltage:** The mean bipolar voltage was similar in both groups at baseline (P=0.2). Representative examples of electroanatomic maps are shown in Figure 3.
There was a marked improvement in bipolar voltage in the RFM group but not in controls (P=0.02). This was consistent at all regions assessed (Figure 4).

**Conduction velocity.** Patients in both groups had similar mean conduction velocity at baseline (P=0.1). There was a marked improvement in conduction velocity in the RFM group but not in controls (P<0.001). Figure 4 details the changes in conduction velocity by regions assessed.

**Complex electrograms.** Patients in both groups demonstrated similar burden of double potentials or fractionated signals at baseline (P=0.1). At final follow-up, RFM group demonstrated significantly fewer double potential or fractionated signals versus controls (P=0.002).

1.27.6 Structural Remodeling
Table 4 summarizes the findings related to structural changes.

1.27.6.1 Echocardiogram:
Indexed LA volume decreased with RFM from 36±8.7 to 30.8±4.4 ml/m² (P<0.001) while this increased in controls from 37.1±7.4 to 39.5±12.1 ml/m² (P=0.04). Similarly, IVS thickness decreased with RFM (10.8±2.0 to 9.3±0.1, P<0.001) but increased in controls (10.0±0.1 to 10.6±0.1, P=0.03). RFM was also associated with a significant improvement in Indexed LVEDd (P<0.001) and E/e’ (P<0.001).

1.27.6.2 Cardiac MRI:
**Atrial volumes:** Both the groups had similarly dilated atria at baseline (P=0.8). At the final follow-up, the RFM group demonstrated significant reduction in both LAESV (P=0.01) and LAEDV (P<0.001).
Ventricular mass and volumes: Indexed LV mass increased from 60.2±11.5 to 70.5±11.8 g/m² (P=0.001) in the control group, whereas the RFM group showed a reduction from 64.4±14.4g to 53.0±11.2g/m² (P<0.001). LVEDV was unchanged with RFM (P=0.95) but increased in controls (P<0.001).

Pericardial Fat: With RFM, there was significant reduction in both aPAT (P=0.008) and vPAT (P=0.002). In contrast, aPAT was unchanged (P=0.1) and vPAT was increased (P<0.001) in controls.

Serum Fibrosis Biomarkers: With RFM, there was a significant decline in all the fibrosis markers: MMP-9 (P=0.03), TIMP (P=0.04) and TGF-β (P=0.03), whereas these levels remained high and unchanged in the control group.

1.27.7 Platelet, Endothelial and Inflammatory Markers

Table 5 summarizes the changes related to platelet and endothelial function.

Platelet Activation: At baseline, CD62P (P-Selectin) expression was similar in both groups (P=0.07). At final follow-up the P-Selectin expression increased in control but decreased in the RFM group (P <0.001). PAC-1 binding (glycoprotein IIb/IIIa expression) did not differ significantly between the two groups at both time-points (P =0.2).

Thrombin generation: Thrombin generation (TAT) was similar at baseline in both the groups (P=0.1). At follow-up, there was significant decrease with RFM (P =0.03) and increase in the control group (P=0.006).
**Platelet aggregation:** Platelet aggregation to ADP 2.5μM and 5 μM was similar in both the groups at baseline (P=0.9). At final follow-up, this decreased significantly after RFM (P <0.001) with no significant difference in controls.

**Endothelial dysfunction:** Similar endothelial function was seen in both groups at baseline (P=NS). However, there was a significantly greater improvement with reduction in ADMA (P<0.001) and plasma ET-1 levels (P= 0.03) following RFM.

**Inflammation:** Systemic inflammatory markers were similar at baseline in both groups (P=NS). With RFM, there was a significant decline in the inflammatory state with reduced mean hs-CRP (P=0.001), IL-6 (P=0.007) and MPO levels (P=0.04).

### 1.28 DISCUSSION

This prospective, randomized controlled study demonstrates that in patients with AF, a structured physician-directed RFM program results in significant reversal of the abnormal atrial substrate. Aggressive RFM was associated with:

1: Marked structural improvement with a reduction in atrial size, regression of ventricular mass and normalization of bipolar voltages;

2: Significant improvement in the electrophysiological properties including conduction and ERP parameters;

3: Reduced pericardial fat volumes and serum fibrosis markers (MMP-9, TGF-β 1 and TIMP levels);
4: Improved endothelial function (ET-1 and ADMA), platelet function (ADP, Thrombin, collagen and P-Selectin levels) and inflammatory markers (HsCRP, IL-6 and MPO);

Perhaps as a consequence of the above changes, there was a reduction in AF vulnerability during electrophysiological study and clinical AF burden. These findings demonstrate that the substrate predisposing to AF is reversible by aggressive targeting of the primary conditions leading to AF. In addition, it suggests that altering the individuals’ risk profile may also modify the propensity for thromboembolic complications.

1.28.1 Importance of the predisposing substrate

AF is a self-perpetuating arrhythmia, the dynamic adaptive changes in the atria in response to AF, enhances the ability of the arrhythmia not only to sustain itself, but also to recur. This remodeling process has been demonstrated to be reversible shortly after restoration of SR. In the contrary, the profound structural changes seen in longer episodes of AF have been suggested to be progressive and irreversible. On the other hand, it was postulated that early cardioversion would prevent the remodeling due to AF itself and allow “sinus rhythm to beget sinus rhythm”. However, when evaluated clinically, prompt termination of AF did not impact the maintenance of SR. Thus the role of a “second factor” i.e. atrial substrate responsible for propagation of AF, has been implicated. Indeed, abnormal atrial changes have been observed even in ‘lone AF’ patients. In addition, a recent study has observed a progressive atrial substrate even after successful catheter ablation of AF. These findings argue in favor of an underlying atrial substrate responsible for AF.
Li et al was first to highlight the importance of structural changes in maintaining AF. They elegantly demonstrated increased atrial fibrosis and the resultant conduction abnormalities in canine with congestive heart failure. Since this report, various studies have evaluated the substrate for AF in conditions known to be associated with AF and have demonstrated consistent structural changes, suggesting a final common pathway. The maladaptive structural changes occur at both macro- and microscopic levels. The hallmark of macroscopic change is “atrial dilation”. Significant microscopic changes include cellular hypertrophy, fibrosis, apoptosis and fatty infiltration. The complex signaling pathways underlying these structural changes remain incompletely understood and involved, at the very least, the TGF-β1, renin-angiotensin-aldosterone system, connective tissue growth factors, and endothelin-1 system. While the electrical remodeling is more “forgiving”, controversies exist regarding reversibility of these ultra-structural changes on withdrawal of the initiating stimulus. Some changes may be reversible; others such as atrial fibrosis have been suggested to be irreversible.

1.28.2 Reversibility of the substrate for AF
Various upstream therapies have demonstrated beneficial effects on AF. Antihypertensive therapy has been shown to reduce left atrial size and left ventricular hypertrophy leading to a lower risk of AF in hypertensive individuals. Angiotensin-receptor blockade (ARB) has also been shown to attenuate atrial fibrosis and conduction abnormalities due to heart failure. More recent studies have also demonstrated protective effects on atrial remodeling with other novel upstream pharmacotherapeutic agents. In model heart failure models, n-3 polyunsaturated fatty acids and tranilast have been demonstrate to attenuate the development of the
substrate for AF. In addition, in the established substrate of mitral stenosis, treatment of the primary cause was surprisingly associated with an improvement in atrial voltage and conduction with a reduction in abnormal and fractionated electrograms when studied ≥6 months later. Recently, we have presented results from an ovine study, where weight reduction over a prolonged period of 8 months was associated with reversal of hemodynamic abnormalities, atrial fibrosis, and the electrophysiological abnormalities resulting in reduced AF vulnerability. However, reversal of heart failure by cessation of rapid pacing for 5 weeks was associated with a hemodynamic improvement but persistent atrial fibrosis, conduction heterogeneity and inducibility of AF.

Recently, our group has demonstrated that weight and risk factor management could result in significant improvement in left atrial volume, regression in LVH, reduced AF burden and recurrence post ablation in patients with AF. This study provides novel evidence that aggressive RFM over 13±1 month (minimum of 6 months) could result in improved electro-structural remodeling with increased atrial refractoriness, higher myocardial voltage and conduction velocity and a reduction in fractionated electrograms. This was associated not only with a reduced inducibility of AF during the study but a clinical reduction in AF burden. The current study also provides novel insights regarding the mechanisms responsible for this substrate reversal. These include reduction in: left atrial stretch as evidenced by reduced atria size and improved LV diastolic function; pro-inflammatory and fibrotic markers as well as pericardial fat burden which has been shown to have paracrine and pro-fibrotic effects on the contiguous myocardium. We posit that the lack of reverse structural remodeling from
previous work in the heart failure model following cessation of rapid pacing may be due to the significantly shorter period of recovery (at 5 weeks) than our follow-up duration of 13 months.

1.28.3 Cardiovascular risk factors and the risk of stroke in AF

AF confers a 5-fold increased risk of stroke in the absence of valvular heart disease. AF confers a 5-fold increased risk of stroke in the absence of valvular heart disease. This risk is heightened in the presence of other cardiac risk factors as evidenced by the CHADS$_2$-VAS$_C$ scoring system. Mechanistic evaluation of the thrombogenic risk has traditionally focused on Virchow’s triad. The hypercoaguable state is known to involve endothelial dysfunction characterized by an increase in ADMA (an endogenous inhibitor of endothelial nitric oxide synthase) and ET-1 levels (a potent vasoconstrictor and modulator of the load/stretch-induced hypertrophic response); platelet activation with increased expression of P-selectin; and inflammation.

In the current study, RFM was associated with improvement in endothelial function (reduction in ADMA and ET-1 levels), reduced platelet activation (decline in P-selectin expression, platelet aggregation index and thrombin generation) and a marked reduction in serum inflammatory markers (such HsCRP, IL-6 and MPO levels). This improvement in thrombogenic milieu may potentially reduce the risk of stroke in high-risk AF patients. In summary, while risk factors are associated with an increased risk of stroke, this study argues for the reassessment of thromboembolic risk in patients who have well managed risk factors.
1.28.4 Clinical Implications
This clinical study demonstrates the reversibility of the established structural and electrophysiological substrate pre-disposing to AF by aggressive risk factor management. This clinical strategy has been observed to reduce AF symptoms and burden. These finding highlight the essential role of risk factor management in primary and secondary prevention strategies for AF. In addition it raises the possibility that such management strategy may also alter the risk of stroke.

1.28.5 Limitations
This study has evaluated the impact of aggressive risk factor management on the substrate predisposing to AF. However, it is well recognized that AF is due to the complex interplay between triggers, perpetuators with the substrate\textsuperscript{38}, factors that have not been evaluated in this study.
Figure 5-1: Flow diagram demonstrating patient recruitment and attrition

ARREST-AF Substrate study Consort Diagram

Enrollment

Assessed for eligibility (n=67)

Declined Participation (n=7)

Randomized (n=60)

Allocation

Aggressive risk factor management RFM (n=30)

 usual Care Control (n=30)

Lost to follow-up (n=6)
  ♦ Moved interstate (n=2)
  ♦ Refused further participation (n=4)

Follow-Up

Lost to follow-up (n=4)
  ♦ Moved interstate (n=1)
  ♦ Refused further participation (n=3)

Analysis

RFM (n=24)

Control (n=26)
Figure 5-2: Regional effective refractoriness

Regional Effective Refractory Period

Mean ERP at the 4 sites tested after a 600-ms drive train (top) and a 450-ms drive train (bottom) in Control (CTL) and RFM groups. The difference in mean ERP between RFM and Control groups varied significantly according to the region of measurement (P = 0.01 for group by region interaction). * P < 0.05 for post-hoc comparisons. PCS = Proximal Coronary Sinus; DCS = Distal Coronary Sinus; HLRA = High Lateral Right Atrium; LLRA = Low Lateral Right Atrium
Figure 5-3: Example electroanatomic bipolar voltage maps.

A: Representative CARTO map of a patient Pre-RFM (top) and Post-RFM (bottom). B: Representative CARTO map of a control patient at baseline (top) and follow-up (bottom). All RA maps are shown in both RAO (left) and LAO (right) projections at the same scale. The color bar is standardized with red representing low voltage <0.5 mV and purple representing voltage >5 mV.
Figure 5-4: Regional bipolar voltage

Mean bipolar voltage (Top) and Mean conduction velocity (Bottom) of the 7 Right Atrium (RA) regions from the electroanatomic map. *P <0.001 and †P <0.02 for post-hoc comparisons. HL = High Lateral; LL = Low Lateral; HS= High Septal; LS= Low Septal; HP= High Posterior; LP = Low Posterior
Table 5-1: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Control Group (N = 26)</th>
<th>RFM Group (N = 24)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53 ± 11</td>
<td>56 ± 10</td>
<td>0.8</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>17 (65%)</td>
<td>12 (55%)</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Anthropometric Measures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>105.5±15.5</td>
<td>102.9±20.1</td>
<td>0.2</td>
</tr>
<tr>
<td>BMI (Kgm$^{-2}$)</td>
<td>34.0±4.9</td>
<td>33.0±5.5</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>Atrial Fibrillation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Paroxysmal, n (%)</td>
<td>8 (31%)</td>
<td>11 (50%)</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Metabolic Risk Factors</strong></td>
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<td></td>
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<tr>
<td>Hypertension</td>
<td>19 (73%)</td>
<td>14 (64%)</td>
<td>0.5</td>
</tr>
<tr>
<td>DM n (%)</td>
<td>3 (11%)</td>
<td>2 (9%)</td>
<td>0.5</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>12 (46%)</td>
<td>10 (42%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>3 (12%)</td>
<td>1 (5%)</td>
<td>0.4</td>
</tr>
<tr>
<td>AH1&gt;30, n (%)</td>
<td>8 (31%)</td>
<td>8 (36%)</td>
<td>0.7</td>
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<td>Alcohol excess (&gt;30g/week), n (%)</td>
<td>10 (38%)</td>
<td>5 (23%)</td>
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<tr>
<td>Smoker, n (%)</td>
<td>13 (50%)</td>
<td>10 (42%)</td>
<td>0.4</td>
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<tr>
<td><strong>Medication Use</strong></td>
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<td>Mean no. of Anti-Arrhythmic</td>
<td>1.2±0.3</td>
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<td>Mean no. of Anti-Hypertensive</td>
<td>1.6±1.3</td>
<td>1.5±1.2</td>
<td>0.3</td>
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<td><strong>Echocardiographic Measures</strong></td>
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<td>LA Volume Indexed (mls/m$^2$)</td>
<td>29.74 ± 7.6</td>
<td>35.83 ± 8.5</td>
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<td>LV septum (mm)</td>
<td>10.0 ± 1.3</td>
<td>10.8 ± 2.1</td>
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<td>LVEVDd Index (cm)</td>
<td>2.36 ± 0.30</td>
<td>2.63 ± 0.29</td>
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<td>E/e’</td>
<td>8.61 ± 2.65</td>
<td>10.55 ± 2.87</td>
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<td>Risk Factors</td>
<td>Control Group (N=26)</td>
<td>RF Mx Group (N=24)</td>
<td>P value*</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>----------------------</td>
<td>--------------------</td>
<td>----------</td>
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<td>Weight (Kg)</td>
<td>105.5±15.5</td>
<td>104.4±16.5</td>
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<td>BMI</td>
<td>34.0±4.9</td>
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<td>Mean SBP (mmHg)</td>
<td>151±18</td>
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<td>0.06</td>
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<td>DM with HbA1c≥7, n (%)</td>
<td>3(11%)</td>
<td>2(7%)</td>
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<td>AHI&gt;30, n (%)</td>
<td>8(31%)</td>
<td>5(19%)</td>
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<td>Alcohol (&gt;30g/week), n (%)</td>
<td>10(38%)</td>
<td>5(19%)</td>
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<td>Smoker, n (%)</td>
<td>13(50%)</td>
<td>3(12%)</td>
<td>-</td>
</tr>
<tr>
<td>Atrial Fibrillation detected by 7 days Holter</td>
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<td></td>
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<tr>
<td>≥1 episode, No. (%)</td>
<td>18 (69)</td>
<td>22 (84)</td>
<td>0.002</td>
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<tr>
<td>Mean no of AF Episodes</td>
<td>3.5±1.1</td>
<td>3±1.0</td>
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<tr>
<td>Total Duration, min</td>
<td>1526±300</td>
<td>1497±298</td>
<td>0.2</td>
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</table>

Table: Risk Factor control and AF burden changes from baseline to follow-up. *P value refers to within group difference (baseline to follow-up); †P value refers to between group differences over time (group-time interaction). ‡Median follow-up: 15.7±2.5 months for RF Mx group and 15.6±3.4 months for control group.
Table 5-3: Electrical remodeling

<table>
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<tr>
<th></th>
<th>Control Group (N=26)</th>
<th>RF Mx Group (N=24)</th>
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</thead>
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<tr>
<td><strong>Electrophysiologic Study</strong></td>
<td>Baseline</td>
<td>Follow-up‡</td>
<td>P value*</td>
<td>Baseline</td>
<td>Follow-up‡</td>
<td>P value*</td>
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<tr>
<td>CSNRT at 600MS (ms)</td>
<td>461±180</td>
<td>468±130</td>
<td>0.2</td>
<td>469±131</td>
<td>298±92</td>
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<td>P wave duration (ms)</td>
<td>138±9</td>
<td>140±8</td>
<td>0.8</td>
<td>139±10</td>
<td>119±10</td>
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<td>Mean Atrial ERP at 600MS</td>
<td>249±44</td>
<td>246±47</td>
<td>0.6</td>
<td>248±43</td>
<td>273±25</td>
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<td>Heterogeneity of ERP, (%)</td>
<td>17±4</td>
<td>19±3</td>
<td>0.5</td>
<td>17±3</td>
<td>9±3</td>
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<td>Mean Atrial Conduction time (ms)</td>
<td>107±18</td>
<td>105±14</td>
<td>0.5</td>
<td>104±15</td>
<td>90±9.5</td>
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<td>No of DP</td>
<td>7±2</td>
<td>6±2</td>
<td>0.08</td>
<td>6±2</td>
<td>3±1</td>
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<td>DP duration (ms)</td>
<td>95±15</td>
<td>94±12</td>
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<td>97±13</td>
<td>78±11</td>
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<td><strong>Electro anatomical Mapping</strong></td>
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<td>Mean Voltage, (mV)</td>
<td>1.5±0.7</td>
<td>0.8±0.3</td>
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<td>Mean Conduction Velocity, m/s</td>
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<td>1.0±0.4</td>
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<td>0.8±0.2</td>
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<td>Heterogeneity of CV (%)</td>
<td>30±8</td>
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<td>29±6</td>
<td>15±4</td>
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<td>No Of Complex Electrogram</td>
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<td>35±8</td>
<td>22±9</td>
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<td><strong>AF Inducibility</strong></td>
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<tr>
<td>AF Inducibility (%)</td>
<td>3±3.8</td>
<td>3.7±2.8</td>
<td>0.08</td>
<td>4±3</td>
<td>1.9±2</td>
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<tr>
<td>Pts with AF episodes (&gt;5Min), (n)</td>
<td>6</td>
<td>7</td>
<td>0.4</td>
<td>5</td>
<td>1</td>
<td>0.03</td>
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</tbody>
</table>

Table: Risk Factor and AF severity changes from baseline to follow-up. *P value refers to within group difference (baseline to follow-up); †P value refers to between group differences over time (group-time interaction). ‡Median follow-up: 15.7±2.5 months for RF Mx group and 15.6±3.4 months for control group. ERP: Effective refractory period; DP: Double Potential; CV: Conduction velocity; AF: Atrial Fibrillation
Table 5-4: Structural remodelling

<table>
<thead>
<tr>
<th>Echocardiographic Measures</th>
<th>Control Group (N=26)</th>
<th>RF Mx Group (N=24)</th>
<th>Baseline</th>
<th>Follow-up‡</th>
<th>P value*</th>
<th>Baseline</th>
<th>Follow-up‡</th>
<th>P value*</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA Volume Indexed (mls/m²)</td>
<td>37.1±7.4</td>
<td>39.5±12.1</td>
<td>0.04</td>
<td>36.05±8.7</td>
<td>&lt;0.001</td>
<td>30.81±4.4</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>LV septum (mm)</td>
<td>10.0 ± 1.3</td>
<td>10.6±0.1</td>
<td>0.03</td>
<td>10.8 ± 2.1</td>
<td>&lt;0.001</td>
<td>9.3±0.1</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>LVEDD Index (cm/m²)</td>
<td>2.36±0.3</td>
<td>2.43±0.4</td>
<td>0.41</td>
<td>2.63±0.3</td>
<td>&lt;0.001</td>
<td>2.29±0.3</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>E/e’</td>
<td>9.61±2.7</td>
<td>11.31±3.0</td>
<td>&lt;0.001</td>
<td>10.0±2.9</td>
<td>&lt;0.001</td>
<td>7.25±1.9</td>
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Cardiac MRI

<table>
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<tr>
<th>Echocardiographic Measures</th>
<th>Control Group (N=26)</th>
<th>RF Mx Group (N=24)</th>
<th>Baseline</th>
<th>Follow-up‡</th>
<th>P value*</th>
<th>Baseline</th>
<th>Follow-up‡</th>
<th>P value*</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDV (ml)</td>
<td>148.1±35.9</td>
<td>157.2±36.1</td>
<td>&lt;0.001</td>
<td>144.0±28.1</td>
<td>&lt;0.001</td>
<td>144.5±33.1</td>
<td>0.95</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>LVESV (ml)</td>
<td>50.6±19.6</td>
<td>63.8±22.8</td>
<td>&lt;0.001</td>
<td>57.8±13.0</td>
<td>&lt;0.001</td>
<td>47.4±9.8</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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</tr>
<tr>
<td>LV Mass Index (g/m²)</td>
<td>60.2±11.5</td>
<td>70.5±11.8</td>
<td>0.001</td>
<td>64.4±14.4</td>
<td>&lt;0.001</td>
<td>53.0±11.2</td>
<td>&lt;0.001</td>
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<tr>
<td>LAEDV (ml)</td>
<td>103.1±38.5</td>
<td>116.2±39.7</td>
<td>&lt;0.001</td>
<td>118.7±38.1</td>
<td>&lt;0.001</td>
<td>98.4±26.7</td>
<td>0.001</td>
<td>0.25</td>
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<tr>
<td>LAESV (ml)</td>
<td>56.2±27.2</td>
<td>71.7±35.3</td>
<td>0.006</td>
<td>69.2±42.9</td>
<td>0.01</td>
<td>50.8±21.3</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>LA EF Index (%/m²)</td>
<td>1.5±0.5</td>
<td>1.2±0.5</td>
<td>0.004</td>
<td>1.4±0.5</td>
<td>&lt;0.001</td>
<td>1.8±0.3</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>aPAT (ml)</td>
<td>18.3±8.7</td>
<td>19.6±8.5</td>
<td>0.1</td>
<td>14.9±7.0</td>
<td>0.008</td>
<td>11.2±3.8</td>
<td>&lt;0.001</td>
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<tr>
<td>vPAT (ml)</td>
<td>110±35.2</td>
<td>142±56.8</td>
<td>&lt;0.001</td>
<td>107.1±42.0</td>
<td>0.002</td>
<td>77.3±22.8</td>
<td>&lt;0.001</td>
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Fibrosis Markers

<table>
<thead>
<tr>
<th>Echocardiographic Measures</th>
<th>Control Group (N=26)</th>
<th>RF Mx Group (N=24)</th>
<th>Baseline</th>
<th>Follow-up‡</th>
<th>P value*</th>
<th>Baseline</th>
<th>Follow-up‡</th>
<th>P value*</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMP-9 (ng/ml)</td>
<td>49±22.4</td>
<td>42.5±15</td>
<td>0.46</td>
<td>48±21.6</td>
<td>0.01</td>
<td>32.7±8.4</td>
<td>0.03</td>
<td>0.03</td>
<td></td>
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<tr>
<td>TIMP (ng/ml)</td>
<td>107±29</td>
<td>105±25</td>
<td>0.85</td>
<td>106±33</td>
<td>0.03</td>
<td>90±16</td>
<td>0.04</td>
<td>0.04</td>
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</tr>
<tr>
<td>TFG-beta (pg/ml)</td>
<td>341±57</td>
<td>363±58</td>
<td>0.30</td>
<td>348±76</td>
<td>0.18</td>
<td>323±42</td>
<td>0.03</td>
<td>0.03</td>
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</tr>
</tbody>
</table>

Risk Factor and AF severity changes from baseline to follow-up. *P value refers to within group difference (baseline to follow-up); †P value refers to between group differences over time (group-time interaction). ‡ Median follow-up: 15.7±2.5 months for RF Mx group and 15.6±3.4 months for control group. LA: Left atrium; LV: Left Ventricle; EDV: Left Ventricular end diastolic volume; ESV: End Systolic Volume
<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Control Group (N=26)</th>
<th>RF Mx Group (N=24)</th>
<th>P value*</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow-up‡</td>
<td></td>
<td>Baseline</td>
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<tr>
<td><strong>Endothelial Function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADMA, umol/L</td>
<td>0.6±0.2</td>
<td>0.7±0.4</td>
<td>0.01</td>
<td>0.7±0.2</td>
</tr>
<tr>
<td>ET-1, pg/ml</td>
<td>1.9±0.9</td>
<td>2.4±1.0</td>
<td>0.06</td>
<td>2.2±1.1</td>
</tr>
<tr>
<td><strong>Platelet Function Test</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PA to ADP 5μM (AU)</td>
<td>82.1±27.2</td>
<td>99.2±20.1</td>
<td>0.008</td>
<td>82.2±24.7</td>
</tr>
<tr>
<td>Thrombin (AU)</td>
<td>89.0±33.5</td>
<td>116.89±13.6</td>
<td>0.006</td>
<td>98.32±26.8</td>
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<tr>
<td>Collagen (AU)</td>
<td>61.3±33.0</td>
<td>87.62±39.5</td>
<td>0.06</td>
<td>59.06±37.4</td>
</tr>
<tr>
<td>P selectin (%)</td>
<td>2.8±4.1</td>
<td>6.67±5.4</td>
<td>0.03</td>
<td>5.38±3.7</td>
</tr>
<tr>
<td>PAC (%)</td>
<td>1.12±2.0</td>
<td>7.90±13.2</td>
<td>0.2</td>
<td>0.64±1.4</td>
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<tr>
<td><strong>Biomarkers</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hs CRP, mg/L</td>
<td>2.3±1.2</td>
<td>2.5±1.3</td>
<td>0.25</td>
<td>2.5±1.0</td>
</tr>
<tr>
<td>IL-6, pg/ml</td>
<td>3.2±1.2</td>
<td>3.5±1.6</td>
<td>0.13</td>
<td>3.7±1.5</td>
</tr>
<tr>
<td>MPO, ng/ml</td>
<td>24±10.7</td>
<td>22.5±11.0</td>
<td>0.46</td>
<td>22.0±12.0</td>
</tr>
<tr>
<td>Fasting Insulin, mU/L</td>
<td>17±2</td>
<td>15±3</td>
<td>0.7</td>
<td>16±3</td>
</tr>
<tr>
<td>BNP, ng/ml</td>
<td>629±762</td>
<td>839±1091</td>
<td>0.2</td>
<td>627±846</td>
</tr>
</tbody>
</table>

Risk Factor and AF severity changes from baseline to follow-up. *P value refers to within group difference (baseline to follow-up); †P value refers to between group differences over time (group-time interaction). ‡Median follow-up: 15.7±2.5 months for RF Mx group and 15.6±3.4 months for control group.
Chapter 6: Cost Effectiveness and Clinical Effectiveness of The risk factor management clinic versus usual care study in Atrial Fibrillation patients (CENT-AF Study)

1.29 Background

Recently reported epidemiological data confirms the emergence of AF as a global epidemic.\textsuperscript{1} This has significant and progressive impact on health care cost due to its association with increased cardiovascular morbidity, reduced quality of life, stroke and mortality.\textsuperscript{5, 430, 431} The incremental cost of AF in US is estimated to range between $6.0 billion and $26.0 billion per year.\textsuperscript{432} Hospitalization, increased medication and procedural requirements constitute the major contributor to the total treatment cost of AF patients.\textsuperscript{12, 433, 434} Although population ageing is regarded as an important contributor to the growing burden of AF, increasing prevalence of risk factors such as obesity, hypertension, diabetes mellitus (DM), and obstructive sleep apnea (OSA) have been implicated.\textsuperscript{18, 33} Therefore, there is an urgent need for improved primary and secondary AF prevention strategies to reduce the impact of this potentially enormous health burden.

Despite recent advances, effectiveness of treatment for AF remains suboptimal. Medical therapy for AF aimed at either rate or rhythm control has been disappointing. Large randomized trials have failed to demonstrate a mortality benefit of a pharmacologically based rhythm control strategy compared with a rate-controlled strategy.\textsuperscript{35, 302} However, subsequent post-hoc analyses found that patients who
remained in sinus rhythm, had fewer strokes\textsuperscript{435} and better survival\textsuperscript{305} than patients who had recurrent AF, suggesting that the beneficial effects of sinus rhythm may have been offset by the side effects of antiarrhythmic therapy\textsuperscript{305}. Additionally, the efficacy of antiarrhythmic drugs in maintaining sinus rhythm in long term is limited beyond first year.\textsuperscript{436}

Catheter ablation of AF has evolved as an effective therapy for drug-refractory symptomatic AF.\textsuperscript{310, 312, 403} However, it is resource intensive with high up initial cost and reports of the long-term outcomes demonstrate attrition in success with time.\textsuperscript{322, 325, 327} The cost-effectiveness of AF ablation is greatly influenced by the number of procedures, their success rate and procedural complications.\textsuperscript{437, 438} Studies have associated cardiac risk factors with the more frequent recurrence of AF, increased risk of complication and direct medical costs.\textsuperscript{324, 337, 439, 440} Aggressive management of these risk factors in a dedicated physician led clinic has been shown to reduce the burden of AF and improve the long-term success of ablation.\textsuperscript{352, 362, 441}

In the LEGACY study, progressive weight-loss had a dose-dependent effect on long-term freedom from AF. Weight loss facilitated by a dedicated clinic was more effective, sustained and progressive.\textsuperscript{380} However, it was not clear if the use of the resources directly involved in providing risk factor management, in conjunction with the impact of this intervention, is cost-effective. In this study, we aim to evaluate the clinical utility and cost-effectiveness of a dedicated risk factor management clinic in overall management of AF.
1.30 METHODS

1.30.1 Study Population
We have previously presented results of weight loss and its impact on AF outcomes in the LEGACY Study. In the LEGACY study, all suitable patients (with body mass index $\geq 27\text{kg/m}^2$ and $\geq 1$ risk factor) were offered risk factor management (RFM) in a dedicated physician-directed clinic at the time of initial assessment. Here we compared the clinical and cost effectiveness of a dedicated RFM clinic for long-term results of patients diagnosed with AF. Patients were dichotomized on the basis of whether they accepted this strategy and formed the intervention group (RFM Group) while those who declined formed the Control group.

All patients provided written informed consent for the ablation procedure and collection of their clinical data. The study protocol was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital and University of Adelaide.

1.30.2 Risk Factor Management
Patients in RFM group attended a physician-directed RFM clinic (in addition to their arrhythmia follow up) at least every 3-months and encouraged to utilize support counselling and schedule more frequent reviews as required. Risk factors were managed according to ACC/AHA guidelines. The details of our RFM have been previously presented.$^{380}$ In brief, a structured motivational, goal-directed program using face-to-face counseling was used for weight management and increased physical activity. The meals plans advised were low fat, high protein, low carbohydrate
containing food items. A simple menu with common multiple healthy food choices were designed in discussion with patients based upon their preferences. If patients did not lose at least 3% weight in 3 months, then meal replacement was prescribed and was bought by the patients. Weight, hypertension, glucose intolerance, dyslipidemia, sleep apnoea, alcohol and tobacco use were screened for and managed individually according to AHA/ACC guidelines. The Control group was given information on management of risk factors and encouraged to begin risk factor management under the direction of their treating physician.

1.30.3 Arrhythmia Management
Management of AF was undertaken in a separate arrhythmia clinic by physicians blinded to the patient’s study group. The use of rate and rhythm control strategies was at the discretion of the treating physician. In patients who remained symptomatic despite the use of anti-arrhythmic agents, AF ablation was offered. The ablation technique utilized at our institution has been previously described.442 AF was determined by clinical review, 12-lead electrocardiogram and 7-day Holter monitoring. AF was taken as any atrial arrhythmia ≥30 seconds. If patients developed recurrent arrhythmia after the blanking period (3-months), repeat ablation was offered. All patients were anticoagulated if the CHADS2 score >1. Reviews were 3-monthly for the first year and 6-monthly thereafter. No patient continued on amiodarone after ablation.

1.30.4 Outcomes for clinical effectiveness
The primary outcome was AF symptom burden as determined by the AF Severity Scale (AFSS, University of Toronto) that quantitates three domains of AF related symptoms:
frequency, duration and severity. The AFSS has been clinically validated and used for assessment of AF burden. The AFSS questionnaire was administered at baseline and final follow-up. Freedom from AF was ascertained with 7-day Holter monitoring. Secondary outcomes included healthcare utilisation (hospitalisation, emergency department presentation, unscheduled specialist clinic presentation), medication use (anti-hypertensive medication, lipid therapy, sleep apnoea device, anti-arrhythmic use), procedural requirements (cardioversion, echocardiography, Transesophageal echocardiography, ablation procedure)

1.30.5 Outcomes for cost effectiveness

Quality-adjusted life-years: Utility values for the health states ‘AF Free’ and ‘Not AF Free’ were included in the analysis to provide an ICER per Quality Adjusted Life Year (QALY). Reynolds’ (35) utility value for a patient in the untreated health states ‘Not AF Free’ of 0.725 was used in conjunction with an increase in utility value of 0.065, to calculate a utility value of 0.79 for the health state ‘AF Free’. Utility values for Years 2 to 4 were discounted by 3% per year.

Costs: Using a bottom-up costing method all costs were calculated in year 2010 AUD. Costs were classified into five categories: interventional procedures, diagnostic procedures, inpatient care, outpatient visits and medication. Hospitalization was calculated using ‘Average Length of Stay’ for AF with the standard price per Occupied Bed Day, provided by the South Australian Department of Health and Ageing. For each patient, the total number of drugs prescribed for arrhythmia, hypertension and lipid disorder was recorded at baseline and at Year 4. Specific prescription prices were averaged across the brands to provide an average annual cost for each condition
A half-cycle correction was used to adjust for medication changes during the course of study. The clinical service costs calculated for use in the decision tree were used as a base to develop the annual cost of each health state for use in the Markov model. For each health state, the likelihood of a patient requiring a clinical service annually was estimated. Annual probabilities of a service were multiplied by the previously determined cost to create a total annual cost per patient, which was summed for each Health State. The annual cost per health state was $1,135 for ‘AF Free’ and $5,207 for ‘Not AF Free’. Annual costs were input into the Markov model, and a discount rate of 3% for Costs and Benefits was applied.

1.30.6 Model structure and modeling framework
The model is comprised of a four-year decision tree and a 10-year Markov model. In the decision tree (Figure-) Decision Tree study data provided the probabilities of patients undergoing ablation procedures and the likelihood that, for each pathway, the patient would be ‘AF Free’ at Year 4. The ‘AF Free’ outcome, collected annually, calculated a QALY value over the study. The UTAFSS AF-specific measure ‘AF Burden’ was incorporated as a separate health outcome of the decision tree to provide an AF-specific quality of life measure.

Incremental cost-effectiveness ratios (ICER) were calculated for ‘Cost per QALY gained’ and ‘Cost per unit of AF Burden reduced’. Non-parametric analysis and bootstrapping improved estimates of the sampling distribution. One-way and two-way sensitivity analyses were performed and plotted in a “tornado” diagram.

A Markov model assessed the long-term cost-effectiveness of RFM over 10 years, corresponding to the longest follow-up of ablation outcomes available. Following
the four-year study, patients entered the Markov model in either the health state ‘AF Free’ or ‘Not AF Free’ based on Year 4 outcomes. For each 12-month cycle, patients could remain ‘AF Free’ or transition to ‘Not AF Free’ or ‘Dead’. It was assumed that patients who transitioned to ‘Not AF Free’ underwent an ablation procedure.

The annual transition probability of moving from ‘AF Free’ to ‘Not AF Free’ was 0.419 (13). Using the Framingham study, annual transition probabilities of 0.05 for ‘AF Free’ to ‘Dead’ and 0.16 for ‘Not AF Free’ to ‘Dead’ was set. The annual transition probability of remaining ‘AF Free’ was calculated at 0.53.8

1.31 RESULTS

1.31.1 Baseline Characteristics
Of the 1415 consecutive patients with symptomatic AF, 825 patients had BMI≥27 kg/m2. After screening for exclusion criteria, the final cohort comprised 355 patients; 208 RFM and 147 controls [Figure-1]. Mean follow-up in the RFM and control groups were 47.03±17.9 and 49.01±17.6 months, respectively (P=0.30). Baseline characteristics were similar in the two groups [Table-1].

1.31.2 Risk Factor Modification
Table-3 shows the impact of RFM on various cardiac risk factors. There was a greater decline in systolic BP with RFM compared to controls (147±17 versus 143±16 mmHg; P=0.02). Weight and BMI decreased in both groups, but significantly more with RFM compared to controls (-10.1±8.8 vs.-3.3±8.4 kg; P n≤0.001; Table-2). At baseline, 49% of RFM and 44% of controls had dyslipidaemia (P=0.35). With diet and life style modification, LDL-C and non-HDL-C were well controlled in 47% of RFM and 15% of
controls (P=0.02). At baseline, 30% of RFM and 27% of controls had history of DM (P=0.36). At final follow up, DM patients in the RFM had significantly better glycaemic control compared to controls; HbA1c < 7% in 8.7% vs. 13%, respectively (P=0.003). At baseline, 53% of RFM and 48% of controls had severe OSA (AHI ≥ 30; P=0.35). At final follow up, 31% in RFM group and 39% in control group had severe OSA (p=0.003) suggesting significant improvement in RFM group.

1.31.3 Effect of RFM Clinic on Atrial Fibrillation Symptom Burden
At baseline, both groups had comparable and high AFSS subscale scores (Table-3). AF frequency, duration, symptom and symptom severity were reduced at final follow up in both groups with a significantly greater reduction seen in the RFM group (p=<0.001).

1.31.4 Freedom from AF without the use of rhythm control strategies
Figure-3A demonstrates the “ablation and drug free” AF freedom based on groups. At final follow-up, 39% of patients RFM group remained free from arrhythmia without antiarrhythmic drugs or ablation, compared to 18% of patients in control group (P<0.001). Univariate predictors of AF recurrence without antiarrhythmic drugs or ablation were: Control group (HR 1.6, 95% CI: 1.2-2.0, P<0.001) and diastolic dysfunction (HR 1.5, 95% CI: 1.2-1.7, P<0.001). On multivariate analysis, Control group (HR 1.7, 95% CI: 1.3-1.8, P<0.001) and diastolic dysfunction (HR 1.4, 95% CI: 1.2-1.8, P<0.001) were independently associated with increased risk of AF recurrence.

1.31.5 Total Arrhythmia-free Survival
Figure-3 demonstrates the arrhythmia-free survival after multiple procedures with a significant attrition in controls compared to RFM. At final follow up, arrhythmia-free survival rates following the last catheter ablation procedure was 79% with RFM
compared to 44% for controls (P<0.001). Univariate predictors of AF recurrence after multiple procedures were: Control group (HR 3.3, 95% CI: 2.3-4.9, P<0.001); Diabetes (HR 1.8, 95% CI: 1.2-2.6, P=0.002) and Tobacco (HR 2.1, 95% CI: 1.12-4.25, P=0.034). Control group (HR: 3.6, 95% CI: 2.4-5.2; P<0.001) remained the most significant predictor of recurrent AF in multivariate analyses.

1.31.6 Healthcare utilisation
Tables 3 and 4 show the details of the healthcare utilisation between groups over the follow up period.

1.31.6.1 Ablation
Mean number of AF ablation procedure performed in RFM group was 0.60 ± 0.69 and in control was 0.72 ± 0.86 (P =0.09). Of the patients who were free from AF at final follow up 41% (86 patients) of patients in RFM group had single procedure vs. 29% (43 patients) in control (P=0.02), 9% (19 patients) in RFM required multiple procedures vs. 29% (43 patients) in control arm (P=0.005).

1.31.6.2 Cardioversion
The average number of cardioversion per patient was 0.89± 1.5 in RFM and 1.51± 2.3 in control group (P=0.002). 48 (23%) number of patients in RFM had >1 cardioversion vs. 54 (37%) in control group (P=0.02).

1.31.6.3 Medications
Mean anti-hypertensive medication in RFM group was 0.53 ± 0.7 and in control 0.78 ± 0.6 (P=0.04). At final follow up, mean anti-arrhythmic use in RFM was 0.26 ± 0.5 and
control was $0.91 \pm 0.6$ (P=0.003). 11% of patients in RFM vs. 38% in control group were on anti-lipid therapy at final follow up (P=0.007).

1.31.6.4 Emergency presentations:
The average number of Emergency Department presentations due to an episode of AF was in RFM was $0.18\pm0.5$ and control was $0.76\pm1.2$ (P<0.001). In RFM 30 (14%) had 1 presentation, 6 (3%) had 2 or more presentation vs. 26 (18%) in control group had 1 and 29 (20%) had 2 or more presentation.

1.31.6.5 Hospital admissions:
Mean number of hospital admission due to AF in RFM was $0.74 \pm 1.3$ and control was $1.05 \pm 1.6$ (P=0.03).

1.31.6.6 Unscheduled Specialists Visit:
Mean number of unscheduled visit to specialist clinic in RFM was $0.19 \pm 0.4$ and control was $1.94 \pm 2.0$ (P<0.001).

1.31.7 Cost effectiveness analysis

1.31.7.1 Quality of Life
In the short-term analysis, average QALY gains in RFM were $3.09 \pm 0.03$ and control was $3.05\pm0.02$. The decrease in AF Burden was $9.25 \pm 2.94$ and $6.66 \pm 2.68$ respectively (P<0.001).

1.31.7.2 Costs
For each pathway and outcome on the decision tree, RFM had a lower average cost per patient. The mean total health-care cost per patient was lower in the RFM group.
($17,421 \pm 9,073), compared with the Control group ($20,388 \pm 7,870). The mean cost difference of providing RFM was a saving of $2,968 \pm 432, attributed to the reduction in ablation procedures.

1.31.7.3 Cost-effectiveness

RFM is cost-saving in the short-term model with an ICER of -$47,260 (saving) per QALY gained. Using bootstrap replication, RFM is dominant with an increase of 0.06 QALYs and a cost saving of $2,986, producing an ICER of -$48,763 (95% CI -$114,092-$222). RFM is 97.5% cost-effective at a societal Willingness to Pay of $0. Long-term Markov modelling, between Years 5 and 10, indicates very little difference in the projected total cost and QALYs, however the ICER is still a saving of $4,098 per QALY gained. Combining the two models for an overall 10-year program creates an ICER of -$13,218 (saving) per QALY gained. The biggest savings are made when the initial ablation procedure or the redo ablation procedures could have been avoided. For a disease-specific measure, RFM provided an ICER of -$1,145 (saving) per unit of AF Burden reduced.

1.31.7.4 Sensitivity Analysis

Sensitivity analysis was undertaken on six factors affecting RFM: the cost of the procedure; the cost and number of clinics attended; the number of hospital admissions for AF-related causes; and the probabilities of undergoing initial and re-do procedures. RFM remained cost saving for all factors.

1.32 Discussion

This study demonstrates that in over-weight and obese individuals with highly symptomatic AF, a structured physician-directed risk factor and weight management
program results in long-term freedom from AF. This program is not only clinically effective but also cost-effective in terms of improvement in QALYs as well as reduction in AF burden. These findings underscore the importance of treating the underlying causes of AF to achieve rhythm control and maintenance of sinus rhythm.

This study is a first attempt to determine the cost effectiveness of aggressive risk factor management as a concurrent treatment strategy in the patients with AF. Our results did not compare the clinical and cost-effectiveness of RFM and AF ablation as treatment option exclusive of each other. Also, we did not focus on cost-effectiveness regarding rate vs. rhythm control. However, this study does highlight the order in which treatment should be offered. In the study, successful risk factor management was associated with 38% reduction in need for initial AF ablation procedure and a 20% reduction in a need for redo ablation. In sensitivity analysis, the cost was most sensitive to need for initial AF ablation followed by redo ablation procedure. Reducing the number for patients require AF ablation will reduce the cost substantially. However, if the ablation cannot be avoided, RFM should still be offered to prevent need for any redo procedure and to improve the procedural outcomes. In conclusion, our results showed that RFM should be offered as first line therapy in AF patients. However, this study indicates that RFM in AF patients is a cost saving measure irrespective of the management strategy adopted.

Hospitalizations represent the major cost driver in AF care. Recent studies have found a 23-125% growth in the AF hospitalization. The increasing incidence of AF with age is an obvious contributor. However, the age-specific rate of AF hospitalizations is also increasing, possibly due to worsening risk factor profile. The cost of AF
hospitalizations increases proportionately with an increase in CHADS2 score. In this study, we found that RFM was associated with 36% reduction in hospitalization. In addition, even if managed with rate control strategies the cost of AF care is still driven by medication use, ED presentation and specialist appointments. We found RFM improvement in the overall healthcare utilization with, 20% reduction in medication use, 58% reduction in ED presentation and 1.8 fold reduction in unscheduled specialist reviews.

Catheter ablation is an effective therapy for rhythm control in patients with drug-refractory or intolerant AF and it is increasing utilized. Although it is associated with upfront cost but it is more effective in maintaining sinus rhythm with a downstream cost saving, due to avoided hospitalizations, reduced ant-anti-arrhythmic drugs use, and greater improvement in quality of life. However, clinical and cost-effectiveness studies of catheter ablation of AF are sensitive to the time horizon for the analysis. Short-time horizons bias against ablation due to the high initial costs associated with the procedure. In contrast, there is gradual attrition of success after ablation with time, reducing the clinical effectiveness and dragging the cost-effectiveness. In long-term perspective, cost-effectiveness of catheter ablation of AF depends upon single-procedure efficacy. Cardiac risk factors are associated with increased risk of AF recurrence post ablation, increasing need for redo procedures.

RFM improves the long-term freedom from AF and thus improves the cost and clinical effectiveness of the AF ablation. We utilized quality-of-life adjustment as it pertains to sinus rhythm maintenance, which permits the expression of results in dollars per QALY. RFM was associated with gain in QALY at a cost saving of $3,423.
These results were insensitive to changes in the cost estimates explored in the sensitivity analyses. Regardless of which cost scenario was used, RFM was both more effective and less costly than usual care. However, the total costs of AF care based on above mentioned factors are probably an underestimation of the true costs of AF. The indirect societal costs related to the lost productivity and time costs associated with primary care and specialist visits are considerable. Although not assessed in the current study, if the reduced AF burden seen in this study in long term is associated with reduced risk of dementia, stroke and institutionalization of elderly and potentially reduced mortality, the cost effectiveness of RFM can be many folds making already cost effective measure “bang really worth the buck”.

1.33 Study Limitation

This study has the potential for bias inherent to observational studies. However, measurement bias has been reduced through standardized processes in our clinic and the evaluation by operators blinded to the patient’s weight management regimen. AF burden assessment using 7 days holter may miss some AF episodes especially in patients with low AF burden. However, this was utilized for AF freedom assessment in both the groups and was a limitation for all groups. Ascertainment bias was reduced through the routine collection of outcome data. As always with cost-effectiveness modeling studies, ours required simplifying assumptions and use of some uncertain parameters. A limitation of this cost analysis is its calculations based on economic conditions from a single country. In this study the “societal cost” has not been included and cost analysis is only for the healthcare system. It is possible that various other
societal factors may play important role in the broader picture. However, the societal aspect of the RFM is beyond scope of this paper. Additionally, no assessment was made for stroke risk and the associated cost.

1.34 CONCLUSION

A structured physician-directed risk factor and weight management program is effective and results into long-term freedom from AF. This approach is both clinically and cost effective. With the growing epidemic of AF and the healthcare cost burden this strategy should be increasingly utilised.
Table 6-1: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Control Group (N=147)</th>
<th>RFM Group (N=208)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58.6±11.3</td>
<td>59.4±11.3</td>
<td>0.51</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>98 (66.7)</td>
<td>136 (65)</td>
<td>0.8</td>
</tr>
</tbody>
</table>

**Anthropometric Measures**

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (Kg)</td>
<td>99.7±16.3</td>
<td>100.5±17.1</td>
<td>0.67</td>
</tr>
<tr>
<td>BMI (Kgm⁻²)</td>
<td>32.7±4.8</td>
<td>33.4±4.6</td>
<td>0.21</td>
</tr>
</tbody>
</table>

**Atrial Fibrillation**

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxysmal AF, n (%)</td>
<td>76 (52)</td>
<td>112 (54)</td>
<td>0.7</td>
</tr>
<tr>
<td>Non-Paroxysmal, n (%)</td>
<td>70 (48)</td>
<td>96 (46)</td>
<td></td>
</tr>
</tbody>
</table>

**Metabolic Risk Factors**

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>101 (69)</td>
<td>143 (68)</td>
<td>0.11</td>
</tr>
<tr>
<td>DM n (%)</td>
<td>40 (27)</td>
<td>63 (30)</td>
<td>0.36</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>65 (44)</td>
<td>102 (49)</td>
<td>0.35</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>18 (12)</td>
<td>26 (13)</td>
<td>0.93</td>
</tr>
<tr>
<td>AHI&gt;30, n (%)</td>
<td>71 (48)</td>
<td>111 (53)</td>
<td>0.35</td>
</tr>
<tr>
<td>Alcohol excess (&gt;30g/week), n (%)</td>
<td>45 (31)</td>
<td>66 (32)</td>
<td>0.82</td>
</tr>
<tr>
<td>Smoker, n (%)</td>
<td>10 (7)</td>
<td>9 (4)</td>
<td>0.60</td>
</tr>
</tbody>
</table>

**Echocardiographic Measures**

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>LA Volume Indexed (mls/m²)</td>
<td>38.9±4.6</td>
<td>38.4±5.6</td>
<td>0.48</td>
</tr>
<tr>
<td>LV septum (mm)</td>
<td>1.1±0.2</td>
<td>1.1±0.2</td>
<td>0.79</td>
</tr>
<tr>
<td>LVIDd (cm)</td>
<td>5.0±0.6</td>
<td>5.0±0.6</td>
<td>0.83</td>
</tr>
<tr>
<td>LH PW</td>
<td>1.0±0.2</td>
<td>1.0±0.2</td>
<td>0.29</td>
</tr>
</tbody>
</table>

**Atrial Fibrillation Severity Scale (AFSS)**

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency [1-10]</td>
<td>7.1±1.4</td>
<td>6.9±1.7</td>
<td>0.25</td>
</tr>
<tr>
<td>Duration [1-10]</td>
<td>7.0±1.6</td>
<td>6.9±1.9</td>
<td>0.74</td>
</tr>
<tr>
<td>Severity [1-10]</td>
<td>6.9±1.4</td>
<td>7.0±1.8</td>
<td>0.52</td>
</tr>
<tr>
<td>Symptom [0-35]</td>
<td>17.9±4.7</td>
<td>18.6±6.0</td>
<td>0.28</td>
</tr>
</tbody>
</table>
# Table 6-2: Showing effect of RFM on risk factors

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Control Group (N=147)</th>
<th>RFM Group (N=208)</th>
<th>Baseline</th>
<th>Follow-up†</th>
<th>P value*</th>
<th>Baseline</th>
<th>Follow-up†</th>
<th>P value*</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (Kg)</td>
<td>99.7±16.3</td>
<td>96.4±17.3</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td>100.5±17.1</td>
<td>90.4±17.0</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (Kgm⁻²)</td>
<td>32.8±4.8</td>
<td>31.7±5.4</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td>33.4±4.6</td>
<td>30.1±4.6</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean SBP (mmHg)</td>
<td>143.2±16.5</td>
<td>135.6±13.5</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td>147.3±17.2</td>
<td>132.0±14.3</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DM with HbA1c≥7%, n(%)</td>
<td>40 (27)</td>
<td>19 (13)</td>
<td></td>
<td></td>
<td></td>
<td>63 (30.3)</td>
<td>18 (8.7)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>N with AH1&gt;30, n(%)</td>
<td>71 (48)</td>
<td>57 (39)</td>
<td></td>
<td></td>
<td></td>
<td>110 (53)</td>
<td>65 (31)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Mean MET achieved</td>
<td>6.7±1.2</td>
<td>7.5±1.1</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td>7.1±1.1</td>
<td>9.6±1.0</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

## Echocardiographic Measures

<table>
<thead>
<tr>
<th>Echocardiographic Measures</th>
<th>Control Group (N=147)</th>
<th>RFM Group (N=208)</th>
<th>Baseline</th>
<th>Follow-up†</th>
<th>P value*</th>
<th>Baseline</th>
<th>Follow-up†</th>
<th>P value*</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA Volume Indexed (mls/m²)</td>
<td>38.8±4.6</td>
<td>37.5±7.0</td>
<td>0.035</td>
<td></td>
<td></td>
<td>38.4±5.6</td>
<td>33.5±9.0</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV septum (mm)</td>
<td>1.13±0.2</td>
<td>1.10±0.16</td>
<td>0.017</td>
<td></td>
<td></td>
<td>1.13±0.19</td>
<td>1.04±0.19</td>
<td>&lt;0.001</td>
<td>0.008</td>
</tr>
<tr>
<td>LVIDd (cm)</td>
<td>5.0±0.6</td>
<td>4.9±0.7</td>
<td>0.077</td>
<td></td>
<td></td>
<td>5.0±0.6</td>
<td>4.8±0.8</td>
<td>&lt;0.001</td>
<td>0.011</td>
</tr>
<tr>
<td>LV PW (%)</td>
<td>1.03±0.2</td>
<td>1.01±0.1</td>
<td>0.242</td>
<td></td>
<td></td>
<td>1.04±0.2</td>
<td>0.94±0.1</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

## Atrial Fibrillation Severity Score (AFSS)

<table>
<thead>
<tr>
<th>Atrial Fibrillation Severity Score (AFSS)</th>
<th>Control Group (N=147)</th>
<th>RFM Group (N=208)</th>
<th>Baseline</th>
<th>Follow-up†</th>
<th>P value*</th>
<th>Baseline</th>
<th>Follow-up†</th>
<th>P value*</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF frequency</td>
<td>7.1±1.4</td>
<td>4.3±1.7</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td>7.0±1.5</td>
<td>3.3±1.8</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>AF duration</td>
<td>7.0 ±1.6</td>
<td>5.4±2.2</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td>6.8 ±1.9</td>
<td>4.3±2.4</td>
<td>&lt;0.001</td>
<td>0.004</td>
</tr>
<tr>
<td>AF episode severity</td>
<td>6.9 ±1.4</td>
<td>4.9±2.1</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td>7.0±1.8</td>
<td>3.8±1.9</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AF symptom subscale</td>
<td>17.9±4.7</td>
<td>12.8±4.9</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td>18.9±5.8</td>
<td>10.0±5.0</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Table 6-3: Healthcare utilisation

<table>
<thead>
<tr>
<th></th>
<th>Control Group (N=147)</th>
<th>RFM Group (N=208)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medication Use</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-arrhythmic use</td>
<td>0.91±0.6</td>
<td>0.26±0.5</td>
<td>0.003</td>
</tr>
<tr>
<td>Anti-Hypertensive medication</td>
<td>0.78±0.6</td>
<td>0.53±0.7</td>
<td>0.043</td>
</tr>
<tr>
<td>Lipid Therapy</td>
<td>81 (64)</td>
<td>73 (40)</td>
<td>0.032</td>
</tr>
<tr>
<td>CPAP Use</td>
<td>62 (43)</td>
<td>70 (34)</td>
<td>0.098</td>
</tr>
<tr>
<td><strong>Interventional Requirement</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardioversion</td>
<td>1.51±2.3</td>
<td>0.89±1.5</td>
<td>0.002</td>
</tr>
<tr>
<td>Single AF Ablation</td>
<td>43 (29)</td>
<td>86 (41)</td>
<td></td>
</tr>
<tr>
<td>2nd Procedure</td>
<td>24 (16)</td>
<td>15 (7)</td>
<td>0.009</td>
</tr>
<tr>
<td>3rd Procedure</td>
<td>5 (3)</td>
<td>3 (1)</td>
<td></td>
</tr>
<tr>
<td><strong>In Patient Visits</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ED presentation</td>
<td>0.76±1.2</td>
<td>0.18±0.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hospitalization for AF</td>
<td>1.15±1.6</td>
<td>0.74±1.3</td>
<td>0.034</td>
</tr>
<tr>
<td><strong>Out Patient Visits</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specialist - Planned</td>
<td>14±3</td>
<td>10±2</td>
<td>0.01</td>
</tr>
<tr>
<td>Specialist Visit - RFM Clinic</td>
<td>Nil</td>
<td>16±4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Specialist Visit - Unplanned</td>
<td>1.94±2.0</td>
<td>0.19±0.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Table 6-4: Healthcare Cost</td>
<td>Unit</td>
<td>Control</td>
<td>RFM</td>
</tr>
<tr>
<td>---------------------------</td>
<td>------</td>
<td>---------</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>Price</td>
<td>Volume</td>
<td>Cost</td>
</tr>
<tr>
<td><strong>Diagnostic Procedures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise Stress Test</td>
<td>$152</td>
<td>1</td>
<td>$152</td>
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<tr>
<td>Glucose Tolerance Test</td>
<td>$19</td>
<td>1</td>
<td>$19</td>
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<tr>
<td>Holter Monitor</td>
<td>$164</td>
<td>4</td>
<td>$657</td>
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<tr>
<td>TransThoracic Echo</td>
<td>$231</td>
<td>5</td>
<td>$1,153</td>
</tr>
<tr>
<td>Blood Pressure Machine</td>
<td>$125</td>
<td>0</td>
<td>$0</td>
</tr>
<tr>
<td>Polysomnography</td>
<td>$588</td>
<td>0</td>
<td>$0</td>
</tr>
<tr>
<td>CPAP Machine</td>
<td>$1,100</td>
<td>0.48</td>
<td>$531</td>
</tr>
<tr>
<td><strong>Sub-Total</strong></td>
<td></td>
<td></td>
<td>$2,513</td>
</tr>
<tr>
<td><strong>Interventional Procedures</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Ablation</td>
<td>$13,847</td>
<td>0.72</td>
<td>$9,985</td>
</tr>
<tr>
<td>Cardioversion</td>
<td>$1,075</td>
<td>1.51</td>
<td>$1,624</td>
</tr>
<tr>
<td><strong>Sub-Total</strong></td>
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<td>$11,609</td>
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<tr>
<td><strong>Inpatient Care</strong></td>
<td></td>
<td></td>
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<tr>
<td>ED Presentation</td>
<td>$545</td>
<td>0.76</td>
<td>$415</td>
</tr>
<tr>
<td>Hospital Admission for AF</td>
<td>$1,910</td>
<td>1.05</td>
<td>$2,014</td>
</tr>
<tr>
<td><strong>Sub-Total</strong></td>
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<tr>
<td><strong>Outpatient Visits</strong></td>
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</tr>
<tr>
<td>Specialist Visit - Initial</td>
<td>$151</td>
<td>1</td>
<td>$151</td>
</tr>
<tr>
<td>Specialist - Planned</td>
<td>$76</td>
<td>10</td>
<td>$760</td>
</tr>
<tr>
<td>Specialist Visit - RFM Clinic</td>
<td>$76</td>
<td>0</td>
<td>$0</td>
</tr>
<tr>
<td>Specialist Visit - Unplanned</td>
<td>$76</td>
<td>1.94</td>
<td>$147</td>
</tr>
<tr>
<td><strong>Sub-Total</strong></td>
<td></td>
<td></td>
<td>$1,058</td>
</tr>
<tr>
<td><strong>Medications (Change in)</strong></td>
<td></td>
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</tr>
<tr>
<td>Anti-Arrhythmic</td>
<td>$308.24</td>
<td>-281</td>
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Figure 6-1: Sensitivity analysis

One-Way Sensitivity Analysis

- Cost of Ablation ($20,000 - $6,000)
- Initial Ablation Procedure (30% - 60%)
- Requiring Re-do Ablation (10% - 50%)
- Hospital Admissions for AF (0.1-0.05)
- Cost of RIFM Clinic ($50-$100)
- No. of RIFM Clinics Attended (10-32)

ICER ($/QALY Gained)
Figure 6-2 Decision Tree

1. Patients with AF
2. Risk Factor Management
3. First Ablation
   - No First Ablation
     - AF Free
     - Not AF Free
   - Second Ablation
     - No Third Ablation
       - AF Free
       - Not AF Free
     - Third Ablation
       - AF Free
       - Not AF Free
Figure 6-3: ICER graph for cost effective analysis
Figure 6-4: KM curve showing outcomes of AF ablation according to group

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<th>730</th>
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Chapter 7: Conclusion and future directions

This thesis highlights the importance of aggressive risk factor management in overall management of atrial fibrillation. It demonstrates the dose-dependent effect of sustained weight-loss, particularly with avoidance of weight-fluctuation in long-term freedom from AF. This is in conjunction with favourable changes in cardio-metabolic risk factor profile, inflammatory state and cardiac remodeling. Subsequently it emphasizes the importance of cardiorespiratory fitness and fitness gain through a structured exercise program on overall management of AF. It also demonstrates that risk factor management significantly improves the long-term outcomes of AF ablation. It then investigates the mechanistic explanations of reduced burden of AF and improved ablation outcome with aggressive management of risk factors. Finally, it looks at the cost effectiveness of the dedicated risk factor management clinic in the overall management of AF and its impact on healthcare utilization.

In extension of our group’s previous work on weight loss in the short term and impact on AF burden. The long-term impact of weight loss was determined. In the LEAGCY study, it looks at the impact of weight loss on long-term freedom from AF and the effect of weight fluctuation in the process. Sustained weight-loss, particularly with avoidance of weight-fluctuation, was associated with a dose-dependent reduction in AF burden and maintenance of sinus rhythm. This occurs in conjunction with favorable changes in cardio-metabolic risk factor profile, inflammatory state and cardiac remodeling.
This thesis then highlights the impact of baseline cardiorespiratory fitness on risk of AF recurrence. Furthermore, it shows the impact of cardiorespiratory fitness gain with a graded exercise program along with weight-loss on AF outcome. In the **CARDIOFIT study**, it demonstrates that in overweight and obese individuals with symptomatic AF, preserved baseline cardiorespiratory fitness had a dose-response relationship with a 20% reduction in the risk of AF recurrence for each metabolic equivalent (MET) increase in fitness. Cardiorespiratory fitness gain with a structured exercise program had an additive effect to weight-loss in improving the long-term outcome of AF. MET gain in cardiorespiratory fitness of ≥2 METs on top of weight-loss was associated with 2-fold greater freedom from AF. These findings highlighted the prescriptive role of exercise in managing patients with AF, particularly as a strategy for rhythm control.

Subsequently, the thesis demonstrates the impact of aggressive management of cardiovascular risk factors through a structured physician-directed risk factor and weight management program, on AF ablation outcome. The **ARREST-AF Cohort study** demonstrated that in patients with highly symptomatic AF undergoing ablation, a structured physician-directed risk factor and weight management program resulted in significant improvement in the long-term outcomes. These effects were associated with structural remodeling with significant improvement in left atrial volumes and left ventricular hypertrophy. These findings underscore the importance of treating the underlying causes of AF to achieve rhythm control and maintenance of sinus rhythm.

Having looked at the effect of weight and risk factor management on AF burden and ablation outcome, the **ARREST AF-Substrate study** investigates the mechanistic explanation for these outcomes. In particular, the study looks at the effect of risk
factor management on structural and electrical remodeling of the atria. It demonstrates the reversibility of the established structural and electrophysiological substrate pre-disposing to AF by aggressive risk factor management. This study extends the seminal observation from animal studies from our group and testifies with equal force in humans. The finding underscores the essential role of risk factor management in primary and secondary prevention strategies for AF. In addition, it raises the possibility that such management strategy may also alter the risk of stroke.

This thesis finally explores the cost effectiveness of RFM through a physician directed dedicated clinic. On the background of growing epidemic of AF and the enormous healthcare cost burden, the CENT-AF Study, adjures the role of risk factor management in overall management of AF. The study found the program was not only clinically effective but also cost-effective in terms of improvement in Quality of Life Years as well as reduction in AF burden. RFM was associated with significant reduction in healthcare utilization and provides a compelling evidence for use as a first line therapy in all AF patients.

Despite recent advances, effectiveness of treatment for AF remains suboptimal. Medical therapy for AF aimed at either rate or rhythm control has been disappointing. Catheter ablation of AF has evolved as an effective therapy for drug-refractory symptomatic AF. However, it is resource intensive and reports of the long-term outcomes demonstrate attrition in success with time. Studies have associated cardiac risk factors with the more frequent recurrence of AF. This thesis solicits the pivotal role of aggressive risk factor management in overall management of AF. However, for the broader use of this approach at a primary care level remains to be determined. The
iCARE study has been designed to investigate the impact of risk factor management by a nurse led clinic and in the primary care settings. Additionally, a multicentre ARREST-AF: RCT is well underway. This study is investigating the ARREST AF cohort study in clinical trail settings.
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