

THE CHARACTERISATION OF RISK FACTORS,
SUBSTRATE AND MANAGEMENT STRATEGIES
FOR
ATRIAL FIBRILLATION

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A thesis submitted to The University of Adelaide in fulfilment of the
requirements of the degree of

Doctor of Philosophy

August 2014

To my parents, Abhay and Suniti

To my sister and brother in law, Devyani and Harshit

In loving memory of my grandparents

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Abstract

The rising global incidence and prevalence of atrial fibrillation (AF) imposes significant burden on health care systems. Recently, several novel risk factors for AF have been identified. However, there remains a need to understand the differential impact of more established predisposing factors for incident AF. Further, there is insufficient knowledge surrounding the atrial changes that occur at the advent of AF and how this arrhythmia is managed on presentation to health care facilities. This thesis seeks to improve our understanding of the risk factors associated with this arrhythmia; to characterise any detrimental changes that occur upon its onset and to identify the AF patients that are most likely to significantly burden the hospital system. To this effect, the focus of each of the chapters is presented forthwith.

Chapter 2 focuses on the independent risk factors for incident non-valvular AF via a systematic literature review and meta-analysis. This study provides the absolute and independent effect of each established risk factor on AF development and estimates the proportion of AF cases that could potentially be prevented if modifiable risk factors were targeted at the population level.

Chapters 3 and 4 characterise the entity of newly diagnosed AF. Chapter 3 determines the existence of structural and electrical remodelling that may be present at an early stage of this arrhythmias' evolution. Detrimental changes were found in the form of electrical substrate in paroxysmal new AF and structural substrate in persistent new AF. Chapter 4 examines the thrombogenic risk associated with new onset AF. This study shows the existence of elevated levels of pro-thrombotic bio-markers and

emphasises the need for appropriate anti-coagulation at this early stage of the AF disease process.

Chapters 5 and 6 focus on the burden that AF confers upon the hospital system by way of hospital admissions and readmissions. Chapter 5 identifies the predictors of hospital admission for AF patients presenting via the emergency department and moreover determines if all admissions are medically warranted. This study ascertained that AF patients presenting with congestive heart failure and a concurrent infection were significantly likely to be admitted to hospital for treatment and a significant proportion of patients who were admitted were low-risk AF and admission was not medically justified. This highlights a need for new management strategies in order to prevent unnecessary hospital admissions.

Lastly, chapter 6 examines the factors that increase the likelihood of readmission to hospital among AF patients. The findings showed that a substantial number of patients with index presentation for AF were readmitted to hospital. Patients who were younger and discharged on rhythm control medications were more likely to burden the hospital system with frequent AF readmissions. This study stressed the need for specialised outpatient clinics and educational interventions that could potentially reduce the increasing numbers of AF patients re-presenting to hospital.

Declaration

I certify that this work contains no material, which has been accepted for the award of any other degree or diploma in any university or other tertiary institution. To the best of my knowledge and belief, it 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 will, in the future, be used in a submission for any other degree or diploma in any university or other tertiary institution without the explicit permission of the University of Adelaide and if applicable, any other partner institution.

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Geetanjali Rangnekar

August 2014

Acknowledgements

I would like to thank Professor Prashanthan Sanders, my primary supervisor, for his guidance and support during my doctoral degree. His enthusiasm and constant innovation has been and continues to be inspirational. I would also like to thank my co-supervisor Dr Kurt-Roberts Thomson for his help and encouragement during my studies. Special thanks to my co-supervisors, Dr. Anthony Brooks for guidance provided during the study design and execution phase and for assistance with SPSS; Dr. Scott Willoughby for assistance with the new AF studies and to Dr. Dennis Lau for his patience, assistance and guidance during thesis preparation.

I would like to thank the cardiology fellows at the Centre for Heart Rhythm Disorders for their feedback and encouragement. I have enjoyed and will cherish my time working alongside my fellow PhD candidates at the Centre for Heart Rhythm Disorders: Carlee Schultz, Melissa Neo, Wei Wen Lim. In particular, thank-you to Carlee Schultz for her help during the new AF studies. I would also like to acknowledge the staff at the Cardiovascular Centre, past and present, who helped and accommodated me during the conduction of my PhD studies; Michelle Sanders, Melissa Middledorp, Aimie Paukner, Rebecca Leinonen, Sharon King, Elena Pancewicz, Lorraine Lee, Emily Rasheed and Julia Kim.

Last but not least, I would like to say a huge thank you to my amazing family; parents, sister, brother in law, aunt, uncle, and cousins; without whose unwavering understanding, encouragement and love this PhD would have not been possible. Thank you to my wonderful friends for their unstinting fortitude, humour and love which got me through some of the most trying times.

Communications to Learned Societies

Chapter Two

1. Presentation: Presented at The Australian Society for Medical Research South Australian Annual Scientific Meeting, May 2014, Adelaide, Australia.

Chapter Three

1. Presentation: Presented at the 59th Cardiac Society of Australia and New Zealand the Scientific Meeting, August 2011, Perth, Australia and published in abstract form (Heart, Lung and Circulation 2011, 20:S105).
2. Presentation: Presented at the Heart Rhythm Society 33rd Annual Scientific Sessions, May 2012, Boston, United States of America and published in abstract form (Heart Rhythm 2012, 9:5, S7).
3. Presentation: Presented at the 60th Cardiac Society of Australia and New Zealand the Scientific Meeting, August 2012, Brisbane, Australia and published in abstract form (Heart, Lung and Circulation 2012, 21:S104-5).
4. Presentation: Presented at the 5th Asia-Pacific Heart Rhythm, Society Scientific Sessions, October 2012, Taipei, Taiwan and published in abstract form (APHRS Conference Proceedings 2012).
5. Presentation: Presented at the Heart Rhythm Society 34th Annual Scientific Sessions, May 2013, Denver, United States of America and published in abstract form (Heart Rhythm 2013, 10:5, S218).
6. Presentation: Presented at Heart Foundation National Conference, May 2013, Adelaide, Australia.

7. Presentation: Presented at the 61st Cardiac Society of Australia and New Zealand the Scientific Meeting, August 2013, Gold Coast, Australia and published in abstract form (Heart, Lung and Circulation 2013, 22:S102).

Chapter Four

1. Presentation: Presented at the Heart Rhythm Society 34th Annual Scientific Sessions, May 2013, Denver, United States of America and published in abstract form (Heart Rhythm 2013, 10:5, S1).
2. Presentation: Presented at Heart Foundation National Conference, May 2013, Adelaide, Australia.
3. Presentation: Presented at the 61st Cardiac Society of Australia and New Zealand the Scientific Meeting, August 2013, Gold Coast, Australia and published in abstract form (Heart, Lung and Circulation 2013, 22:S97-98).
4. Presentation: Presented at the Heart Rhythm Society 35th Annual Scientific Sessions, May 2014, San Francisco, United States of America and published in abstract form (Heart Rhythm 2014, 11:5, S106).

Chapter Five

1. Presentation: Presented at The Australian Society for Medical Research South Australian Annual Scientific Meeting, May 2014, Adelaide, Australia.

Chapter Six

1. Presentation: Presented at the Heart Rhythm Society 33rd Annual Scientific Sessions, May 2012, Boston, United States of America and published in abstract form (Heart Rhythm 2012, 9:5, S383).

2. Presentation: Presented at the 60th Cardiac Society of Australia and New Zealand the Scientific Meeting, August 2012, Brisbane, Australia and published in abstract form (Heart, Lung and Circulation 2013, 21:S107-8).
3. Presentation: Presented at the School of Medicine Postgraduate Research Conference, August 2012, Adelaide, Australia.
4. Presentation: Presented at the 5th Asia-Pacific Heart Rhythm, Society Scientific Sessions, October 2012, Taipei, Taiwan and published in abstract form (APHRs Conference Proceedings 2012).

Prizes and Awards During Candidature

1. Best poster presentation (PhD) Award, Australian Society for Medical Research (ASMR), South Australian Scientific Meeting, 2014.
2. Best Poster Prize, The University of Adelaide, Faculty of Health Sciences, Department of Medicine, Postgraduate Research Conference, 2012.
3. Finalist, Best poster prize, Heart Foundation National Conference, 2013.

Chapter One

Literature Review

1.1 Introduction

Atrial fibrillation (AF) is a heart rhythm disorder characterised by the uncoordinated electrical activation of the atria, which induces a disorganised and often rapid response from the ventricles¹. It is the most commonly encountered cardiac rhythm disturbance; the global burden of disease 2010 study estimated that prevalence of AF was ~34 million and the incidence was close to 5 million². The number of AF sufferers is projected to increase 2-3 fold by 2050; independent of the age structure of populations and the common risk factors for AF^{3, 4}. With this arrhythmia burgeoning to epidemic proportions, the burden borne by individual sufferers and health care systems will simultaneously rise².

Atrial fibrillation is classified based on its distinct aetiological origins. *Valvular AF* is associated with a history of valvular heart disease (VHD) such as rheumatic valve disease¹. Whereas, *non-valvular AF*, which is the focus of this dissertation, occurs in the absence of valvular heart disease (VHD),¹ due to other cardiovascular and non-cardiovascular risk factors⁵. The deleterious impact of non-valvular AF on mortality, morbidity and long-term prognosis is significant⁶. Studies report 1.5-1.9 fold increase in all-cause mortality after adjusting for pre-existing conditions⁷, and doubling of cardiovascular mortality⁸. AF is also known to exacerbate the risk of developing certain cardiovascular disease (CVDs) such as congestive heart failure (CHF)⁹. Additionally, it increases the risk of stroke by 5-7 fold, particularly in the 8th and 9th decade of life; making this the most devastating complication of AF¹⁰.

In rare cases (~5% of cases) non-valvular AF presents in the absence of other CVDs or overt risk factors, and is referred to as *lone AF*, in which case the prognosis is usually more favourable¹¹. However, a 30-year follow up of lone AF patients has found that even this subset of AF patients have a 4-fold risk of developing stroke and a heightened risk of developing other CVDs, compared to age matched controls¹².

AF is further classified based on duration, electrophysiological characteristics and symptomatic status. *Paroxysmal AF* (PAF) consists of short self-terminating episodes, usually within a week of onset. *Persistent AF* episodes are recurrent, last longer than a week and require interventions to terminate. *Permanent AF* is the most severe form, episodes last for a year or more, and efforts to terminate are unsuccessful. Less severe forms of AF have a propensity to progress into more chronic forms. In addition, the arrhythmia itself brings about further structural and electrical remodelling, making it a progressive and self-perpetuating disease^{1, 13}. Thus, irrespective of how this arrhythmia presents, it by no means is a benign condition.

1.1.1 The Risk Factors Associated with Atrial Fibrillation

It is often said that 'it is the company that the AF keeps' that determines the prognosis for the patient. There is robust data from large cohort studies such as the Framingham Study and the Cardiovascular Health Study linking a heightened risk of developing AF in individuals with a history of hypertension (HT)^{5, 8, 14-18}, CHF^{5, 14, 17, 18}, coronary artery disease (CAD)^{5, 14, 17, 18}, diabetes mellitus (DM)^{5, 8, 15, 17-19}, and advancing age^{5, 20, 21}. Certain studies have also linked cigarette smoking^{5, 16}, excessive alcohol consumption^{22, 23}, certain electrocardiographic (ECG) abnormalities^{15, 24}, and echocardiographic abnormalities^{25, 26} to AF development. These have been established

as conventional risk factors of AF. However, AF has also been known to occur in the absence of these conditions ²⁷. There is a growing body of evidence from numerous studies suggesting that newer risk factors such as obesity (measured by body mass index, BMI)¹⁵⁻¹⁹, obstructive sleep apnoea (OSA)^{18,28}, inflammatory changes^{17,29} and aortic stiffness^{30,31} may play a significant role in the advent of this arrhythmia.

1.1.1.1 Conventional Risk Factors Associated with Atrial Fibrillation

1.1.1.1.1 Advancing Age

The degeneration of sinus rhythm (SR) to AF is most frequently attributed to senescence^{32,33}. AF is seen in only a small percentage of individuals aged younger than 55 years (0.1%), however, the prevalence increases steeply to 9% in persons older than 80 years³⁴. Similarly, the risk of stroke due to AF increases exponentially from 1.5% in the 5th decade of life to 24% in the 8th decade¹⁰. Furthermore, older AF patients (≥65 years) burden the hospital sector to a much greater extent than their younger counterparts, accounting for longer hospital stays, with greater in-hospital morbidity and mortality³⁵.

The Cardiovascular Health Study found valvular and coronary heart diseases, left atrial dilatation, HT, and DM were some of the strongest predictors for developing AF in the elderly (≥65 years). Interestingly, the use of β-blockers was protective against AF development³³. Indeed, these medications can be the preferred treatment in the elderly due to improvement in symptomatic status and added beneficial effects in treating CAD and HT³⁶. Conversely, the use of rhythm control strategies in the elderly is often complicated by the presence of structural heart disease, adverse drug interactions and renal compromise³⁷. Stroke prophylaxis in older patients with AF is

also more complicated due to a greater likelihood of major bleeding events, further compounded by falls and fractures³⁸.

In the case of advancing age, certain detrimental changes occur that increase the likelihood of AF. In elderly AF-free patients (≥ 60 years of age), there was evidence of reductions in atrial voltage and increase in voltage heterogeneity³², possibly due to aging induced interstitial fibrosis³⁹. Such changes are known to provide the underlying substrate for multiple wavelet re-entry arrhythmias such as AF⁴⁰. Further, electrophysiologic and electroanatomic studies showed generalised slowing in conduction velocity with regional conduction delay, and lastly an increase in sinus node recovery time, which was indicative of sinus node disease³².

In addition to the above changes brought about by senescence, it also increases the risk of CVDs such as HT, CAD, CHF and non-cardiac conditions such as DM, which in turn exert their influence on the risk of AF³³. Thus, given that the worlds ageing population is on the rise; with projections from the US alone estimating a near 2.5-fold over the next 5 decades³⁴, there will be a concomitant rise in the number of AF sufferers.

1.1.1.1.2 Gender

Gender differences exist in most CVDs, with regards to susceptibility and prognostic outcomes⁴¹⁻⁴³. The Framingham Study was one of the foremost to determine that men were 1.5 times more likely to develop AF than women; after adjusting for a number of potential and important AF risk factors such as age, HT, CHF, myocardial infarction (MI), and left ventricular hypertrophy (LVH). Also, in men the incidence of AF increases with age, whereas in women this is not the case⁵.

Indeed, a study in athletes, found that the remodelling in men and women occurs differently, possibly explaining the difference in AF rates. This study found male marathon runners had longer signal averaged P-wave duration, indicative of conduction delay and higher left atrial volumes, suggestive of greater levels of atrial dilatation than female marathoners ⁴⁴. Similar findings have been reported in sedentary males and young healthy subjects ⁴⁵. In fact, an animal study found the pulmonary veins in male rabbits were more electrically excitable and unstable than in female rabbits ⁴⁶.

However, given the fact that women tend to live longer than men, and are diagnosed with this arrhythmia later in life the actual number of men and women with AF usually equalises ⁴⁷. The Euro Heart Study ⁴⁸ examined the effect of gender on a large population of patients and found that female AF sufferers were older, presented with more co-morbidities and symptoms and consequently had a poorer quality of life. The treatment of men and women with AF also differs, with fewer women undergoing cardioversions, ablations and being prescribed anticoagulants ⁴⁸. The success rates for both genders are however similar. Therefore, all these studies show that there is a definite gender impact on the risk of development of AF and the outcomes related to this arrhythmia ⁴⁹.

1.1.1.1.3 Hypertension (HT)

The entity of pre-hypertension (systolic blood pressure 120-139 mmHg or diastolic BP 80-89 mmHg) has emerged as an important risk factor for myocardial infarction, stroke, heart failure and cardiovascular death in the Women's Health Study ⁵⁰. Previous work from the Framingham cohort showed that there was a step-wise

increase in the incidence of AF from optimal, normotensive, to high-normal BP over a 4 year follow-up; which intensified with age (>65 years) and body weight. These findings also highlighted the importance of regularly monitoring individuals with normal and high-normal blood pressure (BP) and introducing lifestyle and pharmacological interventions that may prevent progression to HT⁵¹, and hence reduce the risk of CVDs and even AF⁵².

The association between hypertension and this arrhythmia has been established by many studies^{5, 8, 20, 53}. Hypertension has been described as the most commonly occurring co-morbidity among patients with AF, present in over 70% of Atrial Fibrillation Follow-up of Rhythm Management (AFFIRM) participants⁵⁴. For this reason, HT accounts for a large number of AF cases; its population attributable risk for AF was 14% in both men and women in the Framingham Study⁵. Not only is HT the most prevalent, but it is also a significant, independent risk factor associated with AF⁵⁵. The relative risk of developing AF in hypertensive individuals is two-fold for both sexes, despite adjusting for age and other confounding factors such as pre-existing CVDs⁸.

HT induces a number of electrical and structural changes in the atria of AF patients. Studies have found evidence of structural defects such as left atrial enlargement ($\geq 40\text{mm}$) on echocardiogram^{53, 54} and LVH on ECG of hypertensive patients^{53, 56}. The pathophysiological process associated with HT is reinforced via activation of the renin-angiotensin-aldosterone system (RAAS)⁵⁶, which induces subclinical changes such as atrial fibrosis⁵⁷. Further, electroanatomical mapping and electrophysiological studies of the left and right atria (LA and RA) of hypertensive

individuals have demonstrated conduction delay, decreased conduction velocities, increased conduction heterogeneity indices and hence increased AF inducibility⁵⁶. Indeed even short term HT induces significant atrial remodelling; with proof of delayed and heterogeneous conduction, increased fibrosis and inflammatory infiltrates and functional changes such as enlarged LA and reduced left ventricular ejection fraction in an ovine model^{58,59}.

There is evidence to suggest that anti-hypertensives such as angiotensin-converting enzyme (ACE) inhibitors⁶⁰, angiotensin receptor blockers (ARBs)⁶¹ and statins⁶² are effective in preventing primary and secondary AF. In addition, ARBs have been shown to reduce the structural and electrical remodelling in animal models, which implies that these agents may play a role in the therapeutic management of AF^{63,64}.

The outcomes for patients with concurrent AF and HT are unfavourable, with the risk of stroke escalating to 8-fold⁶⁵ and even in AF patients free of any other coexisting conditions, Verdecchia et al reported a high incidence of stroke⁵³. Thus, high prevalence of this CVD in conjunction with the detrimental changes and the poor outcomes afforded by HT in AF patients make it a very potent risk factor for the development of this arrhythmia.

1.1.1.1.4 Left Ventricular Hypertrophy (LVH)

LVH measured via electrocardiogram and echocardiography and its predictive value with respect to AF have been studied in numerous studies^{5, 8, 15, 24, 66-68}. Although LVH is a marker for ventricular dysfunction, and the fact that ventricular disease may ultimately lead to AF has been established, makes LVH an indirect risk factor for AF⁵.

⁵³. Baseline LVH was determined to be an important predictor, showing a near 2-fold increased risk of developing AF in large prospective population studies ^{5, 7, 15, 53}. The losartan intervention for endpoint reduction in hypertension (LIFE) trial demonstrated a regression in this marker after statin treatment and subsequent analyses of the data showed this correlated to a concurrent regression in AF incidence by 33%, and of associated stroke ⁶⁹. Given that LVH commonly occurs with HT, this could have important implications for AF development, as HT in itself is an important risk factor for this arrhythmia ⁷⁰ (as discussed in section [1.1.1.1.3](#)). Interestingly, a recent study found lower LVH was still associated with a significant reduction in the occurrence of AF even after adjusting for treatment with anti-hypertensive (losartan or atenolol), presence of HT, and other risk factors ⁶⁶. Thus, implying that the effect LVH exerts on AF may be independent of its link with HT. The above findings have implications in the treatment approach for AF, in the setting of HT and independent of this co-morbidity.

1.1.1.1.5 Congestive Heart Failure (CHF)

The inextricable link between CHF and AF was proven over a century ago ⁷¹. CHF was by far the strongest independent predictor of AF in both men and women in the Framingham Study, carrying an odds ratio of 5 ⁵. Moreover, AF is said to develop in 30-40% of CHF sufferers ⁷². Given that this CVD has a high incidence and prevalence in itself ⁷³, makes its impact on likelihood of developing AF very strong indeed.

The manner in which CHF induces and perpetuates AF is thought to be through structural and electrical remodelling of the atria ^{71, 74}. Experimental CHF animal models have shown evidence of atrial enlargement and slow, heterogeneous conduction ⁷⁵. Histological analyses of CHF hearts have shown interstitial ⁷⁶, atrial and ventricular

fibrosis⁷⁷. A more recent study in humans free of the burden of AF has shown anatomical abnormalities such as atrial enlargement and loss of functional myocardium due to scarring. In addition, there were electrophysiological changes including prolonged atrial refractory time, conduction delay and sinus node dysfunction, all leading to circuitous conduction and hence greater AF inducibility. This study provided important evidence for the possible substrate that underlies AF in the setting of CHF⁷⁴. Other mechanisms that trigger this arrhythmia are neurohormonal in nature; the activation of the RAAS at the molecular level involves alterations in stretch activated ionic channels⁷¹.

Research has also shown that AF and CHF share common mechanisms and are thus capable of inducing and exacerbating each other, compounding the adverse effects on patient symptomatic status and mortality⁹. This makes it essential to combine rate and rhythm control therapies with diuretic therapies to curb the rising burden on individual sufferers and on hospitalisation rates⁷¹.

1.1.1.1.6 Coronary Artery Disease (CAD)

Data from angiographic studies have shown the prevalence of AF in patients with proven CAD is low, varying from 0.2-5%⁷⁸⁻⁸⁰. However, the Framingham Study found antecedent CAD to be a significant and independent precursor of AF, increasing the risk of developing both chronic and transient AF in men by 2-fold and the risk of transient AF in women by 4-fold¹⁴.

The pathophysiological correlates of AF in the setting of CAD are varied; ranging from ischemia induced changes to the heart muscle, hemodynamic changes such as increased left atrial pressure, depressed left ventricular function and

subclinical changes such as alterations in the sinoauricular node and intranodal pathways^{78,79}. A recent study compared the angiograms of patients with CAD and AF to those with CAD in and found there was no difference in the extent of stenosis in the main coronary vessels supplying the atria. However, there was a higher prevalence of compromised left ventricular pump function, a surrogate of CHF. Indicating that in patients with CAD, the principle causative mechanism of AF may well be via systolic heart failure rather than ischemia⁷⁹.

1.1.1.1.7 Myocardial Infarction (MI)

Ischemia may play a more important role in the AF substrate associated with acute myocardial infarction (MI), as demonstrated in an ovine model. MI was induced by occluding the left coronary arteries and this lead to the development of underlying substrate by inducing conduction slowing, increasing conduction heterogeneity and thus increasing AF inducibility⁸¹. AF is a common complication of acute MI⁸², occurring in up to 20% of these patients⁸³. There is evidence of left atrial dilatation; compromised left ventricular function; increased pulmonary capillary wedge pressure and right atrial pressure in patients developing AF post MI. Also, they have a higher incidence of CHF, cardiogenic shock, atrioventricular block⁸⁴. AF can be as a result of surgical interventions for MI such as coronary artery bypass graft⁸⁵ and percutaneous coronary intervention⁸⁶.

MI adversely affects the short and long-term survival of the sufferer^{14, 84} as well as peri-operative mortality and morbidity and significantly reduces 1-year mortality of an AF patient⁸⁶⁻⁸⁸. In addition, CAD by itself has a number of deleterious effects and often induces congestive cardiomyopathies⁸⁰. Hence, early detection and

intervention of CAD may improve prognosis among AF sufferers, and possibly help reduce the incidence and prevalence of AF.

1.1.1.1.8 Diabetes Mellitus (DM)

Type-2 diabetes (T2D) was always thought to have a modest contribution to the development of AF. Numerous studies have attributed discrepant relative risks of between 0.4 and 2.6 to the risk of developing AF in the setting of DM ^{5, 16, 20, 89, 90}. However, a large prospective study of women health professionals, free of CVDs at baseline shed light on the temporal relationship between these two diseases ⁹¹. Multivariate models for women with T2D at baseline showed a significant effect on the development of AF (hazard ratio, HR 1.87). Nonetheless, upon adjustment for HT and body mass index (BMI) this relationship was attenuated significantly (HR 1.37). When taking into account time adjusted covariates, again HT and BMI were strongly related to AF development and the relationship between DM and AF was diminished. This study indicated that hypertensive and weight-related changes were more strongly correlated to AF development than DM ⁹¹. This was reiterated by the findings of the VALUE trial, where hypertensive patients with baseline DM had a higher event rate of new onset AF ⁹². However, DM does bring about structural changes such as left atrial enlargement, LVH ⁹³ and inflammatory changes such as elevation in C-reactive protein (CRP), interleukin-6 (IL-6) and adiponectin plasma levels ⁹⁴, all known to be linked to AF ^{17, 25}.

The close relationship between DM, HT and obesity ⁹⁵; all of which are known to be very strong and common risk factors for AF ^{16, 89, 96}, and the myriad of systemic

and localised changes it induces, makes DM in itself a potentially important and modifiable risk factor for AF.

1.1.1.1.9 Congenital Heart Disease (CHD)

Congenital heart diseases that increase the risk of atrial tachyarrhythmias include both left and right-sided congenital cardiac anomalies/disorders. Right-sided conditions include; atrial septal defect (ASD), Ebstein's anomaly, tetralogy of Fallot and uni-ventricular hearts. Left-sided conditions include; bicuspid aortic valve, aortic coarctation, ventricular septal defect and patent ductus arteriosus ⁹⁷. A large population study found that in patients with CHD, the prevalence of AF was 15% and while the lifetime risk increases with age, CHD patients who develop AF still tend to be significantly younger than patients without CHD ⁹⁸. Moreover, the mortality increases by nearly 50% ⁹⁸; the most common causes of death among patients with CHD being CHF- related, sudden cardiac death and due to post operative complications ⁹⁹.

CHD patients with and without the arrhythmia have been shown underlying clinical abnormalities. A small study of patients with ASD found areas of electrical scar, fractionated electrograms, decreased conduction velocity and atrial voltage ¹⁰⁰. Moreover, CHD patients who went on to develop AF had left-sided obstructive lesions, had undergone surgical procedures for left-sided CHD or were patients who had been palliated for left CHD. The aetiology behind this was thought to be due to the increase in left atrial pressure and volume loading to micro-reentrant circuits ¹⁰¹. Bernier et al found that patients with right-sided CHD also had a propensity to develop AF due to increased atrial pressure, decreased refractory periods, and atrial dilatation in the right atria ⁹⁷. While the current guidelines recommend conventional treatments such as

pulmonary vein (PVI) ablation¹⁰² and Cox maze procedure¹⁰³; these interventions are often complicated in CHD patients as vascular and heart chamber access is difficult to obtain due to their complex anatomy¹. However, both sub-sets of CHD patients are vulnerable to AF and require interventions as the frequency of this arrhythmia increases over time¹⁰⁴.

1.1.1.1.10 Valvular Heart Disease (VHD)

Valvular heart disease and CHD have been shown to share certain commonalities with regard to their AF pathophysiology. Histopathological analysis of the atrial tissue from AF patients with mitral valve disease and ASD found that there was a similar degree of atrial dilatation and fibrotic changes even though these disease entities are separate¹⁰⁵. Furthermore, both VHD and CHD¹⁰⁵ are known to increase the risk of heart failure, which is a common risk factor for AF and is known to increase mortality in AF patients⁵.

VHD can occur as a delayed consequence of rheumatic fever and is termed rheumatic heart disease (RHD). It was thought to be a strong predictor of developing AF⁸, but is now more common in developing countries and in the elderly who were exposed to RF during their childhood¹⁰⁶. RHD can lead to stenosis or regurgitation of the heart valves, increasing the likelihood of developing AF. A long-term follow-up of patients with RHD found that mitral stenosis (MS) is the most common cause of AF in this patient population¹⁰⁷, which develops due to left atrial dilatation and pressure overload⁸ and fibrotic changes in the atria¹⁰⁸. Indeed John et al found, in MS patients undergoing commissurotomy, that there were areas of electrical silence indicative of scar tissue. This study also demonstrated conduction anomalies such as; double

potentials, conduction delays, and prolonged P-wave duration; all of which increase susceptibility to AF¹⁰⁹. Mitral regurgitation and aortic valve disease are also aetiologies for developing AF in RHD patients, however, these are less common than MS¹⁰⁷. Irrespective, recent studies have shown that rhythm over rate control may be the most beneficial for long-term prognosis and stroke prevention for AF patients with a background of RHD. Vora et al¹¹⁰ found that restoration of SR with amiodarone improved mortality and morbidity outcomes. Whereas, radiofrequency ablation with valvular surgery was found to be even superior to treatment with anti-arrhythmics¹¹¹; and Wu et al¹¹² found valve replacement combined with the Cox-Maze III procedure yielded effective results even in permanent AF patients.

Non-rheumatic valvular disease or valvular heart disease (VHD) is due to degeneration of heart valves and is more often seen in developed countries and is considered a growing public health issue¹⁰⁶. Data from the Olmsted County shows that the prevalence of VHD was 5.2% in the general population, increasing substantially with age but not with gender. The most common aetiology was mitral regurgitation, followed by mitral stenosis with aortic valve disease being the least common¹¹³. Widgren et al however, found that aortic stenosis carried the most weight; even in the presence of mitral regurgitation; in increasing the risk of AF significantly after adjustment for age, gender, other valvular diseases and echocardiographic abnormalities. The long-term mortality and morbidity in these AF patients was also significantly affected by aortic stenosis¹¹⁴. The risk of thromboembolic events too increases substantially in these patients, particularly in those who have prosthetic heart valves, thus making it imperative for appropriate anti-coagulation, or anti-platelet or combination therapy¹¹⁵.

1.1.1.1.11 Cigarette Smoking

The correlation between cigarette smoking and AF was found to be either weak^{5, 20, 21} or non-existent^{16, 116, 117} by a large number of cohort studies. A recent population-based cohort study focusing only on cigarette smoking as a risk factor definitively showed both former and current smokers have a heightened risk of AF, irrespective of gender and age¹¹⁸. Indeed, another small study found evidence of low bipolar voltage and increased activation time in smokers compared to non-smokers¹¹⁹; electrical substrate known to be present in AF¹²⁰. Cigarette smoking has also been linked to a pro-inflammatory state by way of a heightened CRP levels¹²¹; also known to be elevated in AF patients¹⁷.

In addition to these changes, nicotine, the most potent and addictive substance in cigarettes; increases heart rate, demand on cardiac output and causes myocardial hypoperfusion¹²². Immunohistological analyses of atrial tissue obtained from smokers showed that nicotine had profibrotic properties, which correlated to number of pack years of smoking. In fact, 3 sporadic case studies have reported patients developed new onset AF after the use of nicotine quit smoking aids¹²³⁻¹²⁵.

It is not solely nicotine that has deleterious effects on the heart; as cigarette smoke contains 4000 harmful chemicals including carbon monoxide and polycyclic aromatic hydrocarbons which are hypoxic and pro-inflammatory respectively and could lend a hand in the pro-arrhythmogenic change brought about by this life-style choice¹²⁶.

1.1.1.1.12 Alcohol Consumption

High alcohol consumption^{22, 127, 128} and binge drinking often referred to as; 'holiday heart syndrome' have long been associated with AF^{129, 130}. However, the relationship between low to moderate alcohol consumption and AF is less well defined; with some studies concluding that 1.5-2 standard drinks a day did not, in any way affect the risk of AF, despite the presence of other CVDs^{23, 128, 131, 132}. This could be explained by the meta-analyses on this topic that have found a dose-response effect of alcohol consumption on the risk of developing AF; implicating there may be a threshold below which the relationship is non-existent^{133, 134}.

Alcohol brings about a myriad of changes in the atria that affect the electrical and structural integrity of the myocardium, increasing AF inducibility^{133, 134}. Chronic heavy drinkers are known to have alcohol induced heart muscle disease, which is characterised by cardiomegaly, dilation of the ventricles, deposits of fibrosis, lipids and inflammatory infiltrates in the myocardium¹³⁵. Electrical changes observed include a shortened effective refractory period (ERP), and increased atrial conduction time and a decreased conduction velocity, all of which increase the likelihood of re-entrant circuitous conduction^{136, 137}. Alcohol also induces HT¹³⁸ and dilated cardiomyopathy¹³⁴, both well established risk factors for AF⁵. The current evidence shows that there is a causal relationship between heavy alcohol consumption and the risk of AF, making it another important, life-style risk factor for AF.

1.1.1.2 New Risk Factors Associated with Atrial Fibrillation

The rising trends in the incidence and prevalence of AF are occurring independent of the ageing population and the increased survival of high-risk

individuals carrying conventional risk factors^{2, 139}. Moreover, the concept of *lone AF*, which was thought to present without evident risk factors or overt sub-clinical abnormalities has been challenged¹⁴⁰. Lone AF patients were found to present with occult HT¹⁴¹, and shown signs of age induced degenerative changes¹⁴². Importantly, Stiles et al revealed the existence of underlying structural and electrical remodelling in lone AF patients¹⁴³. These findings have refocused efforts on the search for previously unidentified risk factors.

1.1.1.2.1 Obesity

Obesity is now a recognised epidemic plaguing the developed world and slowly invading developing countries¹⁴⁴. This co-morbidity in itself increases an individual's likelihood of AF¹⁴⁵ and gravely affects longevity¹⁴⁶. The propensity of obesity to induce numerous diseases such as HT, CAD, CHF, DM, obstructive sleep apnoea (OSA); all known risk factors for AF^{5, 18}, further contributes to an increased risk of mortality and morbidity^{147, 148}.

Obesity mediates an increased risk of AF through LVH¹⁴⁹ and left atrial enlargement¹⁵⁰. The Framingham Study not only found every 1 unit increase in BMI correlated to a 4% increase in the risk of AF, but there was also a concurrent increase in left atrial size¹⁴⁵. Similar findings have been reported by other large cohort studies^{16, 20, 117}. Other mechanisms include obesity induced neurohormonal activation of the RAAS system known to contribute to the electrical instability of the atria¹⁵¹. New evidence is emerging with respect to more localised inflammatory changes impacting the myocardium; oxidative stress¹⁵², fibrosis, interstitial inflammatory infiltrates and lipodosis induced by adiposity¹⁵³.

While in the clinic it has not been possible to distinguish the impact of the various co-existing conditions on the AF substrate, a recent animal model has demonstrated a direct impact on the atrial myocardium. With progressive weight gain, there was increasing atrial fibrosis and development of the substrate for AF ¹⁵³.

Population studies have suggested that this process that links obesity with AF is dynamic ¹⁵⁴. Interestingly, recent experimental animal models have shown that the detrimental electrical and structural substrate laid down due to obesity may indeed be reversible ¹⁵³, thus improving the outcomes and prognosis in the setting of AF. This makes obesity another important and potentially modifiable risk factor for AF ¹⁴⁵.

1.1.1.2.2 Obstructive Sleep Apnoea (OSA)

Gami and co-workers established the link between pre-existing AF and OSA when they discovered that AF patients had a much higher incidence of OSA compared to arrhythmia free patients with CVDs ²⁸. Subsequently, this group showed there to be definitive link between incident AF and OSA, albeit only in patients younger than 65 years. In older patients the relationship between OSA and AF was attenuated and made non-significant by obesity ¹⁸. OSA and obesity have long been linked, both causally ¹⁵⁵ and in their pathophysiological mechanisms ¹⁵⁶. Thus, one manner that OSA may influence the development of AF may be through similar mechanisms as those involved in obesity (discussed in section [1.1.1.2.1](#)). Additional mechanisms involved in OSA have been observed in the setting of AF. This disorder has been shown to adversely affect coronary perfusion through prolonged periods of hypoxemia ¹⁵⁷, increase blood pressure, heart rate and ventricular afterload ¹⁵⁸. Additionally, Dimitri and colleagues studied AF patients with OSA and reported changes such as left atrial

dilatation, areas of electrical silence, conduction slowing, and increased fractionated electrograms¹⁵⁹. Thus, there is a strong association between OSA and AF and attempts to control the former could have significant effects on the incidence of AF.

1.1.1.2.3 Aortic Stiffness

The Framingham Study found aortic stiffness to be an independent predictor of AF. Aortic stiffness can be measured via pulse pressure in a simple, albeit indirect manner, and is the difference between the systolic and diastolic pressures³¹. The incidence rates of AF for patients with higher pulse pressures (≥ 61 mmHg) were significantly higher than those with lower pulse pressures (≤ 40 mmHg). Certainly, every 20 mm Hg increase in pulse pressure leads to a 26% increase in the risk of incident AF. In addition, this relationship was unaffected by adjustments for age, gender, HT, CHF, MI, DM, and LVH³¹. Even lone AF patients have shown evidence of increased pulse (peripheral and central) and augmentation pressures. Moreover, these measures were indicative of AF recurrence following catheter ablation, to a greater extent than brachial blood pressure measures³⁰. Emerging data have shown this risk factor may be potentially modifiable through treatment with a vasopeptide (omapatrilat), which may have important implications for AF patients¹⁶⁰.

1.1.1.2.4 Familial Atrial Fibrillation

The offspring of parents with AF are more likely to develop the arrhythmia¹. This has been found to be true after adjusting for numerous CVDs, such as HT, CHF and CAD, which have genetic components to their pathophysiology too. The Framingham Study found the adjusted multivariate relative risk of developing AF in individuals where at least one parent had AF was 1.85, which increased to 3.17 when the pre-

existing HT, CHF and VHD were taken out of the equation ¹⁶¹. Another sub-analysis of the Framingham Study found that even in the case of new onset AF, the familial component had a significant effect, which was not attenuated after adjustment for AF risk factors or genetic variants ¹⁶².

The mechanisms behind familial AF are still being understood and the information surrounding the genetics of AF is ever evolving to identify new genes and loci that increase the likelihood of AF ¹⁶³. Studies have identified loss of function gene mutations that may affect transcriptional activity for normal cardiac development ¹⁶⁴⁻¹⁶⁶. Yang et al recently found that non-sense mutations in a membrane channel protein leads to compromised function of the Connexin40 ¹⁶⁷. Furthermore, mutations limited to certain ethnicities such as those of European ancestry found on chromosomes 4q25 and 16q22 that code for transcription factors; and of Chinese ancestry found on chromosome 11 that code for potassium channels ^{168, 169}; make these sub-groups more susceptible to familial AF. These studies highlight the fact that while the familial aspect of AF is a heterogeneous condition; these could prove to be potential new individualised therapeutic targets for treating this arrhythmia ¹⁷⁰.

1.1.1.3 Summary

The incidence and prevalence of AF is increasing with age, and is seemingly higher in males than females. With overwhelming evidence linking diseases like CHF, ischemic heart disease (IHD), HT and DM with this arrhythmia and the incidence of these disease too on the rise; it must follow that the incidence of AF will also escalate. The novel risk factors of AF contribute further to this increase. Hence, the means to curbing this epidemic would seem to be cultivating a better understanding of the

diseases and conditions that underlie this arrhythmia and perhaps modifying their causal relationship to AF; thus, possibly diminishing the prevalence of AF.

1.2 Characterization of the Substrate Associated with New Onset Atrial Fibrillation

1.2.1 Definition of New Onset Atrial Fibrillation

In patients without a previous history of this arrhythmia, the first clinically detected episode is referred to as 'first-detected'¹⁷¹ or 'new-onset' AF¹⁷². In asymptomatic patients, it may be unclear as to whether the initial episode is indeed the first clinical episode; however in symptomatic patients it is easier to determine the first onset of AF¹. Episodes of new onset AF are classified on the basis of duration and patterns of termination, as mentioned earlier in section [1.1](#) into paroxysmal AF (PAF)¹⁷³, persistent AF and permanent AF¹³.

1.2.2 Management of New Atrial Fibrillation

The type and duration of the arrhythmia forms the treatment basis for newly diagnosed AF. There are two main streams of therapy; rate control and rhythm control (discussed in more depth in sections [1.4.1](#), [1.4.2](#) and [1.4.3](#)). With regard to PAF and persistent AF, the symptoms are usually treated via rate control medication, unless the patient is hemodynamically compromised or has serious co-morbidities such as CHF, in which case maintaining SR may be the priority. Additionally, for persistent AF patients, non-pharmacological treatments such as left atrial or pulmonary vein ablations, atrio-ventricular node ablation and pacing, become an option^{1,13}. Anti-coagulation therapy is recommended according to the stroke risk the individual carries¹⁷⁴ which would be gauged according to the CHADS₂ score (CHF=1 point, HT=1 point, Age >75 years= 1

point, DM=1 point, previous stroke/transient ischemic attack=2 points)¹⁷⁵ or in accordance with the newer risk stratification system of the CHADS₂VaSc score (CHF=1 point, HT=1 point, Age >75 years= 2 points, DM=1 point, previous stroke/transient ischemic attack =2 points, Vascular disease=1 point, Age 65-74 years= 1 years, Sc= sex category, female=1 point)¹⁷⁶. The latter being better at identifying the truly “low-risk” individuals.

1.2.3 Mechanisms of Atrial Fibrillation

AF occurs due to the complex interplay between multiple factors; triggers, perpetuators and substrate¹⁷⁷. In actuality, human AF consists of a number of different patterns of activity, as demonstrated by the recent work of Lee et al. A mapping study in persistent AF patients showed varying patterns of instability including; multiple wavefronts, transient rotors and disorganised activity¹⁷⁸.

1.2.3.1 Role of Triggers in Atrial Fibrillation

The seminal findings of Haissaguerre et al¹⁷⁹, demonstrated triggers originated mainly from the pulmonary veins and to a lesser extent from the atrial muscle and were instrumental in initiating and perpetuating paroxysms of AF. Furthermore, radio frequency ablation could be used to isolate and eliminate majority of these ectopic foci leading to good long-term outcomes in these patients¹⁷⁹. Chen et al also found treatment with β -blockers, calcium channels blockers and sodium channel blockers suppressed ectopic beats and radio frequency ablation eliminated the ectopic triggers¹⁸⁰. Further, Jalife and colleagues discovered that fibrillations could also be initiated by a single drifting rotor that attaches to abnormalities in the atrial wall¹⁸¹ or a self-

sustained anchored rotor¹⁸². The former may give rise to complex activation patterns¹⁸³, while the later may excite the atria at very high frequencies¹⁸⁴, both leading to fibrillatory activation.

Thus, AF can be initiated by a variety of entities including; aberrant triggers; stimulation from the sympathetic or parasympathetic nervous systems and atrio ventricular node accessory pathways, atrial premature complexes, atrial tachycardia or bradycardia. Once initiated, these triggers propagate through the LA and interact with the underlying abnormalities to further perpetuate and maintain this arrhythmia^{177, 185, 186}. The arrhythmia is then maintained by unfavourable electrical and structural changes called substrate.

1.2.3.2 Role of Substrate in Atrial Fibrillation

Remodelling in the atria lays down substrate that allows for AF perpetuation. Evidence of substrate has been noted in numerous conditions predisposing to AF, such as HT, CHF, CAD, obesity among others, as discussed in sections [1.1.1.1](#) and [1.1.1.2](#)). In addition, the notion that electrical and structural remodelling is brought about by the arrhythmia itself has also been purported. Wijffels et al demonstrated the existence of electrical remodelling in a goat model; where the arrhythmia itself brought about progressive shortening of the atrial effective refractory period, leading to sustained arrhythmia and the theory that 'AF begets AF'¹⁸⁷. This was reiterated in numerous animal studies,^{188, 189} where additional abnormalities such as increased heterogeneity of refractoriness and conduction slowing were noted^{190, 191}; and in human studies where shorter effective refractory periods and conduction delays were observed^{192, 193}.

Much after the development of these electrical changes, structural changes have been also observed as a result of the arrhythmia itself. Histological studies have shown there to be degenerative changes in the atria of AF patients including, loss of viable myocardium, apoptotic myocyte death and alterations in the expression of connexions^{194, 195}. It has been implied that these changes may be occur after the rate related electrical remodelling and evolve at a slower rate¹⁹⁶. However, it is the ultrastructural changes that may be the key to the entrenchment of AF¹²⁰.

There is new evidence to suggest that inflammation may also play a role in the substrate predisposing to AF. The entity of inflammation has long been linked to AF following cardiac surgery, which is thought to arise due to activation of the complement system¹⁹⁷⁻¹⁹⁹. AF and infection have also long been linked, particularly in the case of pneumonia²⁰⁰ and pericarditis²⁰¹. However, the notion that various pro-inflammatory biomarkers may play a role in the arrhythmogenesis of non post-operative AF is now coming to light²⁰². One of the first studies that examined the link between inflammation and AF was conducted in lone AF patients on atrial biopsy samples which showed the existence of inflammatory infiltrates, loss of myocytes and fibrosis¹⁹⁸. Presence of inflammation has also been demonstrated in the setting of disease pre-disposing to AF, such as HT⁵⁸ and CAD²⁰³. However, it is still unclear as to whether inflammation is causally linked to AF, or rather is an epiphenomenon of this arrhythmia.

1.2.4 Non Invasive Characterisation of Substrate Associated with Atrial Fibrillation

The aforementioned studies that identified and characterised the existence of substrate in conditions influencing the occurrence of AF and in arrhythmia patients were invasive. Non-invasive techniques have now evolved to such a level that they can be applied in the setting of new AF to characterise the structural, functional, and electrical characteristics of the atria. Also, these methods of testing can be used to identify which specific triggers and/or substrates exist in each individual patient, and thus help target the treatment approach for the arrhythmia on a more individual level²⁰⁴.

1.2.4.1 Ambulatory Holter Monitoring

The pivotal role of atrial ectopy in the initiation of AF was identified in the late 1990's¹⁷⁹. Since then, studies have used ambulatory holter monitoring as a non-invasive diagnostic tool to understand this arrhythmia better and evaluate trigger mechanisms^{204, 205}. Holter recordings are used to predict the occurrence of AF; first onset, occult/silent and AF recurrence following ablations and cardioversions^{206, 207}. This tool is also useful in classifying AF type and identifying patients likely to progress to more severe forms of AF^{208, 209}. The minute yet clinically significant details of a patient's arrhythmia can be identified; ventricular rate, burden of atrial ectopics and their origin, presence of underlying MI or additional arrhythmias, time of onset, and even response to pharmacological treatment. Ectopy burden and the possible source, depending on the morphology may help in planning ablation procedures. Morphological characteristics of the recording can uncover the existence of silent MI

(ST-segment changes), rhythm disturbance like sick sinus syndrome or the need for a pacemaker. Response to treatment by anti-arrhythmics or rate control medications can be evaluated for treatment success or occurrence of unwanted side effects such as further conduction abnormalities. Of course, twelve lead holters are especially useful in determining certain details where standard holters may fall short ²⁰⁴.

Waktare et al performed holter monitoring of PAF patients and found atrial premature beats (APBs) always preceded AF episodes and hence were culprit in triggering the arrhythmia. Importantly also, triggering APBs were shown to have shorter coupling intervals (relative to the previous sinus beat) compared to non-triggering APBs, thus making such APBs more dangerous and likely to induce AF ²¹⁰; findings echoed by Vincenti et al ²⁰⁹. Recent in depth holter analyses of AF subgroups revealed the frequency of APBs in persistent AF and PAF patients was not significantly different; however, the proportions of the 'dangerous' ectopy was lower in the former group. This indicated that the reliance of the arrhythmia sub groups on triggers may be different, possibly making the latter a more trigger and the former more substrate centric. In addition, this study also highlighted that PAF may be more vulnerable to autonomic nervous system fluctuations reflected in the temporal pattern of the triggers ²¹¹.

Thus, there is a wealth of information to be obtained from ambulatory monitoring, which may help understand the pathophysiology behind this arrhythmia, in a non-invasive and low cost manner. In addition, it may be instrumental in indicating whether the arrhythmia is more trigger or substrate based and hence help to refine treatment accordingly ²¹¹.

1.2.4.2 Electrocardiogram (ECG) Abnormalities

Studies have reported that P-wave duration (a non-invasive representation of global atrial depolarization), dispersion and amplitude derived from signal averaged ECG are indicators of AF risk and prognostic predictors of AF outcomes ²¹²⁻²¹⁷. This parameter was predictive of the risk of developing AF; as P-wave duration was significantly longer in paroxysmal AF patients compared to age and disease matched controls ²¹⁴, in lone PAF compared to healthy controls ²¹⁷, and in individuals with a history of AF irrespective of the presence of other CVD's ^{212, 214}. It also proved beneficial in indicating the severity of AF, as P-wave duration was longer in subjects who transitioned from paroxysmal to persistent AF ²¹⁸. Similarly, P-wave dispersion was also suggestive of transition to more severe forms of AF; as longer P-wave dispersion predicted progression to persistent AF from PAF ²¹⁶. Further, the amplitude of the terminal part of the P wave was found to be an effective indicator for the risk of developing idiopathic AF, as the root mean square voltage of the terminal part of the P-wave was higher in individuals with idiopathic PAF compared to healthy controls ²¹⁷. Thus, this provides information on a number of atrial conduction properties in a non-invasive and efficient manner.

1.2.4.3 Echocardiographic Abnormalities

The Framingham Study was amongst the first studies to identify echocardiographic changes that predisposed and hence independently predicted AF. These were; increased left atrial diameter (measure of left atrial dilatation), left ventricular and septal wall thickness (indicative of structural heart disease, SHD) and decreased left ventricular fractional shortening (FS, indicates level of left ventricular

systolic function); after multivariate adjustment for clinical risk factors of AF²⁵. Before this, several studies had shown a stepwise increase in the left atrial diameter and thus left atrial dilatation according to a regression from SR, paroxysmal AF and chronic AF²¹⁹⁻²²¹. It was also suggested that an increase in left atrial dimensions could stem from underlying HT⁵⁶ or IHD; although these changes were recently shown to be present even in patients with lone AF²²². Evidence also suggests that these changes, particularly left atrial dilatation are further enhanced by the AF itself²²³, feeding into the theory that 'AF begets AF'¹⁸⁷.

More recently, however, left atrial volume was suggested as a more sensitive and robust measure of the degree of left atrial dilatation. The Olmsted County studies found left atrial volume was found to be a more accurate predictor of AF and CVD (such as HT & CHF) occurrence than left atrial diameter. These studies implicated that the unidimensional measurement afforded by left atrial diameter in M-mode were found to be inadequate in detecting small changes in the left atrial dilation; whereas, left atrial volume detected these changes more accurately^{224, 225}. This may also be due to the fact in the case of AF; the dilatation may not necessarily be symmetric for estimation by linear measurement²²⁶.

In addition to the aforementioned echocardiographic changes, studies have implicated left atrial area, left ventricular end-diastole volume (LVESV), left ventricular ejection fraction (EF), and spontaneous echo contrast in the prediction AF onset, progression of AF to more chronic forms and determination of thromboembolic stroke risk^{213, 227, 228}. Of these, measures of diastolic dysfunction are most significant in terms of AF, given the LA acts as conduit and its hemodynamics are affected by diastolic

filling in the LV. The existence of left ventricular diastolic dysfunction leads to decreased passive left atrial emptying, increased left atrial diastolic pressure and larger left atrial volume. These changes over time cause atrial stretch, left atrial enlargement and may ultimately bring about electrical remodelling, all resulting in AF. Hence also why AF is associated with other diastolic disease such as HT, CHF, IHD and LVH making it a diastolic disease in itself ^{224, 229}. The use of tissue doppler techniques to help determine left atrial mechanical function, extent of left atrial remodelling and hence a propensity to develop AF have now been acknowledged in a number of studies. Measurements such as early annular mitral annular velocity (E'), late diastolic mitral annular velocity (A'), E/A ratio, and systolic to diastolic duration ratio (S/D) have been shown to be important, independent predictors of AF onset and recurrence of the arrhythmia after cardioversion ²³⁰⁻²³³. In addition, abnormalities in these measurements, indicative of impaired diastolic filling ²³⁴ have been documented in patients with a history of AF.

Thus, echocardiography is a widely used imaging technique, due to its versatility and portable nature. Echocardiographic parameters are capable not only of predicting the onset of this arrhythmia, but are also useful prognostic tools that go beyond the conventional clinical risk factors for AF ²²⁶.

1.2.4.4 Cardiac Magnetic Resonance Imaging (CMR)

CMR is especially advantageous for producing high-resolution dynamic images of the heart in any image plane and during any phase of the cardiac cycle, thus allowing for direct and accurate volumetric measurements of tissue remodelling in the myocardium ²³⁵. PAF patients showed evidence of structural remodelling by way of

greater left atrial volumes and lower left atrial emptying compared to controls as detected by CMR ²³⁶. The use of delayed (late gadolinium) enhancement MRI (DE-MRI) helps in the non-invasive quantification of the level of atrial fibrosis ²³⁵. The intensity of enhancement is capable of identifying AF patients who are more likely to revert back into AF following catheter ablation. This may help in the selection of AF patients that are most likely to benefit from ablation procedures ^{237, 238} and may even help decide upon the most appropriate strategy of ablation ²³⁹. The extent of enhancement on the DE-MRI is also a strong predictor of the severity of this arrhythmia ^{237, 240}. Interestingly, new data shows the intensity of late gadolinium enhancement was correlated to the existence of areas of low atrial voltage as determined by electroanatomical mapping of the LA; thus linking intra-atrial structural and electrical abnormalities in AF patients ²⁴¹. In addition, the percentage of fibrosis on DE-MRI was correlated to a history of stroke and a higher CHADS₂ score in AF patients, indicating that this technology may also be useful in predicting cerebrovascular events in AF patients ²⁴². Hence, DE-MRI has great value in the detection of structural abnormalities in the setting of AF.

1.2.5 Summary

The above studies have characterised substrate and the extent of electrical and structural remodelling in the setting of established or lone AF. While the best practice management strategies for new onset AF have been studied, no studies, to the best of our knowledge have attempted to classify and determine the levels of substrate in the subset of newly diagnosed AF patients. Indeed, if studied and defined more clearly, at the very onset or soon after diagnosis of the arrhythmia, this may provide insights into

what exactly derails normal SR into AF and possibly help target treatment more effectively.

1.3 Consequences of Atrial Fibrillation

1.3.1 Economic Burden of Atrial Fibrillation

Miyasaka et al reported some sobering findings with regard to the incidence rates of AF. This population-based study projected that by 2050, there will be an exponential increase in the number of AF cases, with nearly 16 billion sufferers. Of these, 43% would be due to aging, 22% due to the growing population, and one third (35%) could be attributed to an actual increase in the incidence of this arrhythmia, a statistic that could potentially be altered ⁴. Similar incidence rates have emerged out of other studies from Canada ²⁰, Scotland ¹¹⁷ and the UK ²⁴³. Certainly, a recent review of the epidemiology of AF in the developing world discovered that this arrhythmia is just as prevalent as in the developed world, particularly affecting the elderly, was associated with the same conditions and carried an equivalent stroke risk ²⁴⁴.

These high incidence rates translate into a considerable economic burden on health care systems. Recent cost analyses revealed that annual spending for this arrhythmia was \$14,133(USD) per patient, including \$11,306 for inpatient costs and \$2,827 for outpatient costs in patients with a primary diagnosis of AF. Patients hospitalised with a secondary diagnosis of AF further added to these costs with an additional \$6557, amounting to an annual spending of \$6.5 billion on this arrhythmia in 2006 ²⁴⁵. In the UK, this dysrhythmia consumed ~3% of the National Health Service healthcare annual expenditure as of 2004 ²⁴⁶.

These were the direct costs of the arrhythmia, with an additional burden conferred by adverse consequences of AF such as stroke and stroke-related rehabilitation. This dysrhythmia is also known to cause CHF events, acute MI and respiratory failure in compromised individuals²⁴⁷. Even medication side effects such as bleeding risks from anti-coagulation therapy and antiarrhythmic toxicity contribute to the indirect burden of AF²⁴⁵. Also, given that AF is a common occurrence in general practice, costs from this setting add to expenditure for AF, making it a significant public health burden²⁴⁸.

1.3.2 Hospital Burden of Atrial Fibrillation

Majority of the cost burden for AF, 50-60%, is borne by the hospital sector and this is reflected in the rising number of hospitalisations for this arrhythmia^{246, 249 250-252}. The Framingham Study was one of principal studies to attempt to determine rates of hospitalisations in a population-based cohort and found that over a 12-year period (1982-93), for patients ≥ 65 years there was a dramatic increase in hospital discharge from 30.9 to 59.5 per 10,000; whereas for persons aged 45-64 years the increase was less pronounced, 7.9 to 11.5 per 10,000²⁵³. Epidemiological data obtained from the National Hospital Discharge Survey records observed trends from the US (1996-2001) and uncovered a drastic 34% increase in AF hospital admissions over just 6 years, again being more marked in the >65 year olds²⁵⁴. Indeed, often, AF in the elderly is confounded by a diagnosis of stroke/transient ischemic attack (TIA) and further prolongs and complicates the hospital admission for AF²⁵².

European trends in AF hospitalisations have shown that in the Scottish population alone, from 1986-1996, there was a tripling in AF hospitalisations. The

proportion of short stay hospital admissions rose 17% for men and 11% for women, as did the contribution of AF to cardiovascular hospitalisations (20%) and to cardiovascular bed days (41%). This in turn significantly increased the contribution of AF hospitalisations to the total hospital activity in Scotland from 0.65% to 2%²⁵². In addition to the prevalent cases of AF, the Copenhagen City Heart Study revealed the rate at which individuals presented to hospital for incident AF also increased by 60%, over the same time period as the aforementioned study²⁵⁰. Lastly, more recent observational data from the National Hospital Morbidity Dataset of Australia has reported the most dramatic escalation in hospital admissions for AF of 203% over the past 15 years, which translates to an annual increase of ~8%. Over the same time period, the hospitalisation rates for more common cardiovascular diseases such as CHF and MI demonstrated only modest increases²⁵¹. Thus, trends from the all over the globe, spanning the last few decades show that the resultant hospitalisations from the epidemic of AF are not abating²⁵⁵.

Studies have attempted to elucidate what exactly brings AF patients to hospital in such large numbers, and the impact on resource usage. Conditions often associated with an AF admission were found to be advanced age (>74 years), co-existing IHD, HT and CHF; stroke was an uncommon co-morbidity at the time of admission²⁵⁶. The main symptoms associated with admission were shortness of breath, chest pain and dyspnoea^{256, 257}. However, the principal reason patients were being admitted to hospital as opposed to being treated in the emergency department (ED) or outpatient clinic was to 'rule out an MI', for heart rate control and to undergo cardioversions²⁵⁷. In fact, Zimetbaum et al implemented an intervention that standardised AF management in the ED and performed rate and rhythm control in the ED itself, which

reduced the likelihood of hospital admission by ~50% and saw a subsequent 35% reduction in resource utilisation and costs²⁵⁷. Emergent data from interventions show that AF patients who were under nurse-led integrated care were less likely to present for cardiac hospitalisations compared to patients under usual care²⁵⁸ and this method was also more cost effective and improved quality of life²⁵⁹.

Certainly, there are two types of admission pathways that contribute to the burden of AF hospitalisations; ED admissions for the treatment of acute AF and planned admissions for elective procedures²⁶⁰. Both these pathways have to be targeted with interventions for the overall hospitalisation rates associated with this arrhythmia to see a substantial reduction.

1.3.2.1 Trends in Elective Admissions for Atrial Fibrillation

Prior to the publication of the major 'rate versus rhythm' control trials such as AFFIRM²⁶¹ and Rate Control versus Electrical Cardioversion (RACE)²⁶², the contribution of elective admissions to the total hospital admissions for AF were comparative to that of ED admissions. However, following the revelation that neither rate nor rhythm control offered a superior treatment outcome for AF patients, the analysis of the Healthcare Cost for Utilisation Projects Inpatient Sample from the US found a change in this trend. Previously, elective admissions contributed to 40% of all hospital admissions for this arrhythmia, whereas, after 2002, this contribution dropped significantly to 33%²⁶³.

These trends were further examined to see how cardioversions and catheter ablations contributed to elective AF admissions. The number of cardioversions in patients presenting with AF as a primary diagnosis declined between 2001-2004 and

then stabilised during the latter half of the analysis period, 2005-2006. Conversely, the trends for catheter ablations saw a slight increase over the same period ²⁶³. This was observed in other database surveys from the US; the National Hospital Discharge Survey and the Medicare Provider Analysis and Review. The former examined catheter ablation trends from 1990-2005, and found a 0.79% increase in the proportion of patients undergoing this procedure, across all age ranges ²⁶⁴. The latter analysis found a similar increase in catheter ablation procedure volume, accompanied by an increased complication rate, increased length of stay in hospital and consequently increased hospital costs ²⁶⁵. Indeed, Australian trends show that over the last decade the number of procedures has increased by over 30%, considerably more than that seen in the trends of more common procedures such as a percutaneous coronary intervention ²⁶⁶.

The characteristics of patients presenting for cardioversions and ablations have been studied and were found to be unique from the patients who did not undergo these procedures. Ablation patients for example tended to be younger, healthier with less number of co-morbidities and a lower stroke risk ²⁶⁷. Patients undergoing cardioversions were also similar; with lower age and lower risk of embolic events ²⁶⁸. Indeed, patients undergoing these procedures also differ considerably from patients presenting for acute treatment to the ED, the former being younger, and less burdened with some of the main risk factors of AF ²⁶⁹.

1.3.2.2 Trends in Emergency Department Admissions for Atrial Fibrillation

Trends in ED admissions for AF followed the opposite pattern as those for elective admissions from 2002-2006 ²⁷⁰. A sampling of approximately 85% of US hospitals between 1993-2004 revealed that total ED visits for AF increased by a staggering 88%, while the population-adjusted rate increased 2-fold. The increase was more prominent in patients older than 80 years, but was similar for both genders. In addition, this study also found a large number of the patients, approximately ~64% that presented to the ED tended to be admitted to hospital for additional treatment, further burdening the hospital sector. Interestingly, only 30% of these patients actually required hospital admission, given they were deemed to have a number of co-existing conditions and were at a high risk of stroke ²⁷¹. This was similar to the findings for another study that found hospital admission could not be medically justified for 1/3rd of first onset AF patients presenting to the ED ²⁷². Thus, showing that not only do a large volume of AF patients present to the ED, but these patients go on to burden the hospital with unnecessary admissions.

Canadian statistics on ED admissions for AF showed similar increases ²⁷³ and shed light in the cost of ED admission for AF which amounted to 73\$ million, nearly 10% of all hospital expenditure on AF over just one fiscal year (2007-2008) ²⁷⁴. In addition, results emerging from the world over show that AF places a significant strain on existing ED resources particularly due to increased length of stay in the ED, which can range from 2-24 hours ²⁷⁵⁻²⁷⁷.

As mentioned previously, AF patient characteristics presenting to the acute treatment of AF vary from elective counterparts. ED patients tend to be highly symptomatic, older (median age 72 years) and are also more likely to be female (51%), as found by an 8-year retrospective cohort analysis of ED admissions²⁷⁵. This study, and others also found patients being treated via this medium had a greater number of co-morbidities particularly CHF and MI, and were at a higher risk for stroke, as evidenced by a higher CHADS₂ score of > 2^{269, 271, 275}.

Given the vast number of AF patients passing through the ED, this pathway would make an ideal target for interventions in order to reduce the hospital admission burden of AF, given that even idiopathic AF patients burden the ED for cardiovascular causes ten times more than patients in sinus rhythm with the same baseline characteristics (age, gender, echocardiographic parameters, ECG characteristics)²⁷⁸. However, to date, ED interventions by way of randomisation to accelerated treatment in the ED²⁷⁹ or treatment in an ED observational unit²⁸⁰ compared to usual inpatient care have not been successful in improving treatment outcomes by way of adverse events, complications due to AF and hospitalisations during the follow up period.

1.3.3 Atrial Fibrillation Rehospitalisations

AF hospital readmissions further burden the hospital sector, to which the ED pathway already contributes substantially. Atzema et al examined temporal trends of ED admissions over an 8-year period in Ontario, Canada and found that 20% of their patient cohort represented with AF or AF related complaints²⁷⁵. Indeed, even the implementation of ED practice guidelines in a separate study for treating AF did not reduce ED representations or subsequent hospital readmissions²⁵⁷.

The incidence and temporal trends of hospital readmissions have been studied in various settings and the results are variable. A particularly vulnerable cohort of patients appears to be newly diagnosed AF patients, particularly in the first year following diagnosis. Miyasaka and colleagues reported 1 in 3 patients (~33%) presented to hospital >1 in the year following diagnosis, mainly for AF and the cumulative incidence of these readmissions grew steadily during the 5 years of follow-up²⁸¹. Using patient claims data of over 4000 patients Kim et al found this number to be lower, between 10-12% for chronic and new AF patients within a 12 month period following their index hospitalization. Again, the newly diagnosed patients represented more frequently and sooner after their index presentations (within the first 60 days)²⁸². The aforementioned results suggest that new AF patients may not have their AF adequately controlled during their index presentations, causing them to present to hospital frequently.

Another similar analysis of medical and pharmaceutical claims data of over 38,000 all-comer AF patients found that this cohort presented to hospitals in large numbers and frequently. However, in this case all cause rehospitalisation rates were as high as ~40 and those for AF as a primary diagnosis were ~27% over a 12-month period. Additionally, this study found the first rehospitalisation was more costly (by ~\$1000) and longer in duration (by 2.6 days) than the index hospitalisation. This was the only study that attempted to explain the reasons for these variable and high rehospitalisation rates attributing them to an high Charlson Co-morbidity Index²⁸³ (CCI) ≥ 5 ²⁸⁴. Conversely, other studies did not find any relevant clinical or demographic predictors of high rehospitalisation rates^{252, 281, 285}.

1.3.4 Summary

There are a myriad of reasons that have led and continue to lead to the rise in the AF hospital burden, making it a key public health problem of this millennium. Several studies have speculated as to why the hospitalisation and rehospitalisation rates for AF are rising at such an alarming rate. The principal reason is an increase in the ageing population, and given advancing age is a key risk factor for AF⁵ this is not surprising. However, studies have found that although hospitalisation rates were higher in the older age groups, the temporal trends could not be entirely explained by this variable alone²⁵². Of note, these increasing rates were not linked to male gender either, even though males are estimated to be at nearly a 1.5 greater risk of AF than women⁵; the hospitalisation rates tended to be similar in both genders^{4, 286}.

Another possible reason is the increased survival and decreased in-hospital mortality of patients with MI's and CHF noted in numerous studies²⁸⁷⁻²⁹¹. Indeed, even the prevalence of conditions such as DM²⁹² and HT²⁹³ is on the rise. All these diseases were shown to considerably increase the risk of AF development by the numerous population based studies, as discussed in section [1.1.1.1](#). The escalating incidence and prevalence of aforementioned diseases, leads to a sub-population of individuals with more co-morbidities and higher disease burdens; who are more likely to develop AF and suffer strokes. This, in turn may lead them to present to the hospital and ED and place a greater burden on the health care sector²⁷³.

Additionally, a number of studies have attributed these escalating rates of AF admissions to changes in the approach to AF management in the tertiary care system.^{281, 285} In fact, following the publications of a number of early trials that demonstrated

the efficacy of anticoagulation therapy in preventing stroke in AF patients²⁹⁴⁻²⁹⁶; the hospitalisation rates for AF saw a rise, due to patients being admitted for initiation of anticoagulation therapy. Also, the publication of other trials (eg: RACE, AFFIRM) that made available a number of pharmacological treatments, by way of numerous rate and rhythm control medications and non-pharmacological treatment options to patients, caused these admission rates to increase further^{252, 281}.

1.3.5 Thromboembolic Risk Associated with Atrial Fibrillation

The Framingham Study showed that the risk of stroke in AF increases exponentially with every passing decade, from 1.5 % in individuals aged 50-59 years to 23.5% in individuals aged 80-89 years¹⁰. Even in lone AF, a condition that was previously thought to ensure a good prognosis, the risk is as high as 28%¹². This risk is further compounded by the presence of co-morbidities such as previous stroke or TIA, which is a very potent risk factor^{297, 298}. Heart failure increased the risk four fold, hypertension tripled it and both coronary artery disease and diabetes mellitus doubled the risk of stroke^{10, 299}. More recently, factors such as female gender, left atrial dilatation, interventricular septal thickening, left ventricular posterior wall thickening and diastolic dysfunction were deemed indicators of an increased risk of stroke/TIA^{294, 300, 301}.

The process of thrombus formation in AF is complex and is assessed by the Virchows triad, which involves three main processes. The first being abnormalities in the wall function through endothelial damage, dysfunction, and atrial stretch. The second being abnormalities in blood flow, such as blood stasis. The third component being abnormalities in the blood constituents with abnormal activation of the

platelets, inflammation and activation of the coagulation cascade. AF fulfils all the processes involved in Virchow's triad, and thus lends to a prothrombotic state³⁰².

1.3.5.1 Abnormalities in the Atrial and Vessel Wall

Changes in the atrial wall occur at the macroscopic and microscopic level. At the macroscopic levels, changes such as left atrial dilatation (left atrial diameter is a surrogate of left atrial dilatation, measured in by echocardiography) have been shown to exist in AF patient with known stroke^{303,304}, and in the case of AF patients with HT³⁰⁵. Indeed, left atrial enlargement was deemed an independent predictor of the composite outcome of stroke and death in the Framingham Study³⁰³. Also, an increase in left atrial appendage volume was observed in chronic AF patients, this structure being the site for intra-atrial thrombus formation in AF patients³⁰⁶. Von Willibrand factor (vWF) is another potent pro-coagulant factor, and a marker for endothelial dysfunction. Numerous studies have found intra-cardiac vWF levels and plasma vWF levels to be predictive of the presence of thrombus, cardiogenic thromboembolism and thus risk of future stroke³⁰⁷⁻³¹⁰.

On a microscopic scale; damaged endocardium with oedema and fibrotic thickening and endothelial erosion with thrombotic aggregation has been reported after electron microscopy studies of left atrial tissues obtained from AF patients who suffered embolic events³¹¹. In addition, changes such as endocardial thickening with presence of fibrotic and elastic tissue have been observed in the left atrial appendages of subjects with chronic AF³⁰⁶. Also, fibrotic changes have been observed in the atrial tissue of lone AF patients, a finding further cemented by the observation of enhanced collagen expression³¹².

Abnormalities have been detected in the vessels of AF patients in addition to the abovementioned changes. The presence of complex atherosclerotic plaque has been observed in over 50% of AF patients with concurrent CAD and is a known cause for stroke in these patients. Indeed, given plaque formation is an inflammatory process the heightened levels of inflammatory mediators in the vasculature aids in the identification of these high-risk patients ³⁰².

Lastly, this aspect of the Virchow's triad also includes extracellular matrix (ECM) remodelling. The ECM is key for the structural and geometrical integrity of the heart and abnormalities in it lend to the structural remodelling seen in AF. These abnormalities are accentuated by the co-morbidities that occur with AF, such as HT or LVH. AF patients express abnormally elevated levels of certain matrix metalloproteinases (MMPs) and low levels of tissue inhibitors of MMPs (TIMPs), as also various growth factors, all of which influence the collagen formation and degradation of the ECM ^{74, 313-318}.

1.3.5.2 Abnormalities in the Blood Flow

In AF, there is a loss of atrial systole, which in turn brings about blood stasis within the LA. The rapid ventricular contractions that often occur in response to this arrhythmia leads to reduced ventricular emptying which further accentuates the left atrial blood stasis. The existence of this abnormality can be detected as spontaneous echo contrast, which occurs due to blood stasis on echocardiography ³¹⁹. Spontaneous echo contrast was detected in AF patients and was shown to independently predict the occurrence of thromboembolic stroke ³²⁰. This abnormality was independently correlated to increased left atrial dimensions and was thus indicative of a

hypercoagulable state in AF patients with no previous history of stroke ³²¹. Spontaneous echo contrast remains an independent predictor of thromboembolic outcome of stroke even in AF patients who are anticoagulated ³²⁰. It is also been detected in patients in whom SR has been restored, making it a prognostic marker for this arrhythmia ³²².

In addition to failure of atrial systole, AF itself promotes left atrial dilatation ²²³, which promotes blood stasis and thus the potential for thrombus formation in this chamber. The Stroke Prevention in Atrial Fibrillation cohort found left atrial diameter measured in M-mode, to be an independent predictor of ischemic stroke and systemic emboli in non valvular AF patients ³²³. These findings were supported by another study that found this to be true even after adjusting for echocardiographic and clinical variables known to influence stroke risk ³²⁴.

Further, atrial mechanical dysfunction, which is characterised by the phenomenon of 'atrial stunning', has been implicated in thrombogenesis and was thought to occur following electrical cardioversions ^{325, 326}. However, there is evidence to suggest that this process is related to the arrhythmia itself ³²⁷. This is characterised by reduced left atrial appendage emptying velocity and increase in left atrial spontaneous echo contrast ³²⁸. Additionally, reversal of atrial stunning ³²⁹ is possible by pacing the atrial at high rates and/or administration of intravenous calcium.

1.3.5.3 Abnormalities in the Blood Constituents

Platelets, proteins of the coagulation cascade and the interaction of these components with the vascular endothelium constitute the components that promote thrombus formation in AF ³¹⁹. Various studies have examined the link between platelet

activation and the risk of thromboembolic events. Factors such as β -thromboglobulin³³⁰ and platelet factor 4; markers for platelet activation were up-regulated in chronic and PAF patients^{307, 331, 332}. Furthermore, amounts of platelet microparticles and soluble P-selectin, factors released from activated platelets were also higher in AF patients over SR controls^{319, 333, 334}. This indicated that perhaps platelet activation and aggregation contributes to the prothrombotic state in AF and it may do so indirectly, possibly through the various atherothrombotic vascular co-morbidities and risk factors such as CAD, smoking and peripheral vascular disease^{302, 319}.

Similar results were reported regarding markers of the levels of coagulation activation such as D-dimer, fibrinogen, and thrombin antithrombin (TAT) complexes that were all unregulated in chronic AF patients^{335 336-338}. These factors influence clot formation and induce an increased rate of fibrin turnover. The levels of these prothrombotic factors are further enhanced by the presence of other stroke risk factors such as DM, CHF³³⁵. It has been shown however, that levels of these markers can be decreased by anticoagulation with warfarin³³⁹.

Abnormal changes to fibrinolysis also forms part of the complex prothrombotic process in AF and is measured via levels of tissue plasminogen activator (t-PA) antigen and t-PA inhibitor type-1 (PAI-1) and the plasmin-antiplasmin complex. The levels of these markers are elevated by the presence of this arrhythmia alone³⁴⁰ and are capable of indicating the presence of potential confounders like HT, CHF and IHD; all of which are known to increase inflammation and hence the risk of stroke in AF³³⁴. In addition t-PA levels have been correlated to the existence of structural remodeling in AF, by way of increased LA diameter³⁴⁰. The effects of these factors is multifaceted,

but it can be attenuated by anticoagulation therapy³⁴¹.

1.3.6 Bio-markers of Thrombogenesis in Atrial Fibrillation

Research has linked several surrogate markers to an increased risk of thrombus formation in AF patients. There are numerous markers involved in the different processes that encompass the Virchow's triad and they play an important role in the multifactorial process of thrombus formation in AF and will be discussed forthwith³⁰².

1.3.6.1 CRP and IL-6

CRP is an acute phase protein that is produced in the liver in response to stimuli such as any injury or inflammation and has been widely researched in its connection to AF³⁴². Case control studies have shown levels of this marker were raised in patients with lone AF^{343 344}; and increased in a step wise manner in PAF and persistent AF patients compared to controls³⁴⁵ and was still higher in permanent AF patients over controls³⁴⁴, thus increasing in a stepwise manner in accordance with AF burden. Population level studies have also found there to be an independent and strong correlation between augmented levels of this marker and the risk of AF^{17, 29, 346, 347}; even after adjusting for potential confounders such as age, HT, CAD, and CHF^{17, 29, 346}.

Moreover, studies have linked higher levels of high sensitivity CRP (hs-CRP) to the existence of structural and electrical remodelling in AF patients. Higher quartiles of CRP were correlated to greater left atrial diameter^{348, 349}, left atrial volume, greater triggered activity³⁴⁸, as also depressed left atrial contractile function³⁵⁰ in persistent and PAF patients. The mechanistic link between structural abnormalities, arrhythmia burden and inflammation is unclear. It has been suggested that once AF inducing

triggers originate from the pulmonary veins, the rapid and abnormal atrial activation causes damage at a cellular levels such as apoptosis of the myocytes, which leads to an inflammatory response, including the production of CRP which localises in the atrial tissue bringing about further tissue damage and perhaps the perpetuation and maintenance AF³⁵¹.

In addition to playing a role in the inflammatory processes surrounding AF initiation, this marker has also been implicated in the process of thrombus formation in AF. CRP has been associated with an increased risk of thrombus formation in chronic AF patients^{308, 352, 353}. High levels of CRP were correlated to the presence of spontaneous echo contrast detected via transesophageal echocardiography and thus to LA thrombus formation in patients with persistent AF³⁵². This was consistent with the findings of other larger studies, which found a correlation between high CRP levels, spontaneous echo contrast, left atrial thrombus³⁵⁴⁻³⁵⁶, clinical stroke risk factors³⁵⁶ and a high CHADS₂ score³⁵⁴ and thus high risk of stroke.

IL-6 is a cytokine that has far reaching effects. This is a pro-inflammatory and cytoprotective marker produced by immune and cardiovascular cells and brings about the synthesis of proteins such as CRP^{357, 358}. Gedikli et al found that, like CRP levels, those of IL-6 were also increased according to the AF burden, being high in lone, and still higher in persistent and permanent AF patients over levels seen in age-matched, healthy controls³⁴⁴. The findings of a few other studies are in concurrence with the above mentioned one; in that IL-6 levels were significantly elevated above those in normal arrhythmia free controls in all subtypes of AF, and this relationship existed even after adjusting for age, gender, HT, CHF, DM and CAD among other confounders

^{353, 359, 360}. One study, however, failed to show a relationship between these factors ³⁵². IL-6 was also shown to be an independent predictor for maintaining SR after electrical ³⁶¹ and pharmacological cardioversions ³⁶², ablations ³⁶³ and predicting occurrence of stroke and even composite outcome of death ³⁶⁴ thus found to be prognostic marker for the success of AF therapies. Lastly, levels of these markers have also been strongly correlated to other pro-thrombotic markers such as P-selectin, tissue factor and CD40L ^{352, 353, 365}. Hence, the overwhelming evidence points towards the important contribution of these markers of systemic inflammation to the pro-thrombotic process in AF, both independently and in conjunction with other members of the coagulation cascade.

The findings of the abovementioned studies are novel and open doors to unique therapies targeting the pro-thrombotic pathways that may perhaps help treat this arrhythmia better ³⁴⁶. For instance, evidence for this emerged after a small study conducted in PAF patients showed a decrease in CRP levels and a simultaneous reduction in the number of AF episodes after short term (6 month) treatment with atorvastatin ³⁶⁶. Together, all these findings indicate that the inflammatory process is important for AF initiation and maintenance.

1.3.6.2 Asymmetric Dimethyl Arginine (ADMA)

ADMA is an endogenous inhibitor of nitric oxide synthase, the latter being important for the production of nitric oxide (NO). NO has a number of important functions in the maintenance of endothelial integrity, it is also an inflammatory mediator with antithrombotic properties. Decreased production of NO leads to endothelial dysfunction and damage. The existence of which is detected by measuring

levels of ADMA in the plasma. Levels of this marker have been shown to be elevated in various CVDs and DM³⁶⁷.

ADMA levels were assessed in acute onset (<24 hrs) and chronic (>1 yr) AF patients compared with controls; levels were the highest in the acute group compared to the chronic, both of which were higher than those observed in controls³⁶⁸. A similar acute rise in ADMA levels was found in a recent study conducted in AF patients undergoing catheter ablation. After 15 minutes of AF induction, ADMA levels were elevated over and above that seen in AF patients in SR who were paced at 150 beats/min for 15 minutes, and in AF patients who were not paced³⁶⁹. These studies alluded to an acute elevation of ADMA levels, the presence of endothelial dysfunction and hence a risk of thromboembolism soon after arrhythmia induction. This marker may also be of prognostic significance with regard to outcomes of AF management procedures. Baseline ADMA levels were elevated in patients who had AF recurrence up to 1 year following catheter ablation³⁷⁰ and degenerated into AF a month after electrical cardioversion³⁷¹.

Studies have suggested that this marker may exert its influence by bringing about structural and electrical remodelling in the atria. Indeed, increased levels of ADMA have been strongly correlated to LA size³⁷¹ and have been found to activate the RAAS by bringing about the overexpression of angiotensin converting enzyme³⁷². By the same token, an experimental study in a canine model of sustained AF has shown a decrease in ADMA levels after short term (6 week) treatment with rosuvastatin, which was reflected in a decrease in atrial apoptosis and fibrosis and smaller left atrial size in the treatment group.

Thus, ADMA plays an important role in the process of thrombus formation in AF, but may possibly help in the sustenance and perpetuation of the arrhythmia.

1.3.6.3 Endothelin-1 (ET-1)

Endothelin is derived from the vascular endothelial cells, and is made up of a family of three peptides; ET-1, 2 and 3. ET-1 is produced by vascular smooth muscle cells, leukocytes, cardiomyocytes, fibroblasts, and endothelial cells. It exerts a powerful effect on the cardiovascular system and is an indicator of endothelial dysfunction, mediated by increased activity of ET_A and ET_B receptors³⁷³. The evidence surrounding the correlation of levels of this marker in AF patients with structural heart disease, compromised LV function or CHF have been studied to a certain extent. ET-1 levels were heightened in AF patients with concurrent CHF over SR controls³⁷⁴ and were found to independently predict AF development in patients with CHF³⁷⁵. Left atrial appendages of AF patients with underlying SHD also had higher levels of ET-1 compared to SR controls; these levels were correlated to left atrial size, history of HT and CHF³⁷⁶.

However, in the absence of SHD, particularly CHF, the correlations between ET-1 and AF seem less evident. In persistent AF patients free of LV dysfunction and CHF, levels of ET-1 were no different than those seen in controls³⁷⁷. In addition, another study analysed right atrial samples for ET-1 mRNA, and found levels were only elevated in patients with valvular AF, not those with NVAf³⁷⁸. There is also a lack of consensus regarding the usefulness of ET-1 as a prognostic marker for rhythm outcome after ablation³⁷⁹⁻³⁸¹. The conflicting information that exists surrounding ET-1 and its role in AF makes it an important marker to further investigate.

1.3.6.4 CD40 Ligand (CD40L)

CD40 ligand or CD40L forms part of the CD40-CD40L system associated with platelets. When exposed to CD40 expressing vascular cells, CD40L expressed on the surface of platelets stimulates the release of inflammatory cytokines such as IL-6, adhesion molecules and tissue factor, and thus promotes coagulation. The cleaved product of CD40L is soluble CD40L (sCD40L), a biologically active ingredient which is indicative of platelet activation ³⁸². Elevated levels of which have been observed in various CVDs, such as HT ³⁸³, DM ³⁸⁴, cerebral ischemia ³⁸⁵ and more recently AF, in both the chronic and acute states ³⁶⁹.

This marker was found to be elevated in PAF, persistent and permanent AF patients, independent from pre-existing CVDs and risk factors of AF such as age, HT and DM ³⁸⁶. In addition, a small study of 20 persistent AF and 20 SR controls found the expression of CD40/CD40L was raised in the former group, and it stayed raised even 5 weeks following successful cardioversion ³⁸⁷. Also, rapid atrial rates due to short term AF induction (15 minutes) caused there to be an acute elevation in the levels of sCD40L ³⁶⁹.

Importantly, the prognostic value of sCD40L as a predictor of stroke events in AF patients was established in a number of studies. Elevated levels of sCD40L were noted in non-valvular AF patients and correlated to echocardiographic correlates of stroke occurrence such as left atrial spontaneous echo contrast, left atrial thrombus, and the occurrence of embolic events during a 2-year follow up study ³⁸⁸. Another study reiterated this in all AF subgroups, and found increased CD40L levels were predictive of future stroke and MI in non-valvular AF; thus showing CD40L is involved

in the prothrombotic and atherothrombotic processes that results from AF ³⁸⁶.

Conversely, studies by Lip and co-workers have shown only a modest elevation in levels of this marker in AF patients above that seen in controls and definitely not more than that seen in AF free patients with underlying CVDs ^{389, 390}. Additionally, these levels could not be correlated to the risk of stroke according to the SPAF risk stratification scheme, in AF patients participating in the SPAF III trial, and was thus deemed a poor marker for stroke risk in these patients ³⁹¹.

However, the majority of studies clearly show raised CD40L levels in the acute and chronic setting of AF and that it is a robust prognostic marker of one of the most devastating outcomes of AF; stroke, and also of other adverse cardiovascular events.

1.3.6.5 Cell Adhesion Molecules

The vascular cell adhesion molecule (V-CAM) and intracellular cell adhesion molecule (I-CAM) are part of a large family of adhesion molecules ³⁹². It has been suggested that activation of these molecules may be one of the first processes involved in thrombus formation ³⁹³. More importantly, elevated levels of these markers have been shown to be present in AF patients ^{387, 392, 394, 395}. Majority of studies have examined levels of V-CAM, while the information surrounding I-CAM still remains rather scant.

Levels of both these adhesion molecules were elevated in persistent AF patients over those seen in normal SR, and remained so after CV. More importantly, the levels of these markers were highest in the subset of AF patients who developed atrial thrombi; V-CAM emerging as an independent predictor of this outcome via multivariate analysis ³⁸⁷. The analysis of V-CAM levels in an 'all-comer' AF population

showed elevated levels were correlated to individual adverse outcomes such as stroke and CAD and composite outcome of all-cause mortality³⁹².

Analysis of right atrial appendage tissue from AF patients undergoing CABG confirmed that V-CAM expression was increased in these patients and levels were attenuated in experimental ex vivo human atrial tissue treated with olmesartan³⁹⁴. In fact, the CREATIVE-AF trial, a randomized, double-blinded, placebo-controlled trial is set to test the effects of angiotensin II type I receptor antagonists that may help reduce levels of these adhesion molecules, thereby potentially reducing the risk of thrombus formation³⁹⁶.

1.3.6.6 Extracellular Matrix (ECM) Remodelling Proteins

MMPs are a multi-gene family of enzymes that work in balance with their inhibitors, the TIMPs to regulate the turnover of the ECM, and thus maintain the atrial wall. The MMPs are responsible for collagen degradation, whereas the TIMPs inhibit this process^{302, 319}. There have been imbalances in the MMP/TIMP system reported in the setting of AF pre-cursors such as HT³⁹⁷, CHF³⁹⁸ and CAD³⁹⁹. Of note, the relationship between these markers and non-valvular AF has also been established. Levels of MMP-1 were decreased and TIMP-1 levels increased in chronic non-valvular AF compared to gender and age-matched SR controls. Also, the log ratio of TIMP-1/MMP-1 correlated significantly to the log prothrombin fragment 1+2 levels and thus to the prothrombotic state in AF⁴⁰⁰.

Other studies have implicated that MMPs and TIMPs influence the process of thrombus formation in an indirect manner via atrial ultra structural remodelling³⁰². Members of the MMP/TIMP system, namely MMP-2 and 9 were up regulated while

TIMP-1 and 2 were down regulated in the right atrial appendages of chronic over PAF patients over SR controls, reflecting enhanced fibrogenesis, which was also correlated to increasing AF burden ⁴⁰¹. Similar findings were reported in AF patients with concurrent CHF ³¹⁴ and with dilated cardiomyopathy ⁴⁰² with regard to levels of numerous members of the MMP/TIPM system, along with increase in myocardial collagen content. MMP-9 levels were increased in fibrillating atrial tissue obtained from chronic and PAF patients, detected via increased mRNA expression seen in polymerase chain reaction and by ELISA technique, alluding to the role in atrial dilatation and structural remodelling ⁴⁰³. Lastly, elevated serum MMP-9 levels were correlated to concurrently elevated CD40L and CRP levels, thus linking ECM instability ⁴⁰², platelet dysfunction and inflammation ⁴⁰⁴.

These findings indicate that the contribution of the matrix proteins to the thrombotic process in AF is multifaceted. These effects may be mediated directly with abnormal changes in the ECM, or indirectly, through the links to other inflammatory factors and members of the coagulation cascade, thus affecting the levels of structural remodelling in the atria.

1.3.6.7 Myeloperoxidase (MPO)

MPO is a leukocyte-derived heme enzyme, which is key in regulating the activity of MMP. It is a potent generator of reactive oxygen and nitrogen species, which in turn activate MMPs, to bring about ECM remodelling, contributing to atrial ultra structural remodelling via fibrosis and thus indirectly contributing to thrombosis ⁴⁰⁵. Rudolph et al studied the role of MPO extensively in an animal and human model. MPO was shown to be a pro-fibrotic marker in wild type (WT) mice once the fibrosis

effector angiotensin II was administered, and even independent of it in MPO deficient mice after MPO was administered via osmotic pumps. Both groups were investigated via EP stimulation and found to be electrically unstable and susceptible to arrhythmia. Studies in humans revealed that patients with pacemakers were monitored for up to 5 months; those who developed PAF had higher plasma concentrations of MPO, thereby reiterating the ability of MPO to induce AF in a human model. Furthermore, immunohistochemical analysis of the right atrial appendages of the patients with concomitant AF and CAD showed higher atrial depositions of MPO, thus tying this marker in with an inflammatory disease process as well ⁴⁰⁶.

This biomarker was also linked to the regression into AF after catheter ablation in two separate studies ^{407, 408}. Elevated levels of MPO were interrelated to high hs-CRP levels, in addition to being linked to recurrence of AF as early as 2 days post-ablation ⁴⁰⁷. In a larger study, with a longer follow up, higher recurrence rates were related to higher quartiles of MPO, independent of confounders such as age, gender, LA size and CRP levels ⁴⁰⁸.

In all, the evidence points towards the fact that MPO is closely linked to the pro-fibrotic process in AF, thereby making it a possible initiator and perpetuator of this arrhythmia, but is also indirectly linked to the pro-thrombotic processes in AF.

1.3.7 Summary

Thus, there are various pro-inflammatory and pro-thrombotic processes that drive the coagulation cascade. The thromboembolic processes in AF are evidently multifaceted, and complex. It involves numerous changes like ultra structural abnormalities in the ECM, endothelial dysfunction and macrostructural abnormalities

like left atrial dilatation that work in conjunction with inflammatory, pro-fibrotic, platelet and leukocyte derived biomarkers to complete the Virchow's triad and promote thrombus formation in AF. Indeed, the fact that the hyper coagulable state persists despite successful electrical cardioversion and after catheter ablation, also makes it evident that appropriate anti-coagulation and the monitoring of the same are a necessity in the case of this arrhythmia. Also, these biomarkers have been linked not only to the pro-thrombotic process but also to the arrhythmogenic process in AF; make these potential therapeutic targets for possibly preventing AF and its adverse consequences^{302, 319}.

1.4 Tertiary Care Management Strategies for Atrial Fibrillation

Given tertiary care management has been cited as a possible reason for the current epidemiological trends of this arrhythmia, an examination of the available strategies seemed appropriate¹³⁹. There are two main streams of therapy used for treating this arrhythmia; control of ventricular rate; usually the initial treatment approach to hemodynamically stabilize patients and secondly restoration of SR; usually attempted if the AF does not self-terminate and the heart rate has been controlled⁴⁰⁹. Pharmacological cardioversion has a 40% success rate⁴⁰⁹, whereas pharmacological rate control interventions have up to an 80% efficacy rate⁴¹⁰. In addition to these options, irrespective of the whether the patient is rate or rhythm controlled, attention is to be paid to the prevention of thromboembolic events via appropriate anticoagulation therapy.

However, before a decision can be made about treatment options, knowledge is required regarding the manner of presentation of the AF (paroxysmal, persistent or

permanent) symptomatic status/severity of symptoms, existing co-morbidities (cardiac and non cardiac), thromboembolic risk, and patient age, so as to allow for the achievement of short and long term treatment goals^{409, 411}.

1.4.1 Rate Control Versus Rhythm Control Trials

Several randomised control trials have examined the relative efficacy of rate versus rhythm control strategies in different AF patient populations. These trials examined various parameters in persistent and paroxysmal AF; primary end points included mortality rates (all-cause and CVD related) and rates of thromboembolic events. Secondary endpoints included resting heart rate (HR), maintenance of SR, hospitalisation rates, medication side effects and improvements in quality of life^{174, 261, 262, 412-414}.

All cause mortality^{174, 261, 412, 414}, composite death due to cardiac causes^{413, 415}, and number of thromboembolic events^{412, 413, 415} were similar in patients commenced on rate compared to rhythm control. These results were reiterated by an observational study conducted in a general AF population, which showed there was no significant difference in mortality within 4 years of initiation on rhythm versus rate control therapy⁴¹⁶.

Furthermore, the Pharmacological Intervention in Atrial Fibrillation trial (PIAF) and Strategies of Treatment of Atrial Fibrillation (STAF) study found no symptomatic improvement between the two treatment arms^{413, 414}. Additional secondary endpoints such as decline in heart rate^{262, 413, 414}, occurrence of syncope, improvements in echocardiographic parameters⁴¹³ and the New York Heart Association (NYHA) functional class⁴¹² were similar in both treatment arms in all trials. Of note however,

hospitalisation rates and drug toxicity were significantly higher in the rhythm control group^{261, 412-414}; this being the only parameter where rate control was deemed to be slightly superior to rhythm control therapy. That being said, all these trials highlighted that neither management strategies seemed superior with regard to improving outcomes and survival rates in paroxysmal or persistent AF patients, perhaps indicating the individualisation of treatment as the best option to be considered.

1.4.2 Rate Control Strategies

Rate control is important in the setting of AF, particularly in patients with underlying heart disease. In the case of AF patients that present with heart failure, dyssynchrony between the atria and the ventricle leads to impaired diastolic function and reduced cardiac output⁴¹⁷. Rapid ventricular rates can also lead to tachycardia-induced cardiomyopathy and hence worsen the heart failure^{418, 419}. Indeed the use of rate control medications in the setting of heart failure has been shown to reverse rate induced cardiomyopathy, improve impaired ventricular ejection fraction and increase exercise capacity⁴²⁰. In the setting of acute myocardial infarction, AF induced rapid ventricular rate can lead to increased oxygen demand and further enhance myocardial ischemia, and in the long run worsen prognosis⁷⁸. Rapid ventricular rates lead to symptoms of breathlessness, palpitations, and limit physical functioning, thus having a disruptive and debilitating effect on a patient's overall quality of life. The use of rate control is often used as a means of alleviating these symptoms and improving overall quality of life⁴²¹.

Ventricular rate is deemed to be adequately controlled when resting heart rate is between 60-80 beats per minute (bpm) and between 90-115 bpm on moderate

exercise ⁴¹⁸. It is commonly achieved by administration of beta blockers, calcium channel blockers and digoxin ⁴²². Beta blockers and calcium channel blockers are efficacious in reducing heart rate at rest and during exercise ⁴²³, whereas digoxin is usually used in patients where rate control during exercise is not a treatment goal ⁴⁰⁹. These drugs are administered orally in a hemodynamically stable patient; however, if rate control cannot be achieved via this medium, intravenous administration is used. Careful dose titration is required to achieve proper therapeutic results and avoid adverse effects such as bradycardia and heart block ¹.

Rate control medication is usually the first line of treatment in the tertiary care setting. Freestone et al found it was initiated in 38% of patients who presented to the hospital with acute episodes of AF ²⁵⁶. This was also the preferred treatment in newly diagnosed AF patients ¹⁷². Initiation and use of this treatment strategy in the ED yielded shorter stays and faster discharge. Additionally it also reduced the probability of these patients being admitted to hospital thereby reducing the overall hospital costs for AF ²⁵⁷. Thus showing that appropriate heart rate control in the AF patients improves long and short-term outcomes in AF patients and benefits the tertiary care system.

Lastly, permanent pacemaker implantation (PPM) and atrioventricular (AV) junction ablation is an invasive line of therapy is especially suited to patients when medical rate control is not possible ^{424, 425}. In fact, following these procedures there has been a marked improvement in the NYHA functional class, quality of life scores, symptomatic status, echocardiographic parameters and reduction in health care usage ^{426, 427-429}. However, it can lead to adverse events such as loss of atrio-ventricular and

ventricle to ventricle synchrony, sudden cardiac death and less grave limitations include lifelong dependence on PPM and having to be on anticoagulation medication indefinitely⁴³⁰.

1.4.3 Rhythm Control Strategies

1.4.3.1 Pharmacological Interventions

The decision to convert to SR involves individualised therapy and usually follows ventricular rate control⁴⁰⁹. Patient co-morbid disease profile must be considered, particularly in the case of CHF and in patients with SHD, as there may be pro-arrhythmic interactions with commonly used anti-arrhythmic agents. Patients also have to be adequately anticoagulated as cardioversion may cause thromboembolic complications via systemic emboli⁴³¹.

Trials have shown that IV flecainide is possibly the most effective anti-arrhythmic drug (AAD)⁴³²⁻⁴³⁴; demonstrating high conversion rates (up to 96%) in patients with long standing and new onset AF, over and above those of propafenone (55%)⁴³⁵ and amiodarone (89%)⁴³⁶; with few adverse effects. Class III anti-arrhythmics such as ibutilide, dofetilide have shown modest conversion rates of 47%^{437, 438} and 31%⁴³⁹ respectively, with polymorphic ventricular tachycardia developing as a side effect soon after infusion in ibutilide and both these agents tending to be more successful in terminating and converting atrial flutter rather than AF. Similarly, quinidine was found to be moderately effective in restoring SR, with trials reporting drug withdrawals and deaths following treatment^{440, 441}. Amiodarone tends to be used when other avenues have been exhausted⁴⁴². Although effective in reverting AF

patients to SR, this agent can increase hemodynamic instability especially in hypotensive patients or those with heart failure ⁴⁴³, and is known to cause thyrotoxicosis, hepatic injury and pro-arrhythmia ¹⁷³. Newer agents such as Vernakalant are emerging as potentially superior to aforementioned therapies; it is less pro-arrhythmic, has shorter conversion time and thus results in shorter hospital stays ^{444, 445}.

Often, patients are admitted to hospital for initiation of antiarrhythmic drug therapy, as some drug therapies require a short hospital stay and close monitoring. One analysis proved this to be a very costly practice, which significantly added to hospital cost burden in the US. In-hospital costs for each patient initiated on antiarrhythmic therapy were in excess of \$3000 ⁴⁴⁶. A separate analysis of the benefits of performing pharmacological cardioversion in the ED itself not only found this method to be effective; with 97% patients being discharged home with a 6% complication rates; and also to be cost saving for the hospital ⁴⁴⁷.

The benefits of anti-arrhythmic medications may be negated by the adverse effects of these drugs; which include increased mortality, pro-arrhythmic effects, and drug complications. However, rhythm control via non-pharmacological methods such as ablation may be a better strategy. Whether these are superior to rate control is as of yet unknown ⁴⁴⁸.

1.4.3.2 Non-Pharmacological Interventions

Surgical ablation procedures such as the Cox-Maze procedure have evolved over time (maze I, II and III) boasting success rates of up to 90% in the treatment and prevention of AF ^{449, 450}. Despite these success rates, complications including death, the

need for permanent pacing, post operative bleeding, impaired atrial impulse conduction, delayed onset AF/atrial flutter and atrio-esophageal fistula have been reported ⁴⁵¹. This led to research into modifications to this procedure and the development of less invasive techniques such as catheter ablation ¹.

This led to the advent of catheter ablation, enthusiasm for which escalated when Haissaguerre and co-workers discovered the presence of ectopic foci in the pulmonary veins of patients with recurrent episodes of AF and demonstrated that radio frequency ablation of these foci led to the abolishment of the paroxysms of AF ¹⁷⁹. The existence of similar ectopic potentials was found in areas other than the pulmonary veins, leading to modification of the existing ablation techniques, ^{452, 453, 454,} ⁴⁵⁵ yielding 80-90% success rates, measured primarily by freedom from recurrent episodes of AF in the first 3-6 months following the procedure, and an improvement in the patient quality of life, symptomatic status, exercise capacity and left ventricular function ^{456, 457}. Recently, data has shed light on a new minimally invasive 'hybrid approach' to catheter ablation, involving combination of a box lesion with transcatheter ablation. This procedure yielded high success rates in persistent AF patients, keeping them free of anti-arrhythmic drugs and warfarin ⁴⁵⁸. However, these procedures are not without complications; which include PV stenosis ⁴⁵⁹, thromboembolic events ⁴⁶⁰ (which can be combated by aggressive anticoagulation), atrioesophageal fistulas ^{461, 462}, (a rare but potentially life threatening problem) and left atrial tachyarrhythmias ^{463, 464}. Another issue is that certain patients with established AF require multiple ablation procedures due to pulmonary vein reconnection ⁴⁶⁵. Currently, randomised trials are underway to determine the relative efficacy of different techniques, and the effect on patient outcome including recurrence rates and

quality of life. Such comparative data will yield valuable information, which may shape future treatment strategies.

Electrical cardioversions are another non-pharmacological, non invasive, effective procedure (70%-90% success), which involves delivering a controlled amount of energy in synchrony with the intrinsic activity that restores SR ⁴⁶⁶. Success rates are low in persistent and permanent AF, and cardioversions not recommended in episodes lasting longer than 48 hours as the propensity for thromboembolic events increases ^{467, 468}. Thromboembolic risk remains one of the most serious complications of cardioversions, occurring in up to 7% of patients not appropriately anticoagulated ⁴⁶⁹, whereas arrhythmias such as ventricular tachycardia and fibrillation, supraventricular and ventricular premature beats or bradycardia may also develop in rare cases ⁴⁷⁰.

1.4.4 Anticoagulation in Atrial Fibrillation

Risk stratifications schemes have been put into clinical practice to determine the stroke risk of a patient based on their disease history and demographics, the most utilised schemes in clinical practice are the CHADS₂ and CHADS₂VaSc scoring systems ¹. The CHADS₂ score ^{175, 471} and the CHA₂DS₂VASc score ⁴⁷² are based on a system of points, allocated for the different co-morbidities, age and gender of the patients, as outlined in section [1.2.2](#). Based on the CHADS₂ and CHADS₂VaSc scoring systems, patients who score '0' are excluded from anti-platelet or anti-coagulation treatment, whereas those who have a score ≥ 1 are considered for prophylactic therapy ⁴⁷³.

Randomised control trials have proven the effectiveness of vitamin K antagonists, most popularly warfarin, as a primary and secondary prevention measure, reducing stroke risk by up to 80% ^{296, 474-477}. Numerous trials ⁴⁷⁸⁻⁴⁸¹ have also

demonstrated the efficacy of these agents over and above that of anti-platelet agents such as aspirin, which provide only modest protection against stroke/TIA in patients (up to 33%)^{296, 477, 482}. Newer anticoagulants like dabigatran⁴⁸³, rivaroxaban⁴⁸⁴ and apixaban⁴⁸⁵ are being introduced as these agents significantly reduce the side effect of bleeding associated with warfarin and circumvent the need for international normalised ratio (INR) testing⁴⁸⁶, and even have less interactions with food.

1.4.5 Summary

The management of AF has evolved and is constantly being updated in accordance to the most current guidelines. The initial comprehensive ACC/AHA/HRS guidelines were published in 2001 and have updated in 2011 having taken into account all the aforementioned factors and have laid out algorithms for the optimum management strategy to be applied for every presentation of AF. These algorithms take into account the duration and presentation type of AF (paroxysmal, persistent or permanent), co-existing conditions, and then propose steps towards either restoration of SR or control of ventricular rate and the approach towards anticoagulation or antiplatelet therapy¹. Recent interventional studies have examined the benefit of novel approaches to the clinical management of AF at the ED levels; appropriate performance of cardioversions, administration of rate control medications²⁵⁷ as also the implementation of an intensive ED observational unit⁴⁸⁷. These approaches have yielded encouraging results; both in terms of favourable patient outcomes and in the reduction of treatment costs. Indeed, in the case of a common CVD such as CHF, nurse-led educational interventions both during hospital visits⁴⁸⁸ and after hospital discharge⁴⁸⁹ have generated great success in reducing rehospitalisations, cost of care

and psychosocial outcomes. The application of such novel approaches to AF management may lead to changes in the incidence of AF hospitalisations and rehospitalisations and in turn reduce the substantial public health burden of AF.

Chapter Two

Independent Risk Factors for the Development of Non-Valvular Atrial Fibrillation: a Systematic Literature Review and Meta-Analysis

2.1 Introduction

Conservative estimates from a large population study have shown that in the United States alone AF will increase 2.5 fold by the year 2050 ³. Miyasaka et al used the entire population of the Midwestern United States to project the number of AF patients by 2050 and found the number to be a staggering 16 million ⁴. Even recent global estimates indicate that large numbers of new cases of AF are being added to the existing pool of sufferers annually, which will further compound the mortality and disease burden conferred by AF ². The increasing burden of AF translates into an exponential rise in the number of hospitalisations for this arrhythmia ²⁵¹.

Several factors have been recognized as being associated with an increased risk of developing AF. These factors have been identified from a series of large population-based observational cohorts ^{5, 8, 14, 490}, and case-control studies ⁴⁹¹⁻⁴⁹⁴. However, statistical methods have varied, as have confounders that have been adjusted for, all providing differing results. In addition, studies have circumscribed the generalizability of their results by including only certain sub-populations ^{131 6, 27 33}. Complicating this further is that the prevalence of AF is growing at a rate faster than predicted by these studies ⁴, implying the presence of potentially yet to be recognised risk factors.

The effects of conventional risk factors, such as advancing age, gender, hypertension (HT), congestive heart failure (CHF), coronary artery disease (CAD), diabetes mellitus (DM), and left ventricular hypertrophy (LVH) have been vigorously evaluated^{6,8}. However, there is insufficient information regarding the extent of their absolute impact on AF development in the general population. There is also a lack of consensus in the literature regarding newer factors such as obesity^{16, 145} and sleep apnoea^{18, 495} and contentious risk factors of AF such as cigarette smoking and alcohol consumption⁴⁹⁶. Finally, the relative contribution of each of these risk factors has not been established.

The aim of this systematic review and meta-analysis was therefore to review the studies that identified patient features and co-morbidities in relation to the development of non-valvular AF, and to establish the independent and relative risk rates for the development of AF.

2.2 Methods

2.2.1 Search Strategy

The databases PubMed, Embase and Cochrane were searched for all studies that examined the independent effect of the various cardio-metabolic risk factors on the development of AF. The search criterion was designed in consultation with the research librarian for the School of Medicine, University of Adelaide and is detailed in Figure 1. The search was performed on the 12th of May 2013. This search was supplemented by manually-searching the bibliographers of all relevant review articles, to ensure no applicable studies were overlooked. Both prospective and retrospective observational studies and case control studies were included. All studies had a primary

outcome of incident AF. Atrial fibrillation and flutter were treated as equivalent outcomes.

We identified 5731 articles following the initial literature search using the criteria outlined in Figure 1. Of these, 5598 were excluded; duplicate articles, non-English articles and irrelevant articles after examining titles and/or abstracts. A total of 136 articles were considered for detailed secondary analysis of the full text article.

Studies were excluded for the following reasons: only a single risk factor of interest in isolation and not in the context of other confounders; participants had AF at baseline; conference abstracts with no full text; less than 100 cases of incident AF; valvular instead of non-valvular AF; randomised controlled multi-centre trials which had very specific inclusion and exclusion criteria that would have led to a selection bias and thus affected the generalizability of their results⁴⁹⁷; and those that reported only risk ratios without confidence intervals. Finally, a total of 12 articles were included in our analyses as these fulfilled the inclusion criterion^{5, 15-17, 19, 24, 29, 91, 132, 498-500}.

2.2.2 Risk Factors Examined

The twelve studies included the following risk factors: advancing age; male gender; hypertension (HT); left ventricular hypertrophy (LVH); congestive heart failure (CHF); coronary artery disease (CAD); diabetes mellitus (DM); body mass index (BMI); alcohol consumption; and cigarette smoking (CS). The definitions for the included risk factors differed between studies, as did the factors adjusted for in the multivariate analyses. These are detailed in Tables 2-11 separately for each risk factor. Of note, obstructive sleep apnoea (OSA) was not included in the meta-analysis because of the four relevant articles we retrieved; one included patients with AF at baseline, one

examined OSA in isolation and one was a conference article with no full text, all of these conditions were exclusion criteria. The last remaining article¹⁸ was not sufficient by itself to provide an adequate and accurate pooled independent risk estimate for developing AF in the setting of OSA.

2.2.3 Statistical Analysis

Statistical analyses were performed using Stata version 12. Log relative risks from both unadjusted and adjusted statistical models, along with their standard errors, were pooled across studies using DerSimonion-Laird random effects models⁵⁰¹. Pooled estimates and 95% confidence intervals were back transformed to relative risks. Heterogeneity between studies was quantified using the I squared statistic⁵⁰². This was calculated using the following formula $Q = \sum_i [(1/\text{variance}_i) * (\text{effect}_i - \text{effect}_{pooled})^2]$. Where $\text{variance}_i = ((\text{upper limit} - \text{lower limit}) / (2 * z))^2$.

Some studies provided only univariate results whereas others provided only multivariate for certain variables. These have been outlined in Tables 2-11. For a small minority of studies (n=5) the univariate analyses were not provided for the variables of interest. We determined the relative risk and 95% CI using the following formula⁵⁰³, $Relative\ Risk\ (RR) = (a / (a + b)) / (c / (c + d))$. Where; *a*- Individuals who carried the risk factor and developed AF, *b*-Individuals who carried the risk factor but did not develop AF, *c*- Individuals who did not carry the risk factor and developed AF, *d*-Individuals who carried the risk factor and did not develop AF.

Lastly, the population attributable risk (PAR) of each risk factor was calculated. PAR represents the percentage of AF cases that could potentially be reduced if the causative factor were removed from the population^{504,5}. It was calculated using the

formula $PAR = Pe (RRe-1) / [1 + Pe (RRe-1)]$. Where, Pe is population prevalence of the risk factor in the global population and RRe is the relative risk (pooled multivariate) of the risk factor as calculated by this meta-analysis⁵⁰⁴.

2.3 Results

2.3.1 Study Characteristics

The study and participant characteristics are detailed in Table 1. Included studies were published between 1994-2013 and patient recruitment was initiated in 1948⁵ and ended in 2008⁴⁹⁹. Of the twelve studies, nine were unique cohorts^{5, 15, 16, 24, 29, 91, 498-500} and the remaining three^{17, 19, 132} were part of the Cardiovascular Health Study. Eight studies were prospective observational cohort studies^{5, 15-17, 19, 29, 132, 499}, two were retrospective cohort studies^{24, 498} and two were case-control studies^{91, 500}. The study size varied between 63,386 participants in the Niigata Preventive Medicine¹⁵ and 1847 participants in the Kuopio Ischemic Heart Disease Risk Factor Study⁴⁹⁹. The number of incident AF episodes varied between 1585 cases reported by Jensen et al¹⁹ and 103, reported by Karppi et al⁴⁹⁹. The average years of follow up varied, as did the gender distribution. The studies consisted of participants of different races, including Caucasian, Japanese and African-American. The weights of each of the studies are provided separately for each risk factor in Table 12.

2.3.2 Independent Predictors of Atrial Fibrillation

The univariate and multivariate pooled analyses results are provided in Figures 2 and 3. Each univariate and multivariate analysis for each individual risk factor is presented in Appendix 2. The multivariate pooled analysis of the studies included

identified eight independent predictors of atrial fibrillation. These were, from strongest to weakest; CHF, male gender, CAD, HT, LVH, DM, advancing age, and BMI. However, cigarette smoking and alcohol consumption were not linked to an increased risk of this arrhythmia. The results of the univariate and multivariate pooled analyses for each risk factor are provided forthwith.

2.3.2.1 Chronic Heart Failure (CHF)

The univariate analysis for CHF consisted of four studies^{5, 498-500}. The pooled unadjusted relative risk (RR) for developing AF was 4.34 (2.17-8.65), $P < 0.001$, ($I^2 = 91\%$, $P < 0.001$). The multivariate analysis consisted of three studies^{5, 17, 498}, and showed that the adjusted RR was 4.11 (2.10-8.03), $P < 0.001$, ($I^2 = 90\%$, $P < 0.001$). After adjustment for confounders, the multivariate analysis showed that patients with a history of CHF were over 4 times more likely to develop this arrhythmia, than those free of this disease.

2.3.2.2 Gender

The univariate analysis included five studies^{15, 24, 498-500} and the pooled RR was 2.17 (1.34-3.50), $P = 0.002$ ($I^2 = 94\%$, $P < 0.001$). The multivariate analysis included three studies^{17, 24, 498} and the adjusted RR was 2.67 (1.33-5.4), $P = 0.006$, ($I^2 = 91\%$, $P < 0.001$). The overall RR of developing AF was over 2 ½ times greater in males as compared to females.

2.3.2.3 Coronary Artery Disease (CAD)

The unadjusted risk of developing AF in CAD patients was examined by six studies,^{5, 29, 132, 498-500}. The unadjusted RR was 2.10 (1.64-2.70), $P < 0.001$, ($I^2 = 85\%$,

P<0.001). The multivariate analysis for this study included three studies^{5, 17, 498}. This showed the adjusted RR to be 1.65 (1.23-2.14), P<0.001, (I² =53%, P<0.009). The likelihood of developing AF in patients with a history of CAD was 65% higher than those without a previous history of this CVD.

2.3.2.4 Hypertension (HT)

The univariate analysis, which included nine studies^{5, 15, 16, 18, 19, 29, 127, 499, 500} showed the pooled unadjusted RR of developing AF in hypertensive patients was 1.64 (1.47-1.83), P<0.001, (I² =65%, P=0.001). The multivariate analysis, which included three studies^{5, 16, 17}, showed the adjusted pooled RR was 1.45 (1.30-1.65), P<0.001, (I² =8%, P=0.3). The pooled RR of developing AF in hypertensive patients was 45% greater than those who did not carry this co-morbidity.

2.3.2.5 Left Ventricular Hypertrophy (LVH)

The univariate analysis for LVH included four studies^{5, 15, 24, 500}. The unadjusted RR for this co-morbidity was 2.16 (1.56-2.97), P<0.001, (I² =82%, P<0.001). The multivariate analysis consisted of three studies^{5, 15, 24} and the adjusted pooled RR was 1.36 (1.15-1.59), P<0.001, (I² =0%, P=0.9). The risk of developing AF in the presence of LVH was 36% greater than without.

2.3.2.6 Diabetes Mellitus (DM)

Nine studies provided univariate estimates of the risk of developing AF in patients with DM^{5, 15, 19, 29, 91, 132, 498-500}. The overall unadjusted RR was 1.56 (1.36-1.79), P<0.001, (I² =63%, P=0.001). The multivariate estimates were provided by three studies^{5, 17, 91}. The pooled adjusted RR was 1.22 (1.09-1.37), P=0.001, (I² =0%, P=0.5).

The overall risk of developing AF in patients with diabetes increased by 22% after adjusting for various confounders.

2.3.2.7 Advancing Age

Four studies were included in the univariate analysis^{15, 16, 498, 500}, which showed a pooled RR of 1.08 (1.07-1.09), $P < 0.001$, ($I^2 = 56\%$, $P = 0.06$). Five studies were included in the multivariate analysis^{5, 16, 17, 24, 498}, and the pooled adjusted RR was 1.09 (1.07-1.1), $P < 0.001$, ($I^2 = 78\%$, $P < 0.001$). The overall adjusted estimated RR of developing AF with every one-year increase in age was 9%, for patients older than 40 years.

2.3.2.8 Body Mass Index (BMI)

Seven studies provided univariate estimates for the risk of developing AF with increasing BMI^{5, 15, 16, 19, 24, 498, 500}. The pooled unadjusted RR was 1.04 (1.03-1.05), $P < 0.001$, ($I^2 = 68\%$, $P = 0.001$). The multivariate estimates were provided by two studies^{16, 498}. The overall adjusted RR was 1.07 (1.05-1.08), $P < 0.001$, ($I^2 = 0\%$, $P = 0.6$). With every one unit increase in BMI, the risk of developing incident AF increased by 7%.

2.3.2.9 Alcohol Consumption (AC)

Three studies examined the effect of alcohol consumption on the risk of developing AF^{5, 16, 19}. The unadjusted analysis included all these studies and showed the RR was 1.01 (0.98-1.05), $P = 0.3$, ($I^2 = 34\%$, $P = 0.1$). The multivariate analysis included only the study by Frost et al¹⁶, the results of which showed the adjusted RR was 1.04 (1.0-1.07), $P = 0.02$, ($I^2 = 0\%$, $P = 0.8$). However, given that only one study was included, these results are not an accurate representation of a pooled multivariate analysis for alcohol consumption and risk of incident AF.

2.3.2.10 Cigarette Smoking (CS)

This was not a significant predictor of AF development in univariate and multivariate analyses. The former included five studies^{5, 16, 29, 132, 500}. The RR was 0.98 (0.85-1.13), P=0.7, (I²=55%, P=0.02). The latter adjusted for confounders and included two studies^{5, 16}, but showed the RR was 1.01 (0.80-1.3), P=0.9, (I²=51%, P=0.1).

2.3.3 Population Attributable Risk (PAR)

The population attributable risks of the modifiable risk factors are presented in Table 13. With regard to the modifiable risk factors, HT carried the highest PAR (16%), followed by CHF (9%) and CAD (3%). DM carried a small PAR (2%). Obesity (BMI≥30) carried a small PAR of 0.8%. Although the meta-analysis did not find alcohol consumption to be a significant risk factor for AF development, it carried a PAR of 1%, while cigarette smoking carried a negligible PAR of 0.1%.

2.5 Discussion

This study undertook a rigorous review of the literature to determine the relative risk of developing AF with a variety of previously identified risk factors. It uses data from 249,570 patients in a meta-analysis and demonstrates the following:

1. Chronic heart failure confers the greatest risk of developing AF with an increased risk of 4.1 fold. This is followed by male gender (2.67), coronary artery disease (1.65), hypertension (1.45), left ventricular hypertrophy (1.36), diabetes (1.22), advancing age (1.09) and increasing BMI (1.07).
2. Interestingly, the current literature does not demonstrate cigarette smoking and alcohol consumption as independent predictors of developing AF.
3. Among the modifiable risk factors, although CHF carried the highest RR for developing AF, HT carried the highest population attributable risk for developing AF (15%).

2.5.1 Chronic Heart Failure

CHF was the strongest predictor of AF after adjusting for numerous other factors. This high risk could be attributed to the myriad of pathological changes CHF induces in the atrium. Acute and chronic heart failure cause hemodynamic changes such as atrial stretch and increased left atrial dimensions; demonstrated in both animal^{75, 183} and human^{224, 505} models. CHF also causes ultra structural changes such as fibrosis and cellular hypertrophy^{76, 506}. These changes in turn lead to alterations in the electrical integrity of the atria; all of which increase the likelihood of multiple re-entrant tachycardias, such as AF^{74, 75}. The activation of the renin-angiotensin-aldosterone system feeds into the above changes making it a self-perpetuating disorder^{507, 508}, which ultimately leads to AF. Moreover, even with low global population prevalence, it contributes to 9% of all AF episodes (Table 13). Thus, there exists a need to better understand the interaction between the joint epidemics of CHF and AF, as it may be key in finding a way to curb them⁵⁰⁹.

Interestingly, studies have shown that that CHF is pathologically linked to CAD⁵¹⁰, the latter of which was found to be a robust risk factor of AF development by this meta-analysis. The pathophysiological correlates of CAD and CHF share certain similarities, and hence may exert their influence on AF development in similar ways. In fact, an analysis of angiograms of CAD patients with and without AF found that systolic heart failure may play a larger role in inducing AF than atrial ischemia⁷⁹. CAD also induces hemodynamic changes such as left atrial dilatation and decreased left ventricular ejection fraction⁸⁴, and certain inflammatory changes in the atria, all of which have been observed in the setting of CHF⁵¹¹. The adjustment for CHF in the

studies included in the multivariate analyses^{5, 17, 18} may have attenuated the effect of CAD on AF development; thus leading to lower reported risk estimates, a relatively smaller pooled adjusted RR compared to CHF and hence a lower PAR (Figure 3 and Table 13). In the case of AF patients undergoing cardiac surgery, however, ischemia and associated fibrosis may play a greater causal role in bringing about AF⁵¹². Additionally, unlike CHF, the reversibility of the changes brought about by CAD is more established by treatment with statins^{62, 513, 514}.

2.5.2 Hypertension

Hypertension, even in a nascent stage has the potential for inducing adverse cardiovascular effects⁵⁰. Both short-term and chronic HT bring about a number of changes including conduction abnormalities, enlargement of the left atria (LA), deposition of interstitial fibrosis^{58, 59} and LVH, one of the most common manifestations of HT⁷⁰. The close link between these two entities may explain the similarity in the risk estimates that were obtained for these two disease states from the pooled multivariate analyses (Figure 3). Despite HT being the most commonly occurring co-morbidity with AF^{54,8}, the use of anti-hypertensives by individuals in a number of the studies included in the multivariate analyses^{5, 16, 17, 19, 132} could have normalized/reduced the BP and thus the reported risk of developing AF. Indeed, emerging data from the Losartan Intervention For Endpoint reduction in hypertension (LIFE) trial shows a significant reduction in new-onset AF in hypertensive patients treated with this drug⁵¹⁵. In addition, it has been implied that angiotensin receptor blockers (ARBs) are capable of reducing atrial fibrosis, (a common structural change caused by HT⁵⁸), and hence the risk of AF⁵¹⁶. With regard to LVH, evidence from a sub-

analysis of the LIFE trial has shown that treatment with losartan leads to a decrease in the severity of, or the complete absence of LVH on ECG. This had benefits above and beyond blood pressure control. Indeed, there was a 17% reduction in the incidence of new onset AF independent of other risk factors for this arrhythmia⁵¹⁷. Results from trials such as LIFE are encouraging, given HT (which can induce LVH) has a high population prevalence, and if managed appropriately could lead to a reduction in ~16% of incident AF (Table 13), making it a potent, yet potentially modifiable risk factor for AF.

2.5.3 Metabolic Syndrome (Diabetes Mellitus and Obesity)

Diabetes mellitus^{493, 91, 92} and obesity^{6, 16, 145} too are significant modifiable risk factors of atrial fibrillation. These disease states induce similar changes in the heart; LVH⁹³, left atrial enlargement^{149, 150, 153}, increased myocardial injury and oxidative stress^{152, 518}. Recent weight loss/life-style intervention studies in obese individuals have shown reduction in left atrial area, interventricular septal diameter and reduced AF burden⁵¹⁹. Certainly, glycaemic control leads to a reduced severity and duration of DM, which plays a role in decreasing the incidence of AF^{92, 520}. However, there are a few studies that dispute the effect of DM on AF development, which could be attributed to methodology, small number of patients carrying the disease or a failure to take into account confounders^{243, 521}. Following adjustment for various factors this meta-analysis found that both DM and BMI in their own right, independently and significantly increase the risk of AF development (Figure 3). Even if the reported relative risks (1.2 and 1.09 respectively) of these conditions may be perceived as modest; the close relationship between DM, and HT and LVH^{95, 5, 522} further enhances

the effect of DM on AF. Additionally, in the context of BMI category, the change from overweight (25-30kg/m²) to obese (30-40kg/m²) and so forth would lead to a ~35% increased risk of AF making this a significant predictor variable for AF development. Certainly, the rising global epidemics^{523, 524} and thus the PAR (Table 13) of these metabolic conditions are sure to increase and contribute to more than ~3% of incident AF (Table 12), unless curtailed.

2.5.4 Demographics (Aging and Gender)

Although the burgeoning epidemic of AF has been attributed to the aging population, this study provides context for the relative contribution of age to the risk of developing AF. It could be speculated that with every decade of life, the concurrent increase in risk of AF development would be 10-fold, even after adjusting for confounders (Table 8). There is an increased propensity to develop AF in the aged due to the changes induced by the natural aging process in the atria. Kistler et al showed that AF-free individuals ≥60 years had decreased atrial conduction velocity, atrial voltage and more heterogeneous conduction compared to younger individuals⁵²⁵. Indeed, a small study of elderly patients undergoing catheter ablation found the atrial substrate to be more complex due to extensive fibrosis⁵²⁶. In addition to these detrimental changes, the propensity to develop potent AF risk factors such as HT, CAD, CHF and DM is further enhanced by ageing³³. The influence of gender on AF development however, remains unaffected by senescence. Indeed, both the Framingham⁵ and Cardiovascular Health Studies³³ found that for men between 60-70 years, as well as those between 70-80 years, the incidence of AF is up to 2 times that for women in the same age groups. The Copenhagen City Heart Study also found the

prevalence of AF in men doubled over a 2-decade period but that for women remained steady⁵²⁷. These gender differences are said to be due to etiological variations in the way the structural and electrical substrate for AF develops. Males have recorded higher blood pressures, left atrial volumes, and shown evidence of diastolic dysfunction and P-wave abnormalities compared to women of the same age^{44, 45}. Thus, with male gender contributing a high RR and the ageing global population, the contribution of age, despite its relatively low RR; will only rise⁴. However, give these two are non-modifiable demographic factors, attention must be paid to the other modifiable risk factors in order to reduce the worldwide burden of AF.

2.5.5 Non-predictors of Atrial Fibrillation Development

Studies focusing on the variables of alcohol consumption^{6, 132, 128} and cigarette smoking^{131, 496, 528 529} have conflicting results with regard to the extent of their effect on AF development. Interestingly, studies that have found a significant link have centred around the effects of binge drinking, ('holiday heart syndrome')¹³⁰ or have examined the effect of consumption of high quantities of alcohol (~70gms/day)^{127, 530}, on the likelihood of developing AF. Similarly, only studies that dealt with the effects of chronic smoking or nicotine consumption, found this entity to have a significant effect on AF development^{119, 123, 529}. In addition, patients self-reporting their levels of alcohol intake and smoking has been found to be an inaccurate and at times unreliable⁵³¹. This could also have left room for bias and incorrect reporting and hence downplayed the effect on these factors on AF development, as found by a meta-analysis that suggested interviewer-administered questionnaires or biochemical analyses may yield more consistent results⁵³². However, in addition to the non-significant risk estimates for

these entities, the PAR are also small (Table 13), implicating that alcohol consumption and cigarette smoking may not significantly impact the development of incident AF.

2.6 Clinical Implications

This study encompassed data of a large number of patients, from different study groups, with a decade of follow-up (Table 1). This meta-analysis provided a comprehensive picture of numerous independent risk factors and their relative contribution to the risk of developing AF. Each of these factors exerts a differential impact on the substrate that predisposes to AF. Some risk factors may interact with each other to either compound this effect, such as CHF and CAD⁵¹⁰; while others might attenuate the impact of another factor which nevertheless has a significant impact on AF, as in the case the effect of HT and BMI on DM⁹¹. It has to be acknowledged, however, that very rarely do AF patients present with one single risk factor, and the compounding effect of a number of these variables makes AF a multi-factorial arrhythmia⁵³³. Indeed, it is also important to note that the adverse changes induced by these pre-disposing conditions can be reversed or reduced by treatment with anti-hypertensives^{66, 515}, interventions⁵³⁴ such as catheter ablations and alterations to life-style such as diet and exercise⁵¹⁹. This is of paramount importance in developing targeted preventative strategies that focus on risk factor management, which may help potentially curtail the epidemic of AF.

2.7 Limitations

Several limitations need to be taken into consideration while interpreting the results of this study. Most importantly, the method of AF detection varied between studies and this may have led to an under-detection of this arrhythmia. Studies that

used hospital records to detect AF may have only captured highly symptomatic patients that presented for treatment^{15, 16, 19, 24, 29, 499, 500}.

Importantly, while interpreting the relative risk of each pooled analyses, it must be remembered that there are cases where the severity, duration and effect of medications may influence the absolute impact that a particular risk factor has on the risk of developing AF⁵³⁵. For instance, severity of HT, duration of CHF or the effect of hypoglycemic medication on DM, may have influenced the absolute risk that these risk factors would have had on AF development, which was not accounted for in any of the studies.

Also, although the meta-analysis included risk estimates from a Danish^{16, 500}, Finnish⁴⁹⁹, Norwegian²⁹, Japanese¹⁵ and African American^{17, 132, 19} populations, majority of the participants could be described as Caucasian, which may affect the generalizability of this study to other races. Given the association between certain risk factors and other races can differ, it may be important to explore these potential racial differences in AF incidence. Lastly, the age distribution of the participants in the studies possibly implies the results can only be applied to individuals between the ages of 49-75, and not for young or much older AF sufferers.

2.8 Conclusions

AF is a complex disease, which can be influenced by a myriad of co-morbidities. Demographic factors (age and male gender), cardiac co-morbidities (CHF, CAD, HT, LVH) and non-cardiac diseases (DM and obesity) all independently and significantly increased the risk of developing incident AF. The understanding of these interactions is possibly the key to better appreciating and treating the arrhythmia itself. Also,

aggressive and appropriate risk factor management such as the treatment of HT may well help reduce the number of AF sufferers and ultimately the incidence and prevalence of this arrhythmia.

2.9 Figures

Figure 1 Study search criteria

Electronic database search criteria:

- PubMed: atrial fibrillation AND ("relative risk" OR "hazard ratio" OR "odds ratio"), 2522 references
- Embase: 'atrial fibrillation' AND ('relative risk' OR 'hazard ratio' OR 'odds ratio'), 3182 references
- Cochrane: (atrial fibrillation* OR Auricular Fibrillation* OR atrium fibrillation*) AND (hazard ratio* OR odds ratio* OR relative risk*)(hazard ratio* OR odds ratio* OR relative risk*), 21 references

Date of search: 12th May 2013

5734 total references including 6 systematic reviews

5598 articles excluded:

- Duplicates, n=1725
- Non English articles, n=74
- Irrelevant titles and/or abstracts, n= 3799

136 references examined for relevance

124 articles excluded:

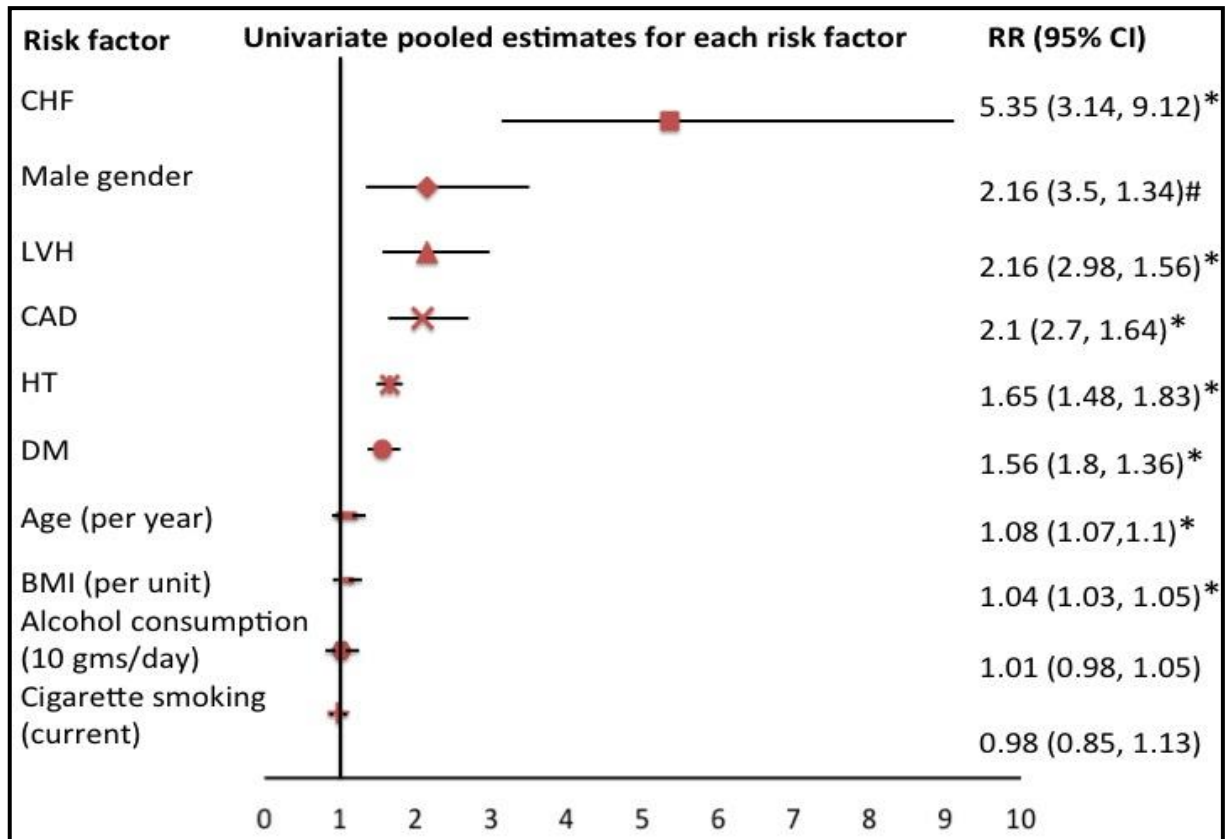
- Reported only 1 risk factor in isolation, n= 37
- Included participants with AF at baseline, n=23
- Conference abstracts only, no full text, n=32
- Less than 100 cases of incident AF, n=14
- Valvular AF, n=7
- RCTs, n=2
- Risk ratios were provided, no confidence intervals, n=3
- Systematic literature reviews, n=6

12 references included in review

- 8 prospective observational cohort studies
- 2 retrospective cohort studies
- 2 case-control observational studies

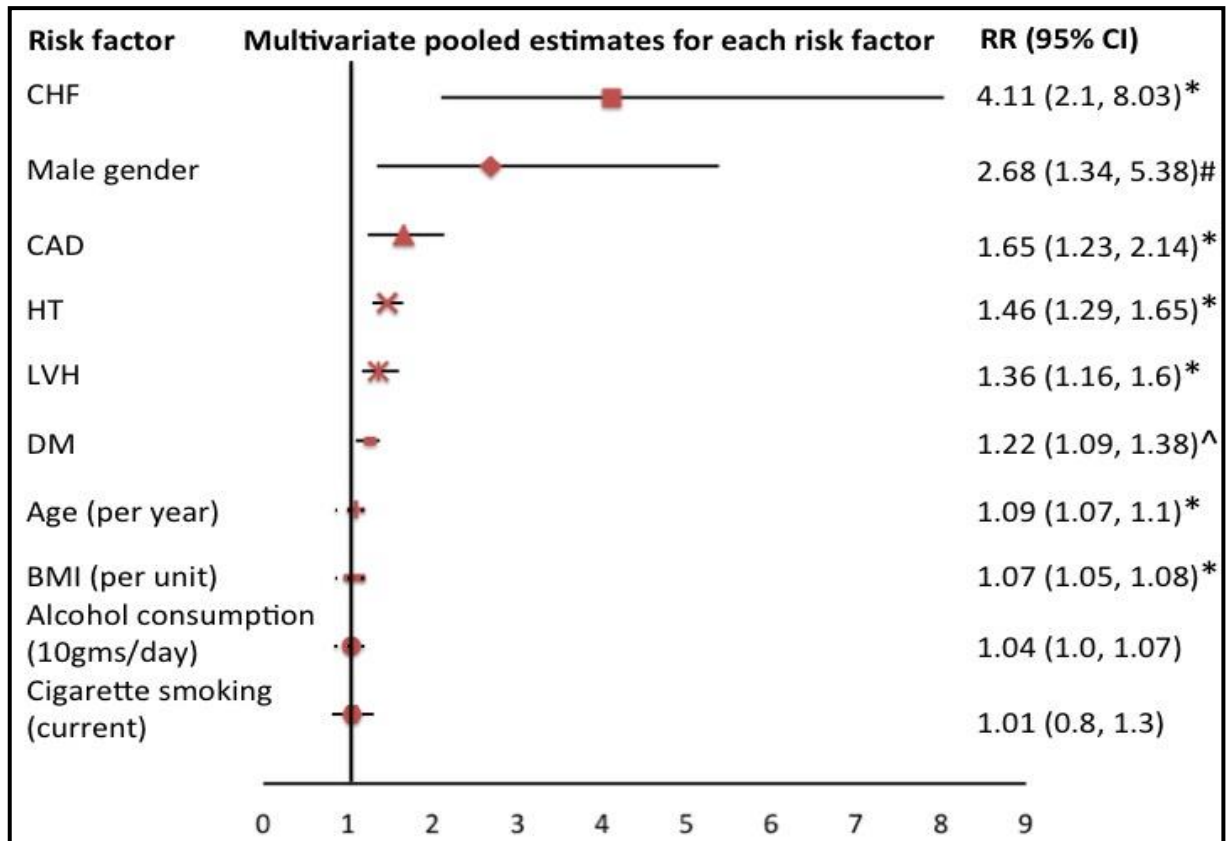
This flow-chart represents the total number of articles retrieved, number excluded at different levels of the review, specific exclusion criterion for these articles, and the number and type of articles included in the review.

Figure 2 Univariate analyses results for all risk factors.



*Indicates $P < 0.001$ and # indicates $P = 0.002$. The significant univariate predictors of AF development were (in decreasing order) CHF, male gender, LVH, CAD, HT, DM, increase in age and BMI. Alcohol consumptions and cigarette smoking were not significant predictors of developing AF.

Figure 3 Multivariate analyses results for all risk factors.



*Indicates $P < 0.001$ and # indicates $P = 0.002$. The significant multivariate predictors of AF development were CHF, male gender, LVH, CAD, HT, DM, increase in age and BMI. Alcohol consumptions and cigarette smoking were not significant predictors of developing AF.

2.10 Tables

Table 1 Study characteristics and baseline characteristics of the study participants

Author (ref. no.)	Year	Study type	Study quality ⁵³⁶	Total participants	Mean f/u (yrs)	Age (mean \pm SD)	Gender (Males, %)	Total No. of AF/flutter	Method of AF detection
Benjamin et al (5)	1994	PC	9	4731	38	72.7	44	562	12-lead ECG: routine exams/ hospital visits/ physician records.
Watanabe et al (15)	2006	PC	8	63,386	10	61.2	30	873	12-lead ECG: follow-up, (Minnesota code ⁵³⁷).
Frost et al (16)	2005	PC	9	47,589	5.7	67.1	47	553	Hospital discharge summaries coded by a physician according to Danish version of ICD 8 th & 10 th revisions.
Gami et al (498)	2007	RC	8	3542	4.7	49	66	133	Query of Mayo Clinic electronic medical index for modified hospital ICD code for AF.
Perez et al (24)	2009	RC	8	42,751	5.3	56.1	85	1050	Computerised ECG system via Palo Alto Veterans Affairs Health Care System.
Aviles et al (17)	2003	PC	8	5806	6.9	73	42	315	Annual 12-lead ECG & hosp. discharge summaries coded according to ICD 9 th revision.

Author (ref. no.)	Year	Study type	Study quality ⁵³⁶	Total participants	Mean f/u (yrs)	Age (mean \pm SD)	Gender (Males, %)	Total No. of AF/flutter	Method of AF detection
Van der Hooft et al (500)	2006	CC	6	6749	10	58.5	40	385	12-lead ECG; baseline & follow-up exams. From information sent by participating GPs. Via linkage to national registry of all hospital discharge Dx.
Karppi et al (499)	2013	PC	8	1847	1.7	74	66	105	12-lead ECG: hospitalisation/ED presentation/outpatient department.
Jensen et al (19)	2003	PC	8	5682	11.2	72.8	42	1585	12-lead ECG, hospital discharge summaries, coded according to ICD 9 th revision.
Mukamal et al (132)	2007	PC	8	5609	9.1	72.7	42	1232	Annual 12-lead ECG, hospital discharge summaries, coded according to ICD 9 th revision.
Nyrnes et al (29)	2012	PC	8	27,158	10.9	60	48	566	ECG records, ICD 9 & 10 codes on national & regional registries, manual search of hospital notes & records.
Schoen et al (91)	2012	PC	6	34,720	7	52.8	0	1079	Via a questionnaire at baseline, at 48 months & annually.

Author (ref. no.)	Year	Study type	Study quality ⁵³⁶	Total participants	Mean f/u (yrs)	Age (mean \pm SD)	Gender (Males, %)	Total No. of AF/flutter	Method of AF detection
Total	N/A	N/A	7.8	249570	10	64	46	8438	N/A

PC=prospective cohort, RC=retrospective cohort, CC= case-control, ICD=international code of disease, GP=general practioners.

Table 2 Congestive Heart Failure

Author	Defn. of RF	Unadj RR (95% CI)	Adj RR (95% CI)	Adj for Age	Adj for Gender	Adj for HT	Adj for CHF	Adj for CAD	Adj for DM	Other RFs
Benjamin et al	As per Framingham Study Dx criteria ⁵³⁸	Men 6.1 (4.5-8.4) Women 8.1 (6.1-10.7)	Men 5.0 (3.2-7.8) Women 4.3 (2.7-7.1)	Y	N	Y	N	Y	Y	CS, LVH
Gami, et al	Not provided	11.76 (7.6-18.2)	7.36 (4.32-13.66)	Y	Y	N	N	Y	N	BMI, decrease in nocturnal oxygen saturation (per 1%).

Author	Defn. of RF	Unadj RR (95% CI)	Adj RR (95% CI)	Adj for Age	Adj for Gender	Adj for HT	Adj for CHF	Adj for CAD	Adj for DM	Other RFs
Aviles et al	Cardiomegaly & pulmonary edema on CXR/ dilated ventricle & wall-motion abnormalities by echo or contrast ventriculography/ CHF Dx by physician, & receiving medical treatment.	Not provided	1.88 (1.45–2.45)	Y	Y	Y	Y	Y	Y	BMI,CRP ,cerebrovascular disease, LV dysfunction,SBP, DBP,race.
Karppi et al	Not provided	3.55 (2.39-5.27)	Not provided	N	N	N	N	N	N	None

Author	Defn. of RF	Unadj RR (95% CI)	Adj RR (95% CI)	Adj for Age	Adj for Gender	Adj for HT	Adj for CHF	Adj for CAD	Adj for DM	Other RFs
Van der Hooft et al	SOB (not attributed to COPD) at rest or exertion, ankle oedema & pulmonary crepitations; 2 of these plus Hx of MI, LVH via CG,CABG, angina/ documented PTA.	2.06 (1.34-3.17)	Not provided	Y	Y	N	N	N	N	None

Defn.=definition, RF=risk factor, Unadj=unadjusted, Adj= adjusted, RR=relative risk, HT=hypertension, CHF=congestive heart failure, CAD=coronary artery disease, MI=myocardial infarction, DM=diabetes mellitus, BMI=body mass index, LVH=left ventricular hypertrophy, CS=cigarette smoking, SBP= systolic blood pressure, DBP= diastolic blood pressure, PAC=premature atrial complexes, LEA=left atrial enlargement, CRP= C-reactive protein, SOB=shortness of breath, CABG=coronary artery bypass graft, PTA= percutaneous transluminal angioplasty.

Table 3 Male Gender

Author	Defn. of RF	Unadj RR (95% CI)	Adj RR (95% CI)	Adj for Age	Adj for Gender	Adj for HT	Adj for CHF	Adj for CAD	Adj for DM	Other RFs
Watanabe et al	Male gender	3.06 (2.67-3.5)	Not provided	Y	N	N	N	N	N	None
Gami et al	Male gender	1.86(1.02-2.85)	2.66(1.3-5.3)	Y	N	N	N	Y	N	BMI, decrease in nocturnal oxygen saturation (per 1%).
Perez et al	Male gender	4.1(3.0-5.7)	4.4(3.10-6.5)	Y	N	N	N	N	N	PR interval, PAC, Abnormal P axis, Pmax>120
Aviles et al	Male gender	Not provided	1.71(1.49-1.96)	Y	N	Y	Y	Y	Y	CRP, race, cerebrovascular disease, LV dysfunction, SBP, DBP

Author	Defn. of RF	Unadj RR (95% CI)	Adj RR (95% CI)	Adj for Age	Adj for Gender	Adj for HT	Adj for CHF	Adj for CAD	Adj for DM	Other RFs
Karppi, et al	Male gender	1.61(1.03-2.48)	Not provided	N	N	N	N	N	N	None
Van der Hooft et al	Male gender	1.23(1.0-1.51)	Not provided	Y	N	N	N	N	N	None

Defn.=definition, RF=risk factor, RR=relative risk, Unadj=unadjusted, Adj= adjusted, HT=hypertension, CHF=congestive heart failure, CAD=coronary artery disease, MI=myocardial infarction, DM=diabetes mellitus, BMI=body mass index, LVH=left ventricular hypertrophy, CS=cigarette smoking, SBP= systolic blood pressure, DBP= diastolic blood pressure, PAC=premature atrial complexes, LEA=left atrial enlargement, CRP= C-reactive protein.

Table 4 Coronary Artery Disease

Author	Defn. of RF	Unadjusted RR (95% CI)	Adjusted RR (95% CI)	Adjusted for Age	Adjusted for Gender	Adjusted for HT	Adjusted for CHF	Adjusted for CAD	Adjusted for DM	Other RFs
Benjamin et al	As per Framingham Study Dx criteria ⁵³⁸ .	Men 2.2(1.6-2.8) Women 2.4(1.7-3.4)	Men 1.4(1.00-2.1) Women 2.1(1.3-3.4)	Y	N	Y	Y	N	Y	CS, LVH
Gami et al	Not provided	5.15(3.56-7.44)	2.66(1.46-4.83)	Y	Y	N	N	N	N	BMI, decrease in nocturnal oxygen saturation per 1%

Author	Defn. of RF	Unadjusted RR (95% CI)	Adjusted RR (95% CI)	Adjusted for Age	Adjusted for Gender	Adjusted for HT	Adjusted for CHF	Adjusted for CAD	Adjusted for DM	Other RFs
Aviles et al	Ultrasonographically/angiographically demonstrated obstruction/ulcerated plaque/absence of doppler pulse major vessel/+ve EST for claudication/ CABG, angioplasty/thrombolysis for PAD/ exertional leg pain relieved by rest & claudication/Dx by physician/ankle-arm systolic ratio of ≤ 0.8 .	Not provided	1.40 (1.21–1.62)	Y	Y	Y	Y	N	Y	BMI, CRP, cerebrovascular disease, LV dysfunction, SBP,DBP, race
Karppi et al	Not provided	2.19(1.51-3.17)	Not provided	N	N	N	N	N	N	None

Author	Defn. of RF	Unadjusted RR (95% CI)	Adjusted RR (95% CI)	Adjusted for Age	Adjusted for Gender	Adjusted for HT	Adjusted for CHF	Adjusted for CAD	Adjusted for DM	Other RFs
Mukama I et al	Ultrasonographically/angiographically demonstrated obstruction/ulcerated plaque/absence of doppler pulse major vessel/+ve EST for claudication/ CABG, angioplasty/thrombolysis for PAD/ exertional leg pain relieved by rest & claudication/Dx by physician/ankle-arm systolic ratio of ≤ 0.8 .	1.55(1.38-1.72)	Not provided	N	N	N	N	N	N	None
Van der Hoof et al	MI on ECG/ Hx of MI in exam or via questionnaire/ Dx in specialists' records.	2.14(1.68-2.72)	Not provided	Y	Y	N	N	N	N	None

Author	Defn. of RF	Unadjusted RR (95% CI)	Adjusted RR (95% CI)	Adjusted for Age	Adjusted for Gender	Adjusted for HT	Adjusted for CHF	Adjusted for CAD	Adjusted for DM	Other RFs
Nyrnes et al	Hx of MI &/or prevalent angina.	Men 1.56(1.23-2.14) Women 1.25(0.77-2.02)	Not provided	N	N	N	N	N	N	None

Defn.=definition, RF=risk factor, RR=relative risk, Unadj=unadjusted, Adj= adjusted, HT=hypertension, CHF=congestive heart failure, CAD=coronary artery disease, MI=myocardial infarction, DM=diabetes mellitus, BMI=body mass index, LVH=left ventricular hypertrophy, CS=cigarette smoking, SBP= systolic blood pressure, DBP= diastolic blood pressure, PAC=premature atrial complexes, LEA=left atrial enlargement, CRP= C-reactive protein, CABG=coronary artery bypass graft, EST=exercise stress test, PAD=peripheral artery disease.

Table 5 Hypertension

Author	Defn. of RF	Unadj RR (95% CI)	Adj RR (95% CI)	Adj for Age	Adj for Gender	Adj for HT	Adj for CHF	Adj for CAD	Adj for DM	Other RFs
Benjamin et al	SBP \geq 160 mmHg &/DBP \geq 95 mmHg on 2 seated measurements/ on anti-hypertensives.	Men 1.8(1.4-2.3) Women 1.7(1.3-2.2)	Men 1.6(1.2-2.2) Women 1.7(1.2-2.4)	Y	N	N	Y	Y	Y	CS, LVH
Watanabe et al	SBP \geq 140 mm Hg &/DBP \geq 90 mm Hg.	1.73 (1.48-2.01)	Not provided	Y	N	N	N	N	N	None

Author	Defn. of RF	Unadj RR (95% CI)	Adj RR (95% CI)	Adj for Age	Adj for Gender	Adj for HT	Adj for CHF	Adj for CAD	Adj for DM	Other RFs
Frost et al	Self-reported HT on questionnaire &/on anti-hypertensives	Men 2.09 (1.59–2.74) Women 1.95 (1.35–2.81)	Men 1.68 (1.26–2.24) Women 1.47 (0.99–2.18)	Y	N	N	N	N	N	BMI, ht, length of education, CS, alcohol consumption, total cholesterol.
Jensen et al	SBP ≥ 140mm Hg &/DBP ≥90 mm Hg/ use of antihypertensives/Dx of HT by a physician.	Blacks 1.55 (1.07–2.23) Whites 1.40 (1.26–1.56)	Not provided	Y	Y	N	N	N	N	None

Author	Defn. of RF	Unadj RR (95% CI)	Adj RR (95% CI)	Adj for Age	Adj for Gender	Adj for HT	Adj for CHF	Adj for CAD	Adj for DM	Other RFs
Gami et al	Not provided.	2.85 (2.02–4.02)	Not provided	Y	Y	N	N	N	N	None
Aviles et al	SBP ≥ 140mm Hg &/DBP ≥90 mm Hg/ use of antihypertensives/Dx of HT by a physician.	Not provided	1.28 (1.08–1.51)	Y	Y	N	Y	Y	Y	BMI, CRP, cerebrovascular disease, LV dysfunction, SBP, DBP, race.

Author	Defn. of RF	Unadj RR (95% CI)	Adj RR (95% CI)	Adj for Age	Adj for Gender	Adj for HT	Adj for CHF	Adj for CAD	Adj for DM	Other RFs
Karppi et al	Avg. of 6 measures of SBP \geq 140mm Hg & DBP \geq 90 mm Hg.	1.63(1.07-2.47)	Not provided	N	N	N	N	N	N	None
Mukamal, et al	SBP \geq 140mm Hg &/DBP \geq 90 mm Hg/ use of antihypertensives/Dx of HT by a physician.	1.35(1.21-1.49)	Not provided	N	N	N	N	N	N	None

Author	Defn. of RF	Unadj RR (95% CI)	Adj RR (95% CI)	Adj for Age	Adj for Gender	Adj for HT	Adj for CHF	Adj for CAD	Adj for DM	Other RFs
Van der Hooft et al	SBP >160mmHg & DBP >100mm Hg/use of anti-hypertensives.	1.55(1.27-1.91)	Not provided	Y	Y	N	N	N	N	None
Nyrnes, et al	SBP ≥ 140mm Hg & DBP ≥90 mm Hg/use of anti-hypertensive medications.	Men 1.17(0.82-1.65) Women 1.65(1.17-2.3)	Not provided	N	N	N	N	N	N	None

Defn.=definition, RF=risk factor, RR=relative risk, Unadj=unadjusted, Adj= adjusted, HT=hypertension, CHF=congestive heart failure, CAD=coronary artery disease, MI=myocardial infarction, DM=diabetes mellitus, BMI=body mass index, LVH=left ventricular hypertrophy, CS=cigarette smoking, SBP= systolic blood pressure, DBP= diastolic blood pressure, PAC=premature atrial complexes, LEA=left atrial enlargement, CRP= C-reactive protein.

Table 6 Left Ventricular Hypertrophy

Author	Defn. of RF	Unadjusted RR (95% CI)	Adjusted RR (95% CI)	Adjusted for Age	Adjusted for Gender	Adjusted for HT	Adjusted for CHF	Adjusted for CAD	Adjusted for DM	Other RFs
Benjamin et al	Voltage criteria for LVH & had lateral polarization changes on 12-lead ECG.	Men 3.01 (1.9-4.8) Women 3.8 (2.6-5.6)	Men 1.6 (0.9-3.0) Women 1.2 (0.6-2.4)	Y	N	Y	Y	Y	Y	CS

Author	Defn. of RF	Unadjusted RR (95% CI)	Adjusted RR (95% CI)	Adjusted for Age	Adjusted for Gender	Adjusted for HT	Adjusted for CHF	Adjusted for CAD	Adjusted for DM	Other RFs
Watanabe et al	High amplitude R-wave criteria (code 3-1 or 3-3) on 12-lead ECG.	1.43(1.13-1.8)	1.39(1.11-1.75)	Y	Y	N	N	Y	Y	BMI,SBP, DBP,high & low frequency.APCs/VPCs, mild & severe ST-segment abnormalities, RBBB, LBBB

Author	Defn. of RF	Unadjusted RR (95% CI)	Adjusted RR (95% CI)	Adjusted for Age	Adjusted for Gender	Adjusted for HT	Adjusted for CHF	Adjusted for CAD	Adjusted for DM	Other RFs
Perez et al	12-lead ECG using Romhilt-Estes criteria >3 ⁵³⁹ .	1.8(1.5-2.2)	1.3(1.0-1.7)	Y	Y	N	N	N	N	PR interval, APC, Abnormal P axis, Pmax >120ms, P index >35ms, LEA, VPC,LBBB

Author	Defn. of RF	Unadjusted RR (95% CI)	Adjusted RR (95% CI)	Adjusted for Age	Adjusted for Gender	Adjusted for HT	Adjusted for CHF	Adjusted for CAD	Adjusted for DM	Other RFs
Van der Hoof et al	Detected via 12-lead ECG.	1.88(1.28-2.76)	Not provided	Y	Y	N	N	N	N	None

Defn.=definition, RF=risk factor, RR=relative risk, Unadj=unadjusted, Adj= adjusted, HT=hypertension, CHF=congestive heart failure, CAD=coronary artery disease, MI=myocardial infarction, DM=diabetes mellitus, BMI=body mass index, LVH=left ventricular hypertrophy, CS=cigarette smoking, SBP= systolic blood pressure, DBP= diastolic blood pressure, CRP= C-reactive protein, wt=weight, ht=height, RBBB=right bundle branch block, LBBB=left bundle branch block, APC= atrial premature beat, VPC=ventricular premature beat, LEA=left atrial enlargement.

Table 7 Diabetes Mellitus

Author	Defn. of RF	Unadj RR (95% CI)	Adj RR (95% CI)	Adj for Age	Adj for Gender	Adj for HT	Adj for CHF	Adj for CAD	Adj for DM	Other RFs
Benjamin et al	Fasting BG ≥ 7.77 mmol/L (≥ 140 mg/dL)/ non-fasting BG ≥ 11.11 mmol/L (≥ 200 mg/dL) /using insulin/oral hypoglycaemic.	Men 1.7(1.2-2.3) Women 2.1 (1.5-2.8)	Men 1.1(0.8-1.7) Women 1.5(1.0-2.3)	Y	N	N	Y	Y	N	CS, LVH
Watanabe et al	Fasting BG ≥ 110 mg/dL and/or HbA1c ≥ 6.0 g/dL.	1.37 (1.02-1.84)	Not provided	Y	N	N	N	N	N	None

Author	Defn. of RF	Unadj RR (95% CI)	Adj RR (95% CI)	Adj for Age	Adj for Gender	Adj for HT	Adj for CHF	Adj for CAD	Adj for DM	Other RFs
Jensen et al	Fasting BG \geq 126 mg/dL/ using oral Hypoglycemic/insulin.	Blacks 1.56 (1.35–1.8) Whites 1.26(0.9–1.77)	Not provided	Y	Y	N	N	N	N	None
Gami et al	Not provided	2.5 (1.66–3.78)	Not provided	Y	Y	N	N	N	N	None

Author	Defn. of RF	Unadj RR (95% CI)	Adj RR (95% CI)	Adj for Age	Adj for Gender	Adj for HT	Adj for CHF	Adj for CAD	Adj for DM	Other RFs
Aviles et al	Fasting BG \geq 126 mg/dL/ using oral hypoglycemic agent/ insulin.	Not provided	1.18 (1.02–1.36)	Y	Y	Y	Y	Y	Y	BMI,CRP ,cerebrovascular disease, LV dysfunction,SBP, DBP, race.
Karppi et al	Fasting BG \geq 6.7mmol/L/ using insulin/diet controlled.	1.02(0.6-1.73)	Not provided	N	N	N	N	N	N	None

Author	Defn. of RF	Unadj RR (95% CI)	Adj RR (95% CI)	Adj for Age	Adj for Gender	Adj for HT	Adj for CHF	Adj for CAD	Adj for DM	Other RFs
Mukama I, et al	Fasting BG of ≥ 126 mg/dL/ using oral hypoglycemic agent/ insulin.	1.23 (1.08-1.39)	Not provided	N	N	N	N	N	N	None
Van der Hoof et al	Random or post-load BG ≥ 200 mg/dL (≥ 11.1 mmol/L)/using hypoglycemics.	1.76(1.35-2.3)	Not provided	Y	Y	N	N	N	N	None

Author	Defn. of RF	Unadj RR (95% CI)	Adj RR (95% CI)	Adj for Age	Adj for Gender	Adj for HT	Adj for CHF	Adj for CAD	Adj for DM	Other RFs
Schoen et al	Via annual questionnaires: Re symptoms, medications, diagnostic testing since baseline. Self reported cases confirmed via telephone interview & validation cohort.	1.95 (1.49-2.56)	1.87 (1.415-2.47)	Y	N	N	N	N	N	CS, alcohol consumption, race, education, hypercholesterolemia, ht, exercise.
Nyrnes et al	Self-reported via questionnaires.	Men 1.3(0.74-2.28) Women 1.27(0.62-2.58)	Not provided	N	N	N	N	N	N	None

Defn.=definition, RF=risk factor, RR=relative risk, Unadj=unadjusted, Adj= adjusted, HT=hypertension, CHF=congestive heart failure, CAD=coronary artery disease, MI=myocardial infarction, DM=diabetes mellitus, BMI=body mass index, LVH=left ventricular hypertrophy, CS=cigarette smoking, SBP= systolic blood pressure, DBP= diastolic blood pressure, BG= blood glucose, CRP= C-reactive protein.

Table 8 Age

Author	Defn. of RF	Unadj RR (95% CI)	Adj RR (95% CI)	Adj for Age	Adj for Gender	Adj for HT	Adj for CHF	Adj for CAD	Adj for DM	Other RFs
Benjamin et al	Per 10 year increase in age, converted to per one year increase.	Not provided	Men 1.08(1.06-1.1) Women 1.1(1.08-1.12)	N	N	Y	Y	Y	Y	CS, LVH
Watanabe et al	Per year increase in age.	1.08 (1.07-1.09)	Not provided	N	N	N	N	N	N	None

Author	Defn. of RF	Unadj RR (95% CI)	Adj RR (95% CI)	Adj for Age	Adj for Gender	Adj for HT	Adj for CHF	Adj for CAD	Adj for DM	Other RFs
Frost et al	Per year increase in age.	Men 1.08(1.06-1.11) Women 1.14(1.1-1.18)	Men 1.09 (1.06-1.12) Women 1.16 (1.12-1.20)	N	N	Y	N	N	N	BMI,SBP, DBP,ht, levelof education,CS,alcohol – consumption, total cholesterol.
Gami et al	Per 10 year increase in age, converted to per one year.	1.08 (1.06-1.09)	1.07 (1.04-1.11)	N	Y	N	N	Y	N	BMI, decrease in nocturnal oxygen saturation (per 1%).

Author	Defn. of RF	Unadj RR (95% CI)	Adj RR (95% CI)	Adj for Age	Adj for Gender	Adj for HT	Adj for CHF	Adj for CAD	Adj for DM	Other RFs
Perez et al	Per year increase in age.	Not provided	1.07(1.06-1.08)	N	Y	N	N	N	N	PR interval, PAC, Abnormal P axis, Pmax>120ms, P index >35ms, LEA, LVH.
Aviles et al	One standard deviation increase in age, converted to per per one year increase in age.	Not provided	1.06(1.05-1.08)	N	Y	Y	Y	Y	Y	CRP, cerebrovascular disease, LV dysfunction, SBP, DBP, race.

Author	Defn. of RF	Unadj RR (95% CI)	Adj RR (95% CI)	Adj for Age	Adj for Gender	Adj for HT	Adj for CHF	Adj for CAD	Adj for DM	Other RFs
Van der Hooft et al	Per year increase in age.	1.08(1.06-1.09)	Not provided	N	Y	N	N	N	N	None

Defn.=definition, RF= risk factor, RR= relative risk, Unadj=unadjusted, Adj= adjusted, HT=hypertension, CHF=congestive heart failure, CAD=coronary artery disease, MI=myocardial infarction, DM=diabetes mellitus, BMI=body mass index, LVH=left ventricular hypertrophy, CS=cigarette smoking, ht=height, SBP= systolic blood pressure, DBP= diastolic blood pressure, PAC=premature atrial complexes, LEA=left atrial enlargement, CRP= C-reactive protein.

Table 9 Body Mass Index

Author	Defn. of RF	Unadj RR (95% CI)	Adj RR (95% CI)	Adj for Age	Adj for Gender	Adj for HT	Adj for CHF	Adj for CAD	Adj for DM	Other RFs
Benjamin, et al	BMI calculated wt(kgs)/ht(mts) ² Per unit increase in BMI.	Men 1.03(0.99-1.06) Women 1.02(1.0-1.05)	Not significant	Y	N	N	N	N	N	None
Watanabe, et al	BMI calculated wt(kgs)/ht(mts) ² Per unit increase in BMI.	1.04(1.01-1.06)	Not significant	Y	N	N	N	N	N	None

Author	Defn. of RF	Unadj RR (95% CI)	Adj RR (95% CI)	Adj for Age	Adj for Gender	Adj for HT	Adj for CHF	Adj for CAD	Adj for DM	Other RFs
Frost et al	BMI normal if 18.5-25 kg/m ² , Overwt if 25-30 kg/m ² , & obese ≥30 kg/m ² . Per unit increase in BMI.	Men 1.09 (1.06–1.12) Women 1.06 (1.03–1.09)	Men 1.08(1.05–1.11) Women 1.06 (1.03–1.09)	Y	N	Y	N	N	N	SBP,DBP length of education, CS, alcohol consumption, total cholesterol.
Jensen et al	BMI calculated wt(kgs)/ht(mts) ² Per 5 units increase in BMI, converted to per unit increase.	Blacks 1.06 (1.03–1.08) Whites 1.02(1.01-1.03)	Not provided	Y	Y	N	N	N	N	None

Author	Defn. of RF	Unadj RR (95% CI)	Adj RR (95% CI)	Adj for Age	Adj for Gender	Adj for HT	Adj for CHF	Adj for CAD	Adj for DM	Other RFs
Gami et al	BMI calculated wt(kgs)/ht(mts) ² Per unit increase in BMI.	1.03(1.02-1.05)	1.07(1.05-1.10)	Y	Y	N	N	Y	N	Decrease in nocturnal oxygen saturation (per 1%).
Perez et al	BMI calculated wt(kgs)/ht(mts) ² Per unit increase in BMI.	1.03(1.01-1.04)	Not significant	N	N	N	N	N	N	None

Author	Defn. of RF	Unadj RR (95% CI)	Adj RR (95% CI)	Adj for Age	Adj for Gender	Adj for HT	Adj for CHF	Adj for CAD	Adj for DM	Other RFs
Van der Hooft et al	BMI calculated wt(kgs)/ht(mts) ² Per unit increase in BMI.	1.05(1.03-1.08)	Not provided	Y	Y	N	N	N	N	None

Defn.=definition, RF=risk factor, RR=relative risk, Unadj=unadjusted, Adj= adjusted, HT=hypertension, CHF=congestive heart failure, CAD=coronary artery disease, MI=myocardial infarction, DM=diabetes mellitus, BMI=body mass index, LVH=left ventricular hypertrophy, CS=cigarette smoking, SBP= systolic blood pressure, DBP= diastolic blood pressure, BG= blood glucose, CRP= C-reactive protein, wt=weight, ht=height.

Table 10 Alcohol Consumption

Author	Defn. of RF	Unadj RR (95% CI)	Adj RR (95% CI)	Adj for Age	Adj for Gender	Adj for HT	Adj for CHF	Adj for CAD	Adj for DM	Other RFs
Benjamin et al	Self-reported consumption of alcohol. Reported in increments of ounces of alcohol per week. Converted to alcohol consumption per 10 grams per day.	Men 1.02(0.98-1.08) Women 0.88(0.75-1.05)	Not significant	Y	N	Y	N	Y	Y	None
Frost et al	Self-reported consumption of alcohol. Reported in increments of per 10grams of alcohol per day.	Men 1.04 (1.01-1.08) Women 1.03 1.01 (0.92-1.12)	Men 1.04(1.01-1.08) Women 1.03 (0.94-1.14)	Y	N	Y	N	N	N	BMI, SBP, DBP length of education, CS, total cholesterol.
Jensen et al	Self-reported consumption of alcohol. Reported in increments of per drink per day. Converted to per 10grams of alcohol per day.	Blacks 0.84 (0.67-1.05) Whites 1.01(0.96-1.04).	Not provided	N	N	N	N	N	N	None

Defn.=definition, RF=risk factor, RR=relative risk, Unadj=unadjusted, Adj= adjusted, HT=hypertension, CHF=congestive heart failure, CAD=coronary artery disease, MI=myocardial infarction, DM=diabetes mellitus, BMI=body mass index, LVH=left ventricular hypertrophy, CS=cigarette smoking, SBP= systolic blood pressure, DBP= diastolic blood pressure.

Table 11 Cigarette Smoking

Author	Defn. of RF	Unadj RR (95% CI)	Adj RR (95% CI)	Adj for Age	Adj for Gender	Adj for HT	Adj for CHF	Adj for CAD	Adj for DM	Other RFs
Benjamin, et al	Self-reported current smoking.	Men 1.0(0.8-1.4) Women 1.4(1.0-2.0)	Men 1.0(0.7-1.4) Women 1.5(1.0-2.2)	Y	N	Y	Y	Y	Y	LVH
Frost, et al	Self-reported current smoking.	Men 0.83 (0.65–1.07) Women 0.83(0.59-1.18)	Men 0.83(0.64-1.07) Women 0.95(0.66-1.35)	Y	N	Y	N	N	N	BMI, SBP, DBP, length of education total cholesterol
Mukamal, et al	Self-reported current smoking.	0.94(0.8-1.1)	Not provided	N	N	N	N	N	N	None

Author	Defn. of RF	Unadj RR (95% CI)	Adj RR (95% CI)	Adj for Age	Adj for Gender	Adj for HT	Adj for CHF	Adj for CAD	Adj for DM	Other RFs
Van der Hooft, et al	Self-reported current smoking.	1.43(1.05-1.96)	Not provided	Y	Y	N	N	N	N	None
Nyrnes, et al	Self-reported current smoking.	Men 0.78(0.61-0.99) Women 0.98(0.75-1.27)	Not provided	N	N	N	N	N	N	None

Defn.=definition, RF=risk factor, RR=relative risk, Unadj=unadjusted, Adj= adjusted, HT=hypertension, CHF=congestive heart failure, CAD=coronary artery disease, MI=myocardial infarction, DM=diabetes mellitus, BMI=body mass index, LVH=left ventricular hypertrophy, CS=cigarette smoking, SBP= systolic blood pressure, DBP= diastolic blood pressure. Table 12 Weights of each study in each unadjusted and adjusted analysis

Table 12 Weights of each study in each unadjusted and adjusted analysis

Author	CHF Una -dj	CHF Adj	Gen der Una -dj	Gen -der Adj	CAD Una -dj	CAD Adj	HT Una dj	HT Adj	LVH Una dj	LVH Adj	DM Una dj	DM Adj	Age Una dj	Age Adj	BMI Una -dj	BMI Adj	AC Una -dj	AC Adj	CS Una -dj	CS Adj
Benjami n et al (5)	33.8	49.6	-	-	25	43.4	15.6	28.2	35.4	12.6	17.1	17.5	-	30	16.2	-	26.6	-	21.7	45.2
Watana be et al (15)	-		21.6	-	-	-	10.9	-	22.5	50.3	9.1	-	30.3	-	9.5	-	-	-	-	-
Frost et al (16)	-		-	-	-	-	12.6	27.1	-	-	-	-	21.5	22.7	16.7	58	42.2	100	23.1	54.8
Gami et al (498)	16.3	23.3	18.8	27.8	11.7	13.7	5.7	-	-	-	6.5	-	24.6	11.0	12.8	42	-	-	-	-
Perez et al (24)	-		20	34.5	-	-	-		23.4	37.1	-	-	-	18.7	12.8	-	-	-	-	-
Aviles et al (17)	-	27	-	37.7	-	43	-	44.8	-	-	-	66	-	17.6	-	-	-	-	-	-
Van der Hooft et al (500)	16.3	-	21	-	13.6	-	9.3	-	18.7	-	10	-	23.6	-	9.7	-	-	-	10.8	-

Author	CHF Una -dj	CHF Adj	Gen der Una -dj	Gen -der Adj	CAD Una -dj	CAD Adj	HT Una dj	HT Adj	LVH Una dj	LVH Adj	DM Una dj	DM Adj	Age Una dj	Age Adj	BMI Una -dj	BMI Adj	AC Una -dj	AC Adj	CS Una -dj	CS Adj
Karppi et al (499)	16.5	-	18.6	-	11.6	-	4.5	-	-	-	4.7	-	-	-	-	-	-	-	-	-
Jensen et al (19)	-	-	-	-	-	-	17.6	-	-	-	21.4	-	-	-	22.3	-	31.2	-	-	-
Mukam al et al (132)	17.2	-	-	-	15.1	-	12.4	-	-	-	13.8	-	-	-	-	-	-	-	17.9	-
Nyrnes et al (29)	-	-	-	-	23	-	11.5	-	-	-	7.4	-	-	-	-	-	-	-	26.5	-
Schoen et al (91)	-	-	-	-	-	-	-	-	-	-	10	16.5	-	-	-	-	-	-	-	-
Total	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100

Adj=adjusted, Unadj=unadjusted, HT=hypertension, CHF=congestive heart failure, CAD=coronary artery disease, DM=diabetes mellitus, BMI=body mass index, LVH=left ventricular hypertrophy, AC=alcohol consumption, CS=cigarette smoking

Table 13 Population attributable risk for modifiable risk factors

Risk factor	% Prevalence in the Australian population	RR as determined by meta-analysis	% Population attributable risk
Hypertension	30 ⁵⁴⁰	1.46	16
Congestive heart failure	1.31 ⁵⁴⁰	4.11	9
Coronary artery disease	3 ⁵⁴⁰	1.65	3
Diabetes mellitus	7.2 ⁵⁴¹	1.22	2
Body mass index (≥30-obese)	25 ⁵⁴²	1.07	0.8
Alcohol consumption (daily drinkers)	10 ⁵⁴²	1.04	1
Cigarette smoking (daily smokers)	19 ⁵⁴²	1.01	0.1

Chapter Three

Characterisation of the Structural and Electrical Remodelling Associated with New Onset Atrial Fibrillation

3.1 Introduction

Worldwide epidemiological data shows that the global burden of atrial fibrillation (AF) is on the rise ². This is highlighted by the fact that over 5 million new cases of AF are added to the existing pool of sufferers every year ². This is indeed alarming, given that the current number of AF sufferers is in excess of 36 million ². This makes it important to understand what occurs at the onset of atrial fibrillation in order to better manage this growing public health problem.

There is substantial evidence that abnormal underlying substrate plays a role in the initiation and maintenance of AF. For instance, structural remodelling in the form of left atrial (LA) dilation has been demonstrated by a number of studies in long-term paroxysmal AF patients and to an even greater degree in persistent AF patients ^{219, 220, 543}. Additionally, a high ectopic trigger burden has been found to exist in paroxysmal AF patients and to a lesser extent in persistent AF ²⁰⁹⁻²¹¹.

Interestingly, recent studies have even shown the existence of substrate in the case of 'lone AF'; which was previously thought to be free of abnormal atrial substrate; but is now deemed a 'non-existent' entity ¹⁴⁰. Studies have observed the existence of underlying structural abnormalities and electrical anomalies ^{30, 141-143, 544} in lone AF patients, the kind that have been known to exist in patients with established arrhythmias ^{211, 545, 546}.

While the role of subclinical substrate in the initiation and maintenance of established and lone AF has been extensively researched, little is known about the extent of substrate present in patients with newly diagnosed AF. Certainly, the reasons behind why some patients present with more persistent forms of AF at the time of diagnosis is also unknown. Hence, we sought to assess the degree of structural and electrical changes in newly diagnosed patients, compared to those seen in arrhythmia free controls.

3.2 Methods

3.2.1 Recruitment of Newly Diagnosed Atrial Fibrillation Patients

The recruitment strategy and exclusion criteria are outlined and detailed in Figure 1 and Table 1. The newly diagnosed AF patients were recruited from among patients presenting to the emergency department (ED) of the Royal Adelaide Hospital with a primary diagnosis of AF (ICD code I48). The recruitment occurred over a 1-year period, from August 2010-August 2011. A total of 858 patients presented with a primary diagnosis of AF during this period. The first level of screening removed 254 representations, leaving 604 unique patient presentations. The second level of screening was performed using unique patient reference numbers and digital discharge summaries from the OACIS system (Open Architecture Clinical Information System, Version 102, DINMAR 2003, US Inc.). We excluded 489 patients at this level of screening for the following reasons: previous history of arrhythmia (including AF), age (<40, >70 years); primary diagnosis of atrial flutter; reversible causes of AF (infection, cardiac surgery); patients deceased during the admission; regionally located patients (>100 km); recent diagnosis of malignancy; renal failure; valvular heart disease

(moderate to severe in intensity or requiring intervention); stroke on AF diagnosis; and misdiagnosis of AF (Appendix 3). The remaining 115 patients were approached via telephone to participate in the study. Of these 31 could not be contacted and 31 did not consent to participate in this study. Fifty-three consecutive new AF patients consented to be part of the study. These were patients who had presented with their first known episode of AF. All patients provided written informed consent to participate. The study protocol was reviewed and approved by the Human Research Ethics Committee of the Royal Adelaide Hospital and University of Adelaide.

3.2.2 Recruitment of Age-matched Controls

The arrhythmia free community controls were volunteers recruited through an advertisement in local newspapers. Volunteers who expressed interest in the study were approached via an initial telephone interview to determine eligibility. Those individuals who had a previous history of any type of arrhythmia or conduction abnormality including AF, atrial flutter, supraventricular tachycardia (SVT), any heart block; and symptomatic palpitations thought to be due to atrial premature beats (APBs) or ventricular premature beats (VPBs) were excluded. In addition, the following individuals were excluded: those aged <40 and >70 years; those with congestive heart failure; coronary artery disease; diabetes mellitus; stroke/TIA (transient ischemic attack); valvular heart disease (as defined above); history of rheumatic fever; and obstructive sleep apnoea (OSA). Forty-two arrhythmia free age and gender-matched controls were recruited.

3.2.3 Structured Clinical Interview

A structured interview was conducted to ascertain baseline information for all participants (detailed in Appendix 1). Demographic characteristics, medical history (cardiac and non-cardiac co-morbidities) and medication use was interrogated. The details are presented in Table 1 for all groups.

The individual's arrhythmia history was determined. The length of the longest sustained episode of symptomatic AF was also determined from clinical history to facilitate AF classification in keeping with current AF consensus classification. The new AF patients were classified in accordance with the Heart Rhythm Society Consensus Statement¹. In brief, Paroxysmal AF (PAF) was defined as self-terminating and lasting less than a week and persistent (perAF) as AF episodes lasting more than a week and/or requiring cardioversion¹. These were treated as separate groups for the purposes of the investigations.

3.2.4 Structural Substrate Assessment

All tests were performed within three months of initial AF diagnosis. All participants underwent transthoracic echocardiography performed by an independent, blinded echocardiographer in accordance with the American Society of Echocardiography guidelines^{226, 547}. The following parameters were determined:

- Left atrial dilation: LA longitudinal (major) axis, LA transverse (minor) axis, LA area, LA volume.
- Left ventricular (LV) hypertrophy: Inter-ventricular septal diameter (IVSd).

- LV systolic function: Ejection fraction (EF) %.
- LV diastolic function: Mitral E velocity, mitral A velocity, E/A ratio, pulmonary S/D ratio, and septal E'.

LA dimensions were measured in 2D mode according to conventional echocardiographic methods⁵⁴⁸. Maximum and minimum LA volumes were assessed using the biplane summation of discs method⁵⁴⁷. LA volume was taken as an average of the LA end systolic (LAESV) in 4-chamber and 2-chamber mode.

Left ventricular EF was assessed using Simpson's biplane method. The parameters of LV diastolic function were measured using trans-mitral Doppler flow profile and septal annular tissue Doppler imaging^{229 549}. Patients in AF at the time of the study (those in perAF) did not have atrial contractions, making the measurement of A velocity and hence E/A ratio, and pulmonary vein S/D ratio impossible in some perAF patients. The two patients who were not in AF did not constitute a large enough sample to warrant comparison between all three groups. However, E velocity and septal E could be obtained as these represent passive LV filling⁵⁴⁷. All normal values were determined using those recommended by the American Society of Echocardiography^{226, 547}.

3.2.5 Electrical Substrate Assessment

All groups of patients underwent 3-lead (leads I, II and III; sample rate 256 Hz) ambulatory Holter monitoring using Medilog AR12 monitors (Schiller AG; Altgasse, Baar, Switzerland) to assess the number of atrial premature beats (APBs) per hour of the holter recording, which served as an indicator for the atrial ectopy burden⁵⁵⁰. The 7-day Holter recordings were imported into Medilog Darwin analysis software (Schiller

AG) and automatically analysed using R-wave detection. The resulting templates and ECG strips were then manually analysed by one experienced blinded technician to remove those with significant artefact. A single blinded investigator ascertained that appropriate beat annotations and post ectopic compensatory pauses were present for all APBs.

Further, the relative earliness of the APBs was also determined for all groups. The atrial premature beats were detected automatically as a minimum 25% reduction in the R-R interval in relation to the previous R-R coupling interval. This was in accordance with previous studies, which have used R-R intervals as a surrogate for atrial coupling intervals during ectopy^{211, 551}. The relative reduction in the coupling interval of the APBs compared to the previous coupling interval index and the clock time of the occurrence of the actual APB were recorded for each premature beat. A greater coupling interval reflected a more closely coupled APB²¹¹.

3.2.6 Statistics

Normally distributed data were expressed as mean \pm standard deviation. Significantly skewed data ($P < 0.05$; Kolmogorov-Smirnov test) were summarised as median and inter-quartile range. Categorical data were expressed as count and percentage. Differences between groups were analysed with a one-way paired analysis of variance (ANOVA) with Sidak-adjusted pairwise post hoc comparisons for continuous data or chi-squared comparisons for count data. Significantly skewed data was analysed using the Kruskal-Wallis non-parametric test. All analyses were carried out using SPSS PASW (Version 21, IBM, Armonk, NY); statistical significance was set at $P < 0.05$.

3.3 Results

3.3.1 Baseline Characteristics of Controls vs AF Patients

The baseline characteristics of the controls and AF groups are presented in Table 1. The controls were matched for age, gender and body mass index with both the AF patient groups ($P>0.05$). With regard to the cardiac co-morbidities; hypertension was present in a significantly smaller proportion of controls compared to the PAF and perAF patients ($P=0.001$, $P=0.003$ respectively). A small number of controls had hyperthyroidism, however not significantly different in number from the PAF or perAF patients ($P=0.5$, $P=0.6$ respectively). With regard to the pharmaceutical profile, a significantly smaller number of controls were on anti-hypertensives compared to PAF and perAF patients ($P<0.001$, $P=0.003$ respectively). None of the controls were on anti-angina medications, anti-coagulants, anti-arrhythmics and diuretics.

3.3.2 Baseline Characteristics of PAF vs PerAF Patients

There was no significant difference in the age distribution of the two AF sub-groups, (59 ± 13 vs 66 ± 10 years, $P=0.1$); the groups were also similar in their gender distribution ($P=0.4$) and BMI ($P=0.9$). Hypertension was the most common co-morbidity in the AF patient groups; there was no significant difference in the proportions of PAF and perAF patients presenting with this co-morbidity ($P=0.5$). The proportions of patients presenting with CHF ($P<0.001$) and DM ($P=0.01$) were significantly higher in the perAF compared to the PAF group. However, these two groups had a similar number of patients with CAD ($P=0.9$), stroke/TIA ($P=0.3$) and OSA

(P=0.8). Lastly, hyperthyroidism was present in similar proportions (P=0.4) in the two AF groups.

Anti-hypertensives were the most common medication among the AF patients; there was no difference in this treatment between the two AF subgroups (P=0.5). The proportions of patients on anti-angina medications (P=0.4) and anti-arrhythmics (P=0.8) were similar in the two AF groups. However, the number of patients on anti-coagulants (P=0.005) and diuretics (P<0.001) were greater in the perAF group compared to the PAF group. Lastly, anti-platelet (P=0.04) medication was more common in the PAF group.

3.3.3 Structural Substrate Assessment

3.3.3.1 Left Atrial Longitudinal Axis

The mean LA longitudinal (major) axis was 4.5 ± 0.5 cm in controls, 4.7 ± 0.6 cm in new PAF group and 6.1 ± 0.7 cm in new perAF group. There was no significant difference between the control and PAF group (P=0.1). However, the LA longitudinal axis was significantly greater in the perAF group compared to the PAF group and controls (P<0.001) (Figure 2a).

3.3.3.2 Left Atrial Transverse Axis

The LA transverse (minor) axis measurement was smallest in the control group, measuring a mean of 3.6 ± 0.4 cm; higher in the PAF group, measuring a mean of 3.9 ± 0.5 cm, although this difference was not significant, (P=0.07). It was the largest in the perAF group, measuring a mean of 4.5 ± 0.9 cm. There was a significant difference

between the perAF group and the controls ($P<0.001$), and between the two new AF subgroups ($P=0.003$) (Figure 2b).

3.3.3.3 Left Atrial Area

Controls showed the smallest LA area, with a mean of 15.3 ± 3.1 cm². The PAF group had a similar LA area, with a mean measurement of 16.7 ± 4.7 cm² ($P=0.3$). The perAF group patients had the largest LA area, significantly larger than both controls and PAF group ($P<0.001$), with a mean measurement of 24.0 ± 6.3 cm² (Figure 2c).

3.3.3.4 Left Atrial Volume

Controls had the lowest volume, with a mean of 43.1 ± 13.1 ml. The PAF group had a mean LA volume averaging 50.2 ± 18.5 ml; this was not statistically significant ($P=0.2$). The perAF patients had the largest LA volume, with a mean of 81.2 ± 28.7 ml. This was significantly greater than the LA volumes of both the controls and PAF group ($P<0.001$) (Figure 2d).

3.3.3.5 Left Ventricular Hypertrophy: Interventricular Septal Diameter (IVSd)

The controls had an average IVSd of 0.9 ± 0.1 cm. Both the AF groups had slightly larger IVSd measurements with a mean value of 1.0 ± 0.2 cm. There was a significant difference between the perAF patients and controls ($P=0.03$). There was however, no significant difference between the PAF patients and controls ($P=0.9$), and the perAF patients ($P=0.1$) (Figure 3a).

3.3.3.6 Left Ventricular Ejection Fraction (LVEF)

LVEF was similar in the controls and PAF; averaging a $63.3\pm 3.7\%$ and $64.4\pm 4.3\%$, respectively, $P=0.6$. However, the perAF patients had a significantly lower LVEF at $55.0\pm 8.1\%$ compared to controls and PAF ($P<0.001$) (Figure 3b).

3.3.3.7 Mitral E Velocity

The average mitral E velocity in the controls was 0.68 ± 0.2 cm/s and 0.74 ± 0.1 cm/s in the PAF patients ($P=0.4$). This measure was higher in the perAF group, with an average of 1.0 ± 0.4 cm/s. There was only a significant difference in the controls and the perAF group ($P=0.003$) (Figure 4a).

3.3.3.8 Mitral A Velocity

The average mitral A velocity in the controls was 0.68 ± 0.1 cm/s, and that for PAF patients was 0.7 ± 0.2 cm/s. There was no significant difference in this parameter between the groups, $P=0.5$ (Figure 4b).

3.3.3.9 E/A Ratio

The controls had an average E/A value of 1.01 ± 0.3 and the PAF patients had an average of 1.1 ± 0.4 . There was no significant difference in this measurement between the controls and PAF group, $P=0.2$, (Figure 4c).

3.3.3.10 Pulmonary Vein S/D Ratio

The controls had an average of 1.4 ± 0.5 and the PAF group had a mean of 1.2 ± 0.3 . There was a significant difference in this measure for these groups, $P=0.01$, (Figure 4d).

3.3.3.11 Pulmonary Vein Septal E'

There was no significant difference in the septal E' between the controls and PAF (8.2±1.7 cm/s vs. 8.5±2.6 cm/s; P=0.9) or perAF (8.5±2.0 cm/s; P=0.9). There was also no significant difference between the PAF and perAF groups (P=1.0), (Figure 4e).

3.3.4 Electrical Substrate

3.3.4.1 Atrial Ectopy Burden and Relative Earliness

Ten of the twelve perAF patients were in AF throughout their holter recording and thus had no APB burden. Given only two perAF patients were AF free at the time of the holter recording, this precluded any meaningful analysis of their holter data and this group was excluded from the analyses. Controls had significantly lower median APBs per hour of 0 [0-1; mean 3.1], whereas the PAF group had 2 [0-5; mean 7.8] APBs per hour, P=0.01. The mean APB coupling interval was significantly higher in the PAF patients compared to controls (0.41±0.1 vs 0.37± 0.05, P<0.001). Importantly, the median proportion of APBs with earlier coupling (i.e shorter coupling intervals, with coupling index >80th percentile of overall distribution) was significantly greater in the PAF patients compared to the controls (P=0.04) (Figures 5a-c).

3.4 Discussion

This study provides new information on patients with new onset AF. The main findings of this cohort study were as follows:

1. A majority (77%) of newly diagnosed patients present in PAF, with atrial structure that is comparable to community controls but higher atrial ectopy burden and more closely coupled ectopy.

2. A small proportion (23%) of patients present for the first time with persistent AF. These patients have evidence of an established structural substrate for AF. This was characterized by atrial enlargement, reduced left ventricular systolic function and some evidence of diastolic dysfunction.

3.4.1 Substrate in New Paroxysmal AF

The PAF patients differed significantly in their ectopy burden to the controls, demonstrating a significantly higher number of APBs per hour of the holter recording (Figure 4a). A long-term follow-up study of patients initially free of AF, who went on to develop AF reported frequent isolated atrial premature beats (mean >100/days)⁵⁵⁰, comparable to those we reported in the new PAF patients. Indeed, Brooks et al too reported PAF patients with an average disease history of 48 months²¹¹ as having a similar median number of APBs as the PAF patients in our cohort. The ectopic burden we reported was however lower than that reported by other studies, that have reported 24 hours APB burdens ranging between 567⁵⁵¹ and 66⁵⁵² per hour. This could be attributed to the fact that the patients in the aforementioned studies had drug-resistant PAF⁵⁵¹, or had the arrhythmia for a minimum of one year, with a history of multiple episodes⁵⁵²; thus allowing for a more established and severe electrical substrate compared to the PAF patients in our cohort, who were captured soon after their AF diagnosis. Nevertheless, our findings still demonstrate the existence of electrical abnormalities soon after AF diagnosis. These results may also have prognostic significance for newly diagnosed PAF, in that Kucher et al demonstrated that patients with a substantial trigger burden may be likely to progress to more severe forms of AF²⁰⁸.

Additionally, the new PAF were found to have more closely coupled ectopic beats. Numerous studies' findings show evidence to the fact that paroxysmal episodes of AF are more likely to be induced by APBs with shorter coupling intervals^{209-211, 553, 554}. In fact, it has been demonstrated that in the recordings of patients who experienced transient episodes of AF, the premature beats with significantly shorter coupling intervals (up to 100-200 ms shorter) preceded AF compared to longer coupling intervals for the premature beats that did not precede AF^{209, 210, 554}. However, none of our PAF patients had AF during their holter recording, thus it can only be postulated from the larger proportion of closely coupled APBs in this group that these triggers may be the likely mode of the AF induction.

Lastly, we found the new PAF patients presented with few co-morbidities, which could be reflected in their comparable echocardiographic parameters with the control group. While previous studies have shown an existence of LA dilatation^{219, 220} and LV dysfunction²²⁹ in PAF patients; these were individuals who suffered with AF for a number of years, who were significantly older^{219 229} and who carried a significantly greater number of co-morbidities^{219 220} than our cohort of PAF patients. Thus, this indicates that although the structural anomalies/remodelling were not evident in the new PAF at this early time, these changes could evolve with a greater number and higher frequency of AF episodes; leading to the concept that AF leads to progressive remodelling²²³.

3.4.2 Substrate in New Persistent AF

There was evidence of LA dilatation as all LA dimensions were consistently higher in the new perAF patients over and above the values seen in the controls and

the new PAF groups (Figures 1a-d). Our results imply that there is an incremental increase in the LA size from sinus rhythm to newly diagnosed AF, but more importantly from paroxysmal to persistent AF. Comparable relationships between LA size and the severity and duration of AF were demonstrated by Henry et al ²²⁰, Probst et al ⁵⁴³ and Takahashi et al ²¹⁹ in patients with a history of AF (minimum of 6 ²¹⁹ to 16 ⁵⁴³ months) and multiple episodes of AF. The findings of our study and those of the aforementioned studies ^{219, 220, 543} also reiterate that in the temporal relationship of LA dilatation and AF; the former precedes arrhythmia occurrence, and the persistence of the arrhythmia may further promote this remodelling ^{223 120}. Invasive characterisation of the human atria in patients with persistent AF also support our findings that persistent AF is not supplemented necessarily by electrical remodelling, but it is by atrial dilatation by way of increased LA volume ⁵⁵⁵. LA enlargement has also been observed in hypertensive, elderly patients with diabetes ⁵⁵⁶; which are baseline characteristics akin to those observed in the perAF patients (Table 1).

In addition to LA dilatation, studies have observed LV hypertrophy as a common change in patients with long-standing AF ^{66, 557, 558}. Although more than half of the perAF patients presented with HT (Table 1), there was no evidence of IVSd thickening; even though this echocardiographic marker is used to detect left ventricular hypertrophy ⁵⁵⁹, which in itself is a manifestation of HT ⁷⁰. Indeed, observable changes in IVSd may evolve over a long period of time and it has been suggested that these changes can only be detected in chronically hypertensive individuals ⁷⁰. Additionally, due to the different patterns in which the left ventricle adapts to HT ⁵⁶⁰, it was found that even patients with mild-moderate HT may not

exhibit this change, which is dependent on the presence of ‘concentric or eccentric ventricular hypertrophy’⁵⁶¹.

Systolic dysfunction (reduced LV EF) is another detrimental change observed in a number of AF precursors such as the structural heart diseases of HT⁵⁶¹ and CHF⁵⁶². The proportions of perAF patients presenting with these co-morbidities were higher than the PAF patients (Table 1), which may have been reflected in the significantly lower values observed (Figure 2b). Additionally, the dilatation of the LA could have played a role in promoting left ventricular remodelling in the form of lowered LV EF; as suggested by an imaging study conducted by Akkaya et al⁵⁶³.

Lastly, the attainable LV diastolic function measures in the new perAF patients may have been indicative of pseudonormal pattern (Figures 3a & 3e). Certainly, Sakabe et al demonstrated that chronic AF patients with a similar age distribution as our perAF patients had a pseudo restrictive pattern of transmitral flow and diastolic dominant pattern of pulmonary venous flow⁵⁶⁴. In addition, there may not have been an observable change in the measures of LV diastolic function as these changes may evolve over time. Studies that have described a degree of LV deterioration in transmitral flow parameters showed these changes developed over a four-year follow-up period^{229, 565}.

3.5 Clinical Implications

Our data suggests that the newly diagnosed PAF patients may not have underlying structural substrate levels. However, these patients did show evidence of electrical substrate, in their ectopy burden, which was higher than the controls and more closely coupled APBs, which may be more capable of inducing paroxysms of AF

^{204, 209, 210}. With growing evidence of the importance of structural change and cardio-metabolic risk factors in the long-term outcomes of ablation^{566, 567}, this data argues for the evaluation of early intervention to prevent the progression of disease.

Furthermore, the patients with the longer duration of AF, i.e. new perAF had a significantly greater disease burden, which was possibly reflected in their LA dilatation levels. While these patients may not have evidence of progressive remodelling by way of LV diastolic dysfunction, they may well have an underlying structural substrate that perpetuates their AF. Thus, these results may also indicate that the subset of new PAF patients may benefit more from trigger based ablation therapy (pulmonary vein isolation), know to reduce the number of aberrant triggers and lengthen the coupling interval, and thus reduce the ability to induce AF episodes⁵⁵¹. Whereas, in the case of the new perAF, where underlying atrial substrate likely played a greater role¹²⁰, risk factor management, particularly of HT and CHF may prevent further atrial remodelling⁵⁶⁸. Indeed, emerging clinical trials are investigating the usefulness of anti-hypertensives to curb structural remodelling in AF patients, which may prove to have therapeutic benefits^{568, 569}.

3.6 Limitations

Certain limitations have to be considered while interpreting the results of this study. There may have been a presence of occult or silent AF that went undetected until patients became symptomatic. Particularly in the case of some patients who presented for the first time with persistent AF. However, we recruited patients who had presented with their first clinical episode of AF, which was confirmed by hospital discharge notes, ECGs performed during emergency department/hospital stay and during patient interview. In addition, the sample size of the study was limited due to

the recruiting period, which was one year. A larger sample size recruited over a longer period may have provided a more robust sample for analysis. Controls were arrhythmia free, but not entirely disease free, as 21% had a history of HT, which could have affected our results.

3.7 Conclusions

Our study was unique in that it characterised patients at the onset of their disease process, which made it possible to perhaps observe what de-escalates normal sinus rhythm into AF and characterise the changes that are present early on in the disease evolution. In the case of our newly diagnosed new AF patients, the higher and more closely coupled APB burden reiterated that this type of AF is indeed more trigger than substrate based. Whereas the evidence of LA dilation in the new perAF group indicates that this type of arrhythmia may be more substrate based. However, both our newly diagnosed patients subgroups showed evidence of remodelling soon after their diagnosis of atrial fibrillation. These data suggest that new AF is not the start of a disease process, but merely a reflection of a critical threshold of a constantly evolving process of substrate development.

3.8 Figures

Figure 1 Recruitment of controls and new AF patient

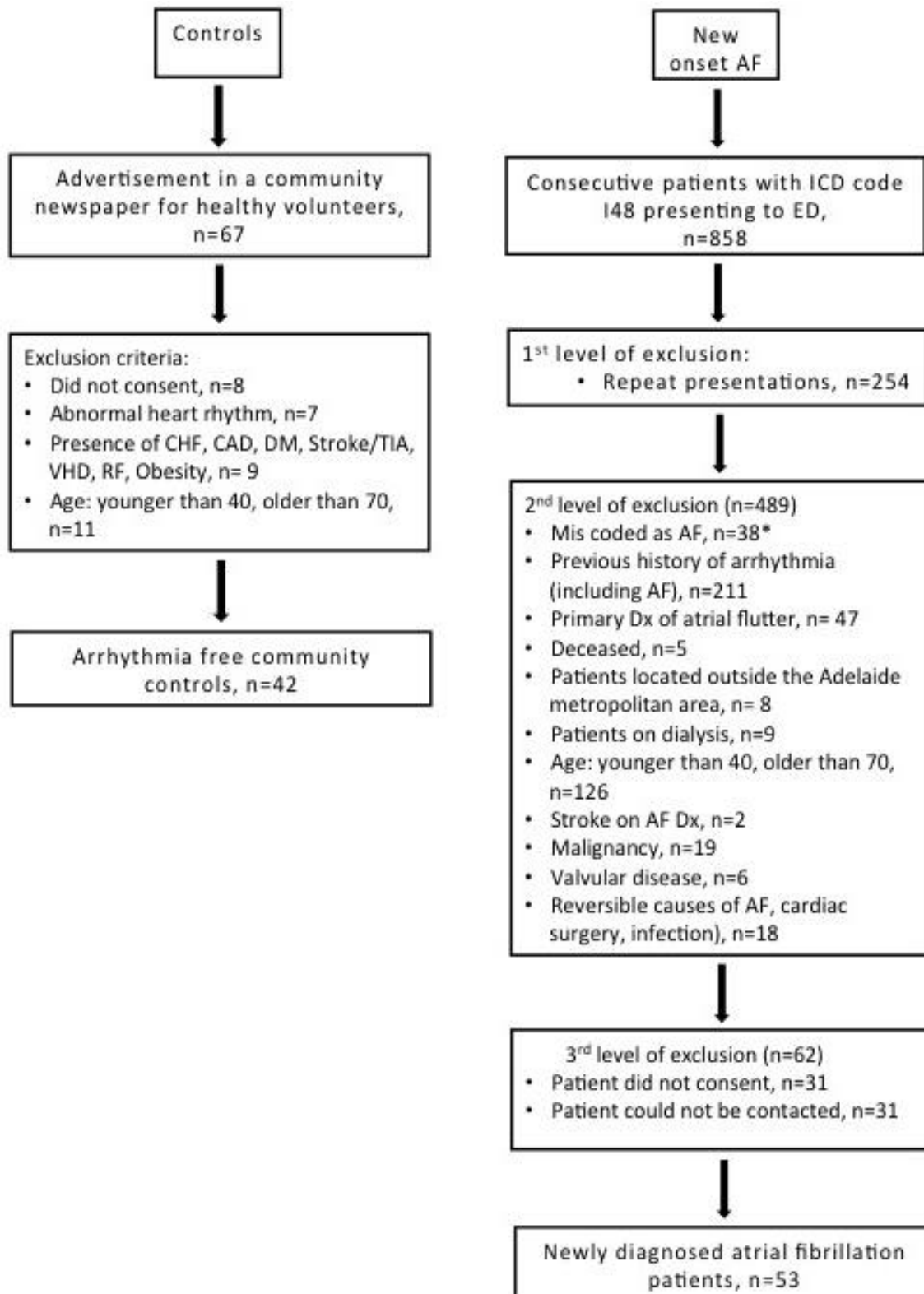


Figure 2 Left atrial dilation parameters in controls, new PAF and new perAF

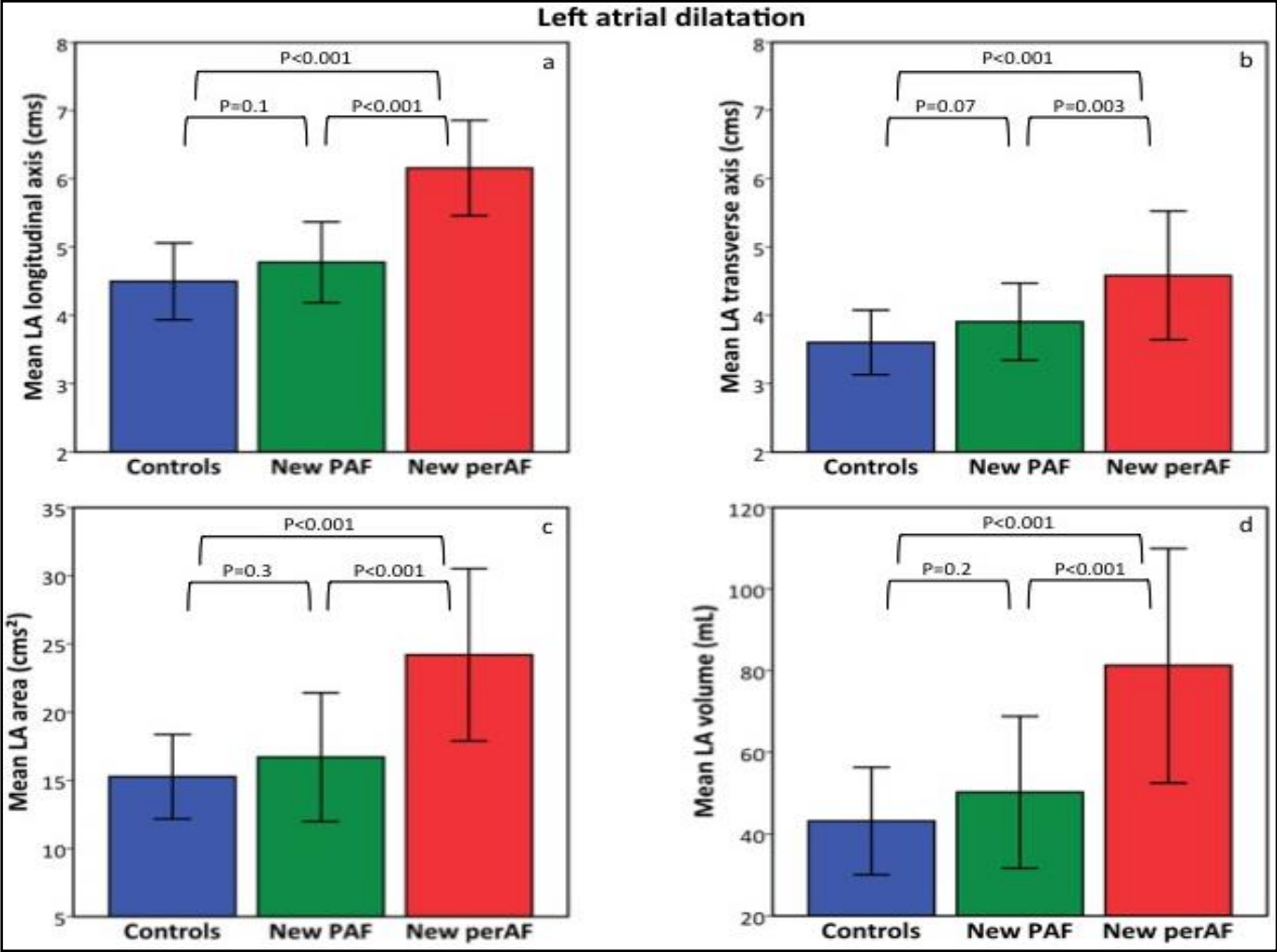


Figure 3 Left ventricular measurements in the controls, new PAF and new perAF patients

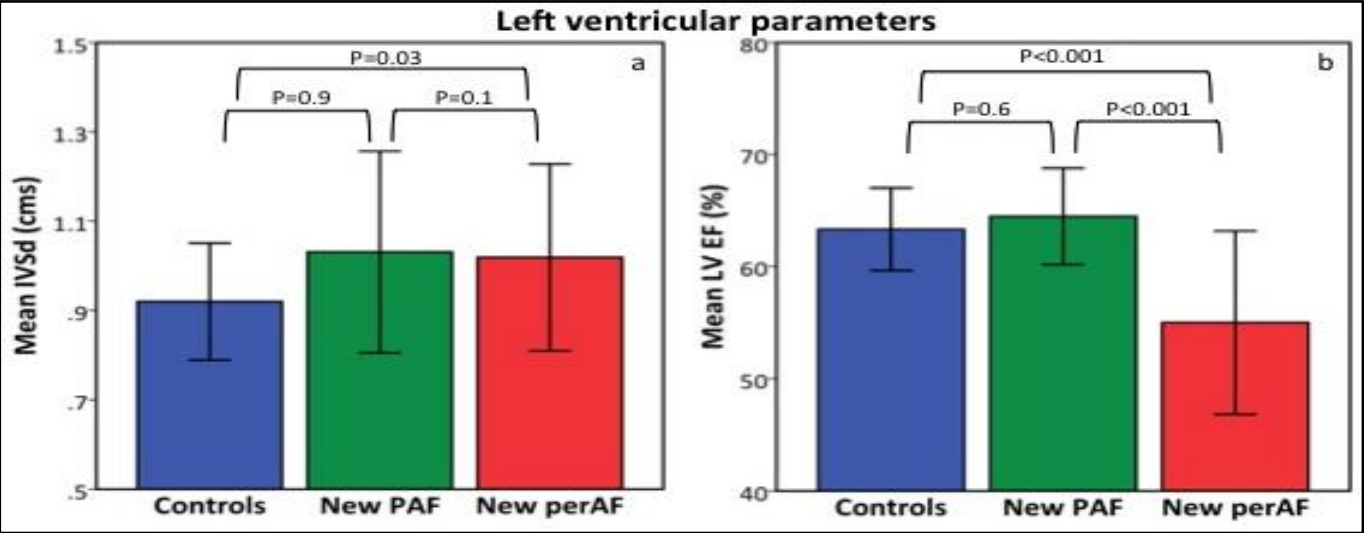


Figure 4 Left ventricular diastolic function in controls, new PAF and new perAF

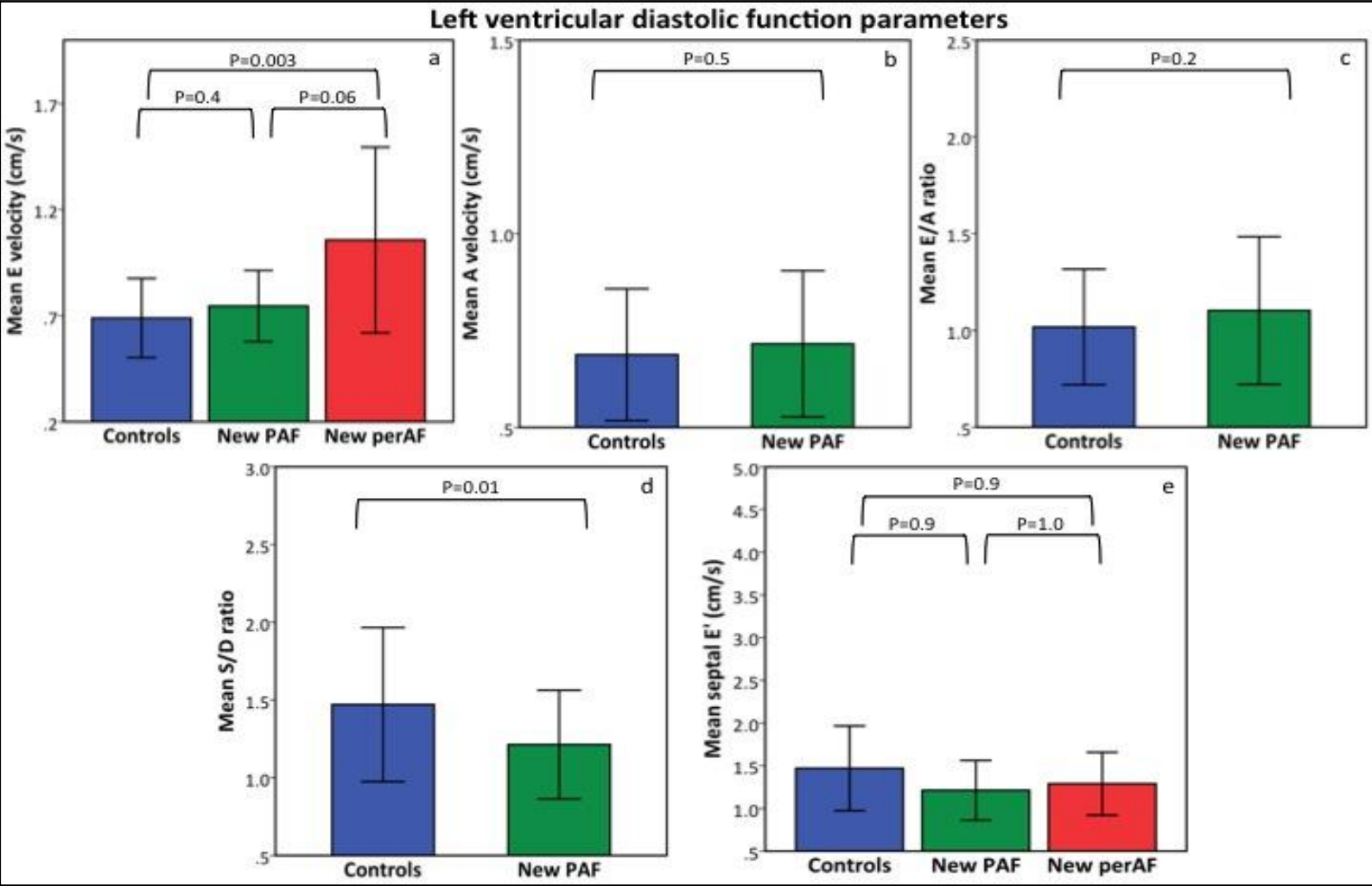


Figure 5 Atrial premature beats per hour in controls and new PAF

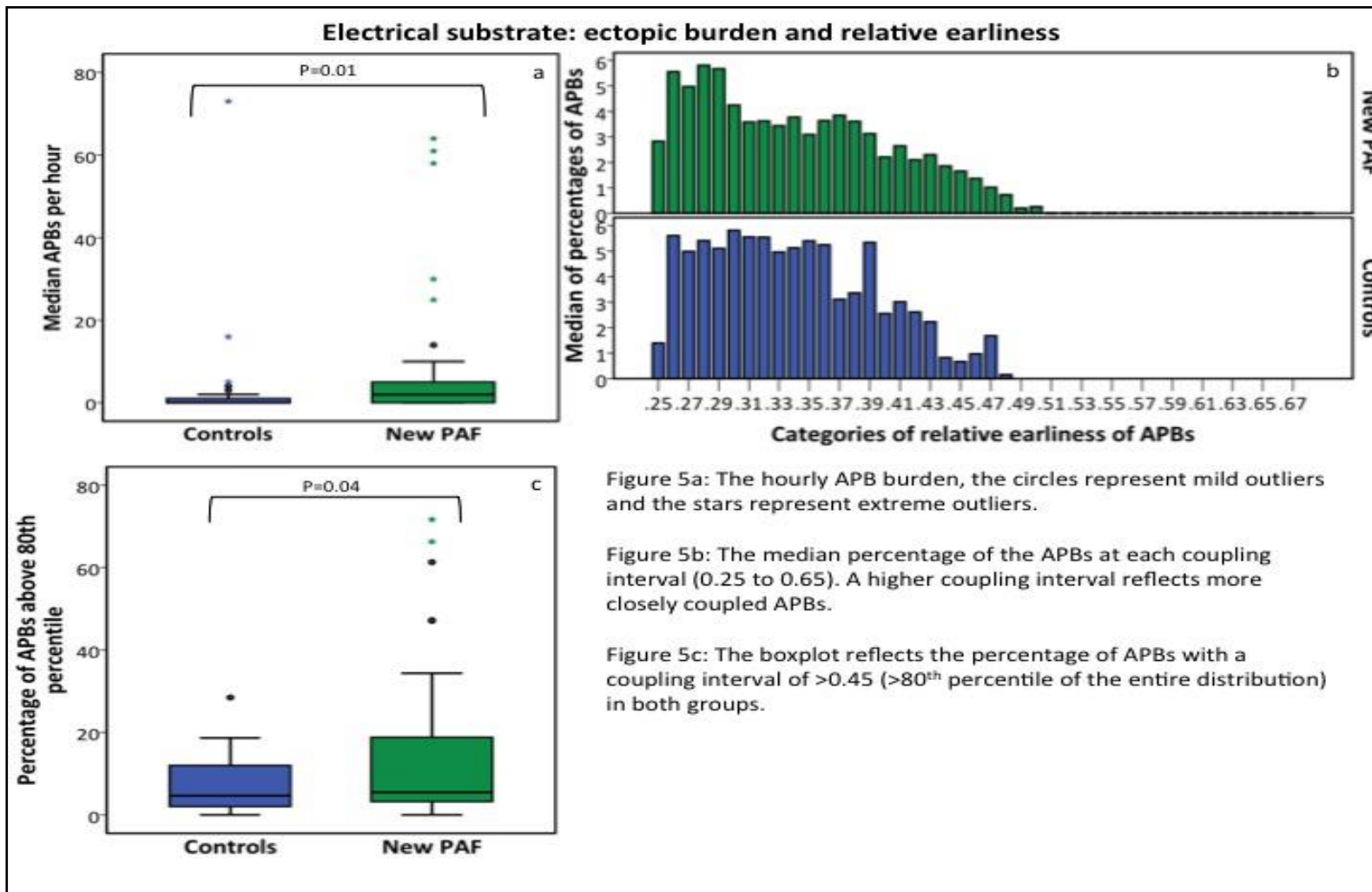


Figure 5a: The hourly APB burden, the circles represent mild outliers and the stars represent extreme outliers.

Figure 5b: The median percentage of the APBs at each coupling interval (0.25 to 0.65). A higher coupling interval reflects more closely coupled APBs.

Figure 5c: The boxplot reflects the percentage of APBs with a coupling interval of >0.45 (>80th percentile of the entire distribution) in both groups.

3.9 Tables

Table 1 Baseline characteristics of the controls and new AF groups

	Controls n=42	P value: controls vs PAF	PAF, n= 41	P value: PAF vs PerAF	PerAF, n= 12	P value:controls vs PerAF
Baseline Charateristics						
Age (years, mean±SD)	63±8	0.4	59±13	0.1	66±10	0.2
Gender (male) n (%)	17 (40%)	0.2	22 (54%)	0.4	5 (42%)	0.9
Body mass index (mean±SD)	25.7±5.3	0.3	27.9±6.4	0.9	27.1±6.0	0.4
Cardiac co-morbidities						
Hypertension	9 (21%)	0.001	23 (56%)	0.5	8 (67%)	0.003
Congestive heart failure	0 (0%)	0.3	1 (2%)	<0.001	6 (50%)	<0.001
Coronary artery disease	0 (0%)	0.07	3 (7%)	0.9	1 (8%)	0.06
Stroke/TIA	0 (0%)	0.07	3 (7%)	0.03	2 (17%)	0.007
Non cardiac co-morbidites						
Diabetes mellitus	0 (0%)	0.09	3 (7%)	0.01	5 (42%)	<0.001
Obstructive sleep apnea	0 (0%)	0.09	3 (7%)	0.8	1 (8%)	0.07
Hyperthyroidism	1 (2%)	0.5	2 (5%)	0.4	0 (0%)	0.6
Pharmacueticals						
Anti-hypertensives	9 (21%)	<0.001	26 (63%)	0.8	8 (67%)	0.003
Diuretics	0 (0%)	0.3	1 (2%)	<0.001	6 (50%)	<0.001
Anti-anginals	0 (0%)	0.1	2 (5%)	0.4	0 (0%)	1
Anti-platelet medications	2 (5%)	<0.001	16 (39%)	0.04	1 (8%)	0.6
Anti-coagulants	0 (0%)	0.001	9 (22%)	<0.001	10 (83%)	<0.001
Anti-arrhythmics	0 (0%)	<0.001	15 (36%)	0.8	4 (33%)	<0.001

Chapter Four

Characterisation of the Inflammatory Changes Associated with New Onset Atrial Fibrillation: Implications for Increased Thromboembolic Risk.

4.1 Introduction

Atrial fibrillation (AF) is associated with significantly increased morbidity and decreased survival^{6, 7}. Thromboembolic stroke remains one of the most devastating co-morbid conditions associated with atrial fibrillation¹⁰. The National Stroke Foundation of Australia annual report estimates that the direct cost of AF-attributable stroke in 2008-09 was in excess of 200 million dollars⁵⁷⁰. In addition, there are indirect costs for disability and aged care, and of course the non-financial impact on productivity⁵⁷⁰. With the number of AF sufferers rising exponentially², the number of AF-related strokes and the economic burden contributed by these two entities will surely rise²⁴⁷.

The risk of stroke increases by 5-6 fold in patients with non-valvular AF¹⁰. This is further compounded by the existence of advancing age and co-morbidities such as congestive heart failure (CHF), hypertension (HT), coronary artery disease (CAD), diabetes mellitus (DM) and even previous stroke^{299, 298}. Thromboembolism has previously been attributed to atrial mechanical function³²⁵. However, recent data has implicated other attributes of the Virchow's triad in the thrombogenic milieu. Links between inflammation, endothelial dysfunction and extracellular matrix remodelling and the prothrombotic state in AF have been documented^{302, 319}. Elevated levels of C-reactive protein (CRP; a potent marker

of inflammation)^{355, 356, 571}, asymmetric dimethyl arginine (ADMA; a marker of endothelial dysfunction)⁵⁷² and CD40 ligand (CD40L; a marker for platelet activation) have been linked to an increased risk of thromboembolic events in paroxysmal and persistent AF patients³⁸⁸. Acute episodes of AF were found to significantly modify levels of ADMA and CD40L and hence the associated prothrombotic risk in patients with a history of AF³⁶⁹.

Interestingly, the temporal relationship between AF and stroke has been observed to be inconsistent. The TRENDS study demonstrated the absence of a temporal relationship between these entities, raising the possibility of a 'thrombogenic atria' where AF was a marker of risk⁵⁷³. Furthermore, in a small sample of the Framingham Study, a clustering of strokes at the time of AF onset was observed⁵⁷⁴. However, the thromboembolic risk associated with newly diagnosed AF is unknown. This prospective cohort study aimed to characterise components contributing to thrombogenic risk in patients with newly diagnosed AF in order to determine if a tangible risk of thromboembolic stroke exists soon after AF diagnosis.

4.2 Methods

4.2.1 Recruitment of Newly Diagnosed Atrial Fibrillation Patients

The recruitment strategy and exclusion criteria are outlined and detailed in Figure 1 and Table 2. The newly diagnosed AF patients were recruited from among patients presenting to the emergency department (ED) of the Royal Adelaide Hospital with a primary diagnosis of AF (ICD code I48). The recruitment occurred over a 1-year period, from August 2010-August 2011. A total of 858 patients presented with a primary diagnosis of AF during this period. The first level of screening removed 254 representations, leaving 604 unique

patient presentations. The second level of screening was performed using unique patient reference numbers and digital discharge summaries from the OACIS system (Version 102, DINMAR 2003, US Inc.). We excluded 489 patients at this level of screening. The reasons for exclusion were: age (<40, >70 years); primary diagnosis of atrial flutter; reversible causes of AF (infection, cardiac surgery); patients who died during their index presentation; remotely located patients (>100km); recent diagnosis of malignancy; renal failure; valvular heart disease (including patients with mitral, aortic, tricuspid or pulmonary stenosis, or regurgitation); stroke on AF diagnosis and misdiagnosis of AF (Appendix 3). The remaining 115 patients were approached via telephone to participate in the study. However, of these, 31 could not be contacted and 44 did not consent to participate in the study. Twenty-three consecutive new AF patients were included in the study. All patients provided written informed consent to participate in this study. The study protocol was reviewed and approved by the Human Research Ethics Committee of the Royal Adelaide Hospital and University of Adelaide.

4.2.2 Recruitment of Age-matched Controls

The arrhythmia free community controls were volunteers recruited through an advertisement in local newspapers. Volunteers who expressed interest in the study were approached via an initial telephone interview to determine eligibility. Those individuals who had a previous history of any type of arrhythmia or conduction abnormality including AF; atrial flutter; supraventricular tachycardia (SVT); atrial premature beats (APBs); ventricular premature beats (VPBs); and heart block were excluded. In addition, the following individuals were excluded; those aged <40 and >70 years, with congestive heart failure

(CHF), coronary artery disease (CAD), diabetes mellitus (DM), stroke/(transient ischemic attack) TIA, valvular heart disease (as defined above), rheumatic fever (RF), obesity (BMI >30) and obstructive sleep apnoea (OSA). Thirty-two arrhythmia free age and gender-matched controls were recruited.

4.2.3 Structured Clinical Interview

A structured interview was conducted to ascertain baseline information for all participants (detailed in Appendix 1). Demographic characteristics, medical history (cardiac and non-cardiac co-morbidities) and medication use was interrogated. The details are presented in Table 1 for both groups.

The individual's arrhythmia history was determined. The length of the longest sustained episode of symptomatic AF was also determined from clinical history to facilitate AF classification in keeping with current AF consensus classification. The new AF patients were classified in accordance with the Heart Rhythm Society Consensus Statement¹. In brief, Paroxysmal AF (PAF) was defined as self-terminating and lasting less than a week and persistent (perAF) as AF episodes lasting more than a week and/or requiring cardioversion¹. Seventeen patients were in persistent AF; this subgroup of patients was excluded, as patients were meant to be free of AF at the time of blood sampling, so as not to acutely increase the levels of the bio-markers and potentially bias the results.

4.2.4 Blood Collection

Peripheral blood samples were obtained by venepuncture and placed into sodium citrate (3.8%) tubes. Plasma samples were prepared by centrifugation of the citrated blood

samples at 2500 rpm at 4°C for 15 minutes. Aliquots of plasma were then stored at -80°C for batch analysis by enzyme linked immunosorbent assay (ELISA).

4.2.5 Bio-markers Measured

The levels of the following biomarkers were measured:

- Asymmetric dimethyl arginine (ADMA): Elevated ADMA levels endogenously inhibit nitric oxide synthase, reducing nitric oxide (NO) production, affecting the structural and functional integrity of the endothelium ⁵⁷⁵, thus making it a marker for endothelial dysfunction.
- Endothelin-1 (ET-1): ET-1 is produced by the vascular endothelium, plays an important role in vasoconstriction and is an indicator of vascular function ⁵⁷⁶.
- High sensitivity C-Reactive protein (hs-CRP): elevated levels of high sensitivity CRP are an indicator of the presence of systemic inflammation ⁵⁷⁷.
- Soluble CD40L (sCD40L): This is the soluble product formed from the interaction of CD40-CD40 ligand system expressed on the surface of activated platelets and is an indicator of platelet derived inflammation ⁵⁷⁸.
- Intracellular cell adhesion molecule-1 (ICAM-1): This is present only on the membranes of leukocytes and endothelial cells in low concentrations and is indicative of localised inflammation ⁵⁷⁹.
- Myeloperoxidase (MPO): This is a heme-protein, expressed on the surface of activated neutrophils, and has been linked to inflammation in AF ⁴⁰⁵.

- Matrix metalloproteinase-9 (MMP-9): This is a matrix metalloproteinase that has been implicated in a number of diseases including AF, and increased levels are suggestive of increased collagen deposition and ECM turnover⁴⁰⁵.
- Tissue inhibitors of matrix metalloproteinase-1 (TIMP-1): This is a marker that is responsible for the breakdown of matrix metalloproteinases; lower levels indicating that there is an abnormally high extracellular matrix turnover⁴⁰⁵.

4.2.6 Enzyme-Linked Immunosorbent Assay

Enzyme-linked immunosorbent assay (ELISA) tests were carried out according to the respective manufacturers' specifications and instructions. Levels of ADMA (Immunodiagnostik®, Bensheim, Germany); ET-1 (Quantikine® R&D Systems, Minneapolis, MN, USA); sCD40L (Quantikine® R&D Systems, Minneapolis, MN, USA); I-CAM (Quantikine® R&D Systems, Minneapolis, MN, USA), MPO (Quantikine® R&D Systems, Minneapolis, MN, USA); MMP-9; and TIMP-1 (Quantikine® R&D Systems, Minneapolis, MN, USA) were determined. All assays were performed in duplicates. Hs-CRP levels were determined by routine blood biochemistry tests.

4.2.7 Statistical Analysis

Continuous variables were expressed as mean \pm standard deviation. Categorical variables were expressed as count and percentage. Continuous variables were compared using a 1-way analysis of variance (ANOVA) and categorical variables were compared using Pearson's chi-square test. The data was tested for normality and log transformed as required. A constant of 1 was added to ADMA, ET-1 and hs-CRP values before log

transformation³⁶⁹. All analyses was carried out using SPSS PASW (Version 21, IBM, Armonk, NY); statistical significance was set at $P < 0.05$.

4.3 Results

4.3.1 Baseline Characteristics

The baseline characteristics of the two groups are outlined in Table 1. The groups were age ($P=0.3$) and gender matched ($P=0.1$). Hypertension was the only co-morbidity that was over represented in the AF group (<0.001). Only small proportions (4%) of the AF patients presented with CHF, CAD and DM and 9% presented with stroke/TIA and OSA. There was no significant difference in the proportions of any of these co-morbidities between the two groups ($P > 0.05$). Lastly, the BMI was also similar between the groups ($P=0.4$).

The number of individuals on anti-hypertensives was significantly higher in the AF group ($P < 0.001$). As expected, anti-platelet, anti-coagulation and anti-arrhythmic medications were also more common in the AF group ($P=0.003$ and $P < 0.001$ respectively). A small, yet similar numbers of patients in both groups were on diuretics and anti-angina medications ($P > 0.05$).

4.3.2 Bio-markers of Thrombogenesis

4.3.2.1 Endothelial Dysfunction and Vascular Function

The plasma ADMA levels in the AF patients were higher than those in the controls (0.2 ± 0.04 vs. 0.15 ± 0.05 $\mu\text{g/mL}$; $P=0.002$, Figure 2a). The levels of ET-1 were significantly

higher in the controls compared to the AF patients (0.38 ± 0.09 vs. 0.31 ± 0.05 pg/mL, $P=0.004$, Figure 2b).

4.3.2.2 Inflammatory Markers

Hs-CRP was higher in the AF group than controls; this difference was not statistically significant (0.48 ± 0.4 vs. 0.35 ± 0.3 pg/mL; $P=0.2$, Figure 3a). The sCD40L levels were significantly higher in the AF patients than controls (2.0 ± 0.14 vs. 2.2 ± 0.3 pg/mL; $P=0.02$, Figure 3b). Levels of I-CAM were similar in the controls and AF patients (2.8 ± 0.1 vs. 2.8 ± 0.2 ng/mL; $P=0.9$, Figure 3c). Lastly, the levels of MPO were also similar between the AF and control groups (0.81 ± 0.2 vs 0.9 ± 0.3 . pg/mL; $P=0.1$, Figure 3d).

4.3.2.3 Extracellular Matrix (ECM) Remodeling

MMP-9 levels were elevated in the AF compared to controls (1.5 ± 0.3 vs. 1.4 ± 0.2 pg/ml; $P=0.3$, Figure 4a), however, not significantly. TIMP-1 levels were significantly lower in the new PAF patients as compared to controls (2.2 ± 0.2 vs. 2.3 ± 0.2 ng/mL; $P=0.006$, Figure 4b).

4.4 Discussion

This study demonstrated important new observations with regard to the potential stroke risk in new onset AF. Compared to controls, new onset AF patients demonstrate the following:

1. Endothelial dysfunction characterised by elevated ADMA levels
2. Platelet derived inflammation characterised by sCD40L levels
3. Higher levels of ECM remodelling characterised by lower TIMP-1 levels

4.4.1 Endothelial Dysfunction and Vascular Function

The existence of endothelial dysfunction has been demonstrated in persistent AF patients with a disease history of ≥ 4 months, who demonstrated raised ADMA levels compared to those seen in SR controls⁵⁷². Acutely elevated plasma ADMA levels have been observed in patients with a history of AF after AF induction by burst pacing. Conversely, patients in whom AF could not be induced and in control subjects; the levels of ADMA were not elevated³⁶⁹. Additionally, Cengel et al found that patients with acute onset AF (24 hours) had higher levels of this marker compared to patients with chronic AF (1 year)⁵⁸⁰. These findings suggest that even a short duration of AF was capable of raising levels of this marker, inducing endothelial dysfunction and hence increasing the risk of thromboembolic events.

Elevated levels of ET-1 have been reported in a number of conditions including hypertension, heart failure, mitral stenosis and AF^{378, 581-583}; indicative of compromised vascular function. However, in the case of AF patients, in the absence of concurrent conditions such as heart failure³⁷⁷ and significant valve disease³⁷⁸; the levels of this marker were not elevated. The AF patients in our cohort were non-valvular AF patients (Figure 1) and the prevalence of CHF was negligible (Table 1). Moreover, Mayyas et al also found ET-1 levels to be associated with persistence of AF⁵⁸², whereas the patients in this study had PAF, with average episode duration of ~39 hours (Table 1). Lastly, it has also been shown that ET-1 is synthesised and released by the vascular endothelium upon stimuli such as mechanical stress and pressure due to conditions such as coronary artery disease⁵⁸⁴; which was present in a minute number of the AF patients (Table 1). Hence, previous studies suggest that

despite the presence of the arrhythmia, this in itself may not have been sufficient to illicit a substantial rise in the ET-1 levels in our patient cohort.

4.4.2 Inflammation

Levels of hs-CRP were elevated in the new AF patients compared to those observed in the controls; however this was not statistically significant (Figure 3a). Being a marker for systemic inflammation, the levels can be affected by generalised infections such as the common cold and rheumatoid arthritis⁵⁸⁵ or the inflammatory processes involved in underlying atherosclerosis⁵⁸⁶. Indeed, even obesity has been shown to be an independent predictor of elevated hs-CRP levels⁵⁸⁷. Additionally, one study suggested that the duration of the AF may be instrumental in elevating the levels of this marker, as this was evident in permanent over paroxysmal AF⁵⁸⁸. Similarly, Chung et al found an incremental increase in the CRP levels and AF burden; low in lone AF, increasing slightly in paroxysmal AF and the highest in persistent AF³⁴⁵. Nevertheless, this marker remains an important prognostic tool for indicating which patients are more vulnerable to AF-induced stroke⁵⁸⁹, but changes may be more evident in patients with a longer duration of AF.

sCD40L levels were consistent with CRP levels, in that the new AF patients had higher levels compared to the arrhythmia free controls (Figure 3b). This is similar to the findings of Chowdhury et al, who found levels of CD40L to be elevated in patients with long standing AF (paroxysmal and permanent) over those seen in healthy control subjects⁵⁹⁰. Similarly, a study in chronic AF patients found that CD40L levels were elevated compared to those seen in SR controls. Additionally, these levels could be correlated to levels of angiogenic markers and tissue factor expression on the endothelium⁵⁹¹. Importantly, levels of CD40L were

significantly upregulated in AF patients after an acute episode of AF, similar to that seen with ADMA levels³⁶⁹, thus further cementing the role of this entity in the prothrombotic process of AF.

Studies have linked I-CAM levels in conjunction with other inflammatory and pro-thrombotic markers to incident AF, after controlling for predisposing factors of AF^{592, 593}. In isolation, however, studies have shown that I-CAM levels increase only during an AF episode³⁸⁷. This could explain why there was no difference between the I-CAM levels observed in the AF and control groups (Figure 3c), as our AF patients were in sinus rhythm at the time of blood sampling. Additionally, Yamashita and co-workers found an over expression of I-CAM and other inflammatory cytokines in human left atrial appendage samples of patients in AF; indicative of a localised inflammatory response in the atrial tissue to AF⁵⁹⁴. This, in addition to the confinement of the expression of this marker to leukocytes and endothelial cells⁵⁹⁵, may explain why we could not sufficiently detect significant changes between the two groups.

Similar to I-CAM, MPO also has limited expression; activated neutrophils and monocytes. This protein has been implied in the pro-inflammatory processes associated with AF⁴⁰⁵. Interestingly, leukocytes and neutrophils are shown to accumulate in fibrillating atria, thus raising the levels of this marker in the anatomical confines of the heart. In fact, histological analysis of the right atrial appendages of AF patients revealed that MPO is deposited in the atria of patients with concurrent AF. Additionally, this study found that levels of MPO correlated with the AF burden⁵⁹⁶. Hence, although MPO is an integral part of the inflammatory processes associated with AF, it may have been hard to detect the

localised response that may have been present in the new AF patients via peripheral blood samples.

4.4.3 ECM Remodeling

Studies have shown that an imbalance between the TIMP/MMP system and thus the ECM turnover not only promotes AF through the electroanatomical remodelling of the atrium ⁵⁹⁷, but also increases the risk of thrombogenesis ³¹⁶. Analysis of left atrial appendages of patients with chronic AF have shown that there was a down regulation of TIMP-1 mRNA and protein expression, which was accompanied by an increased protein and mRNA expression of MMP-9 ⁵⁹⁸. Further, biopsies of the right atrial appendage found similar results, ⁵⁹⁹ in that, the expressions of these markers were affected by fibrillating tissue ⁴⁰³. The levels of these entities were also affected by the burden of AF. Persistent and permanent AF patients had the lowest levels of TIMP-1 and concomitantly the highest levels of MMP-9, followed by paroxysmal AF patients and SR controls; indicating that this marker is dependent on AF burden ⁶⁰⁰.

Despite the AF patients in our study having a short duration of AF and being in SR, the TIMP-1 levels were significantly lower in these patients (Figure 4a). Of note, however, was that the MMP-9 levels were higher, albeit not significantly (Figure 4b). This could be explained in relation to the levels of the other inflammatory markers that were examined in our study. ET-1 levels are known to influence ECM turnover ⁵⁸²; in our study ET-1 levels were not elevated in the AF patients, which may have impacted the components of the ECM and hence of the levels of MMP-9. Additionally, MPO also plays a has pro-fibrotic role in AF; in that it affects the cellular signalling in various cells involved in the coagulation cascade and

leads to activation of MMPs, thus leading to the deposition of collagen and increased turnover of the ECM⁴⁰⁵. MPO levels too were not elevated substantially in the new PAF patients, which also could have affected the results we observed in the MMP-9 levels. However, there was still evidence of an ECM imbalance in the new AF patients, which implies a certain degree of underlying atrial remodelling which may increase the risk of AF progression and thromboembolic events in these patients.

4.5 Clinical Implications

New onset AF patients have a milieu that predisposes to thromboembolic events. This is evidenced by the existence of elevated pro-inflammatory and pro-thrombotic biomarkers soon after the diagnosis of AF. This is of clinical significance as elevated levels of these sub-clinical pro-thrombotic factors may be present even in the absence of, or in addition to, traditional risk factors for stroke⁶⁰¹. Indeed, guidelines stipulate that unless the precipitating factor for the AF is clearly reversible, appropriate anti-coagulation is essential even in new AF patients¹. In addition to being novel indicators for stroke risk in this AF subgroup, these bio-markers could serve as potential therapeutic targets³⁴². Certainly, studies have found that optimized therapy with OAC⁵⁹⁰, anti-hypertensives⁶⁰² and statins^{582 371} have shown promising results in reducing levels of inflammatory markers in conjunction with ablation therapies and cardioversions. Therapies such as these could have long-term benefits for averting potential thromboembolic events.

4.6 Limitations

Certain limitations exist that may have affected the results of the study. The changes induced by AF in the levels of I-CAM and MPO may have been localised to the atria due to the limited expression of these markers, thus reducing the likelihood of detecting subtle

changes in their levels, since the blood was drawn from a peripheral source, rather than central. Patients in both groups may have had undiagnosed infections that may have affected the levels of CRP we observed, particularly the controls, in whom the levels may have been elevated due to undetected inflammatory processes. Also, while it is possible that the arrhythmia alone may have driven the changes we observed in bio-marker levels, every effort was made to exclude patients with recent episodes of AF so as to avoid any confounding effect of the arrhythmia on the results. Lastly, the sample size of the study was limited due to the recruiting period, which was one year. This was the same sample as that used for the study in Chapter 3. A larger sample size recruited over a longer period may have provided a more robust sample for analysis.

4.7 Conclusions

Newly diagnosed AF patients showed evidence of endothelial dysfunction, platelet derived inflammation and extra cellular matrix remodelling. All of these changes have been shown to be present in established/long-standing AF. However, our findings indicate that such detrimental, prothrombotic changes are present soon after the first diagnosis of AF. This indicates that the sub-group of AF patients are potentially at an increased risk of thromboembolic events early in their AF disease process. Targeting these markers with appropriate therapeutic measures may potentially be a way of reducing the high stroke burden caused by atrial fibrillation.

4.8 Figures

Figure 1 Recruitment of controls and new AF patients

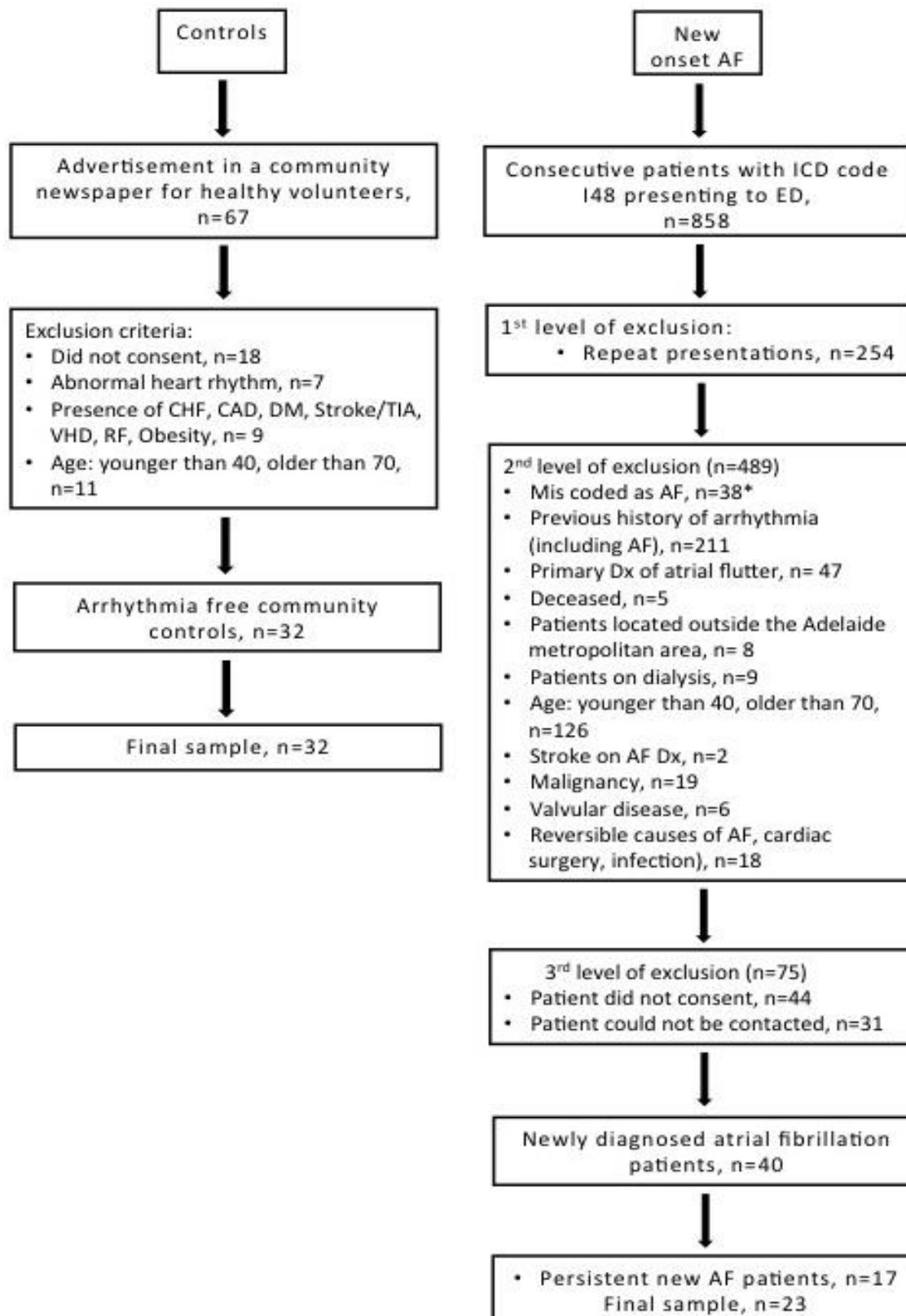


Figure 2 Endothelial dysfunction and vascular function measures in controls and new AF

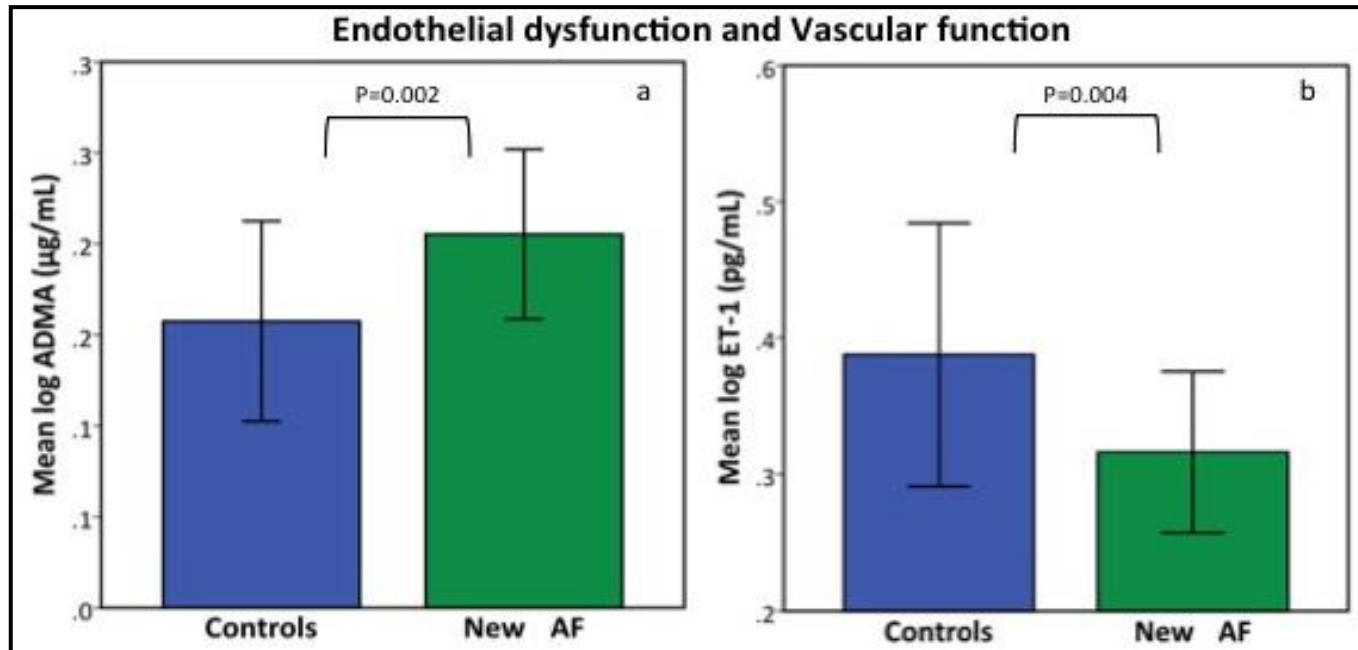


Figure 3 Markers of inflammation in controls and new AF

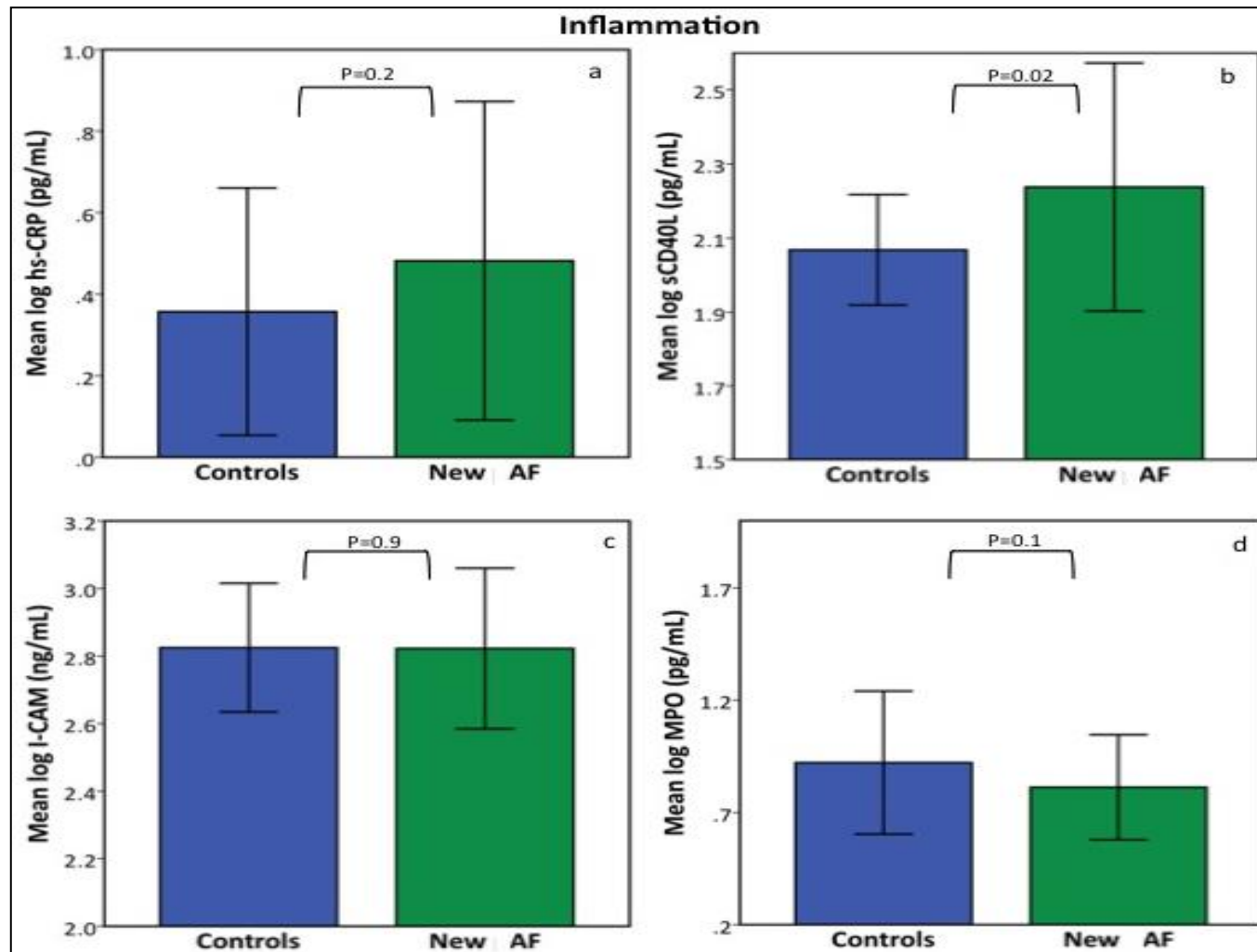
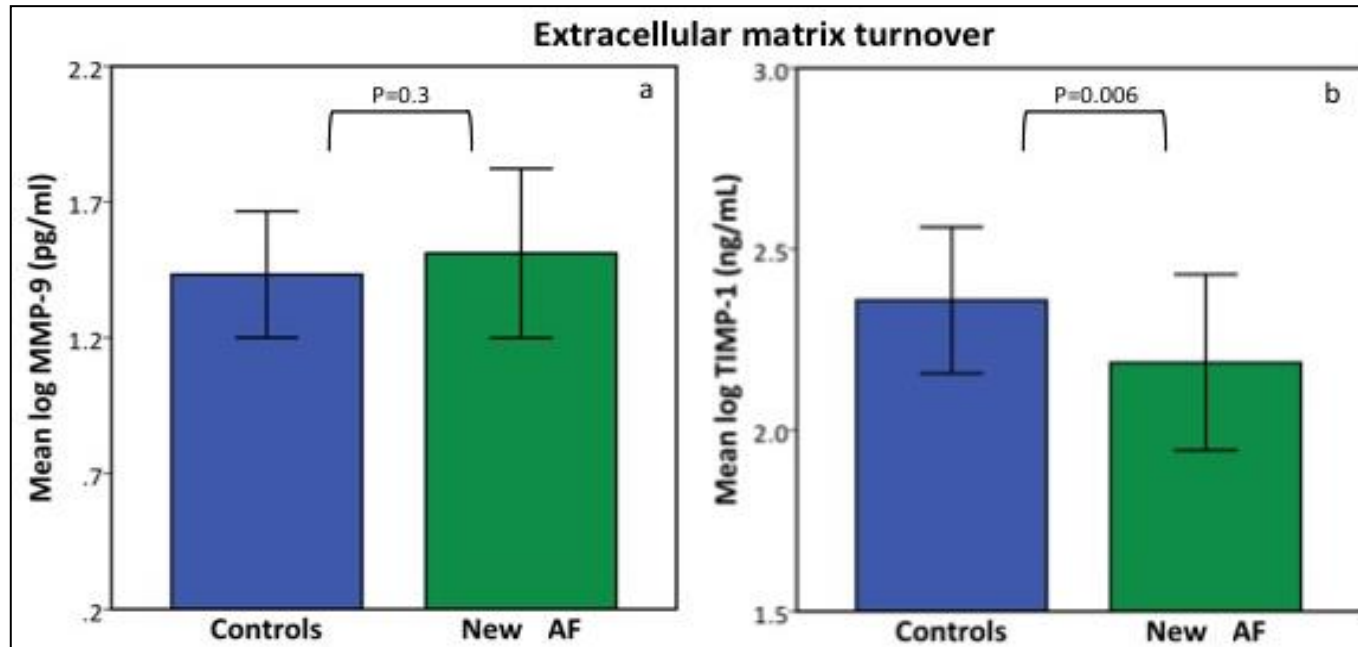


Figure 4 Markers of extracellular matrix remodelling in controls and new AF.



4.9 Tables

Table 1 Baseline characteristics of the controls compared to AF patients.

	Controls n=32	New AF n=23	P values
Baseline Characteristics			
Age (years, mean±SD)	58±14	56±14	0.3
Gender (male) n (%)	15 (47%)	15 (65%)	0.1
Length of longest episode, hours (mean±SD)	n/a	39±7	n/a
Cardiac co-morbidities			
Hypertension	3 (9%)	13 (56%)	<0.001
Congestive heart failure	0 (0%)	1 (4%)	0.4
Coronary artery disease	0 (0%)	1 (4%)	0.4
Stroke/TIA	0 (0%)	2 (9%)	0.1
Non cardiac co-morbidities			
Diabetes Mellitus	0 (0%)	1 (4%)	1.0
Obesity [BMI (mean±SD)]	26±5	27±7	0.4
Obstructive sleep apnea	1 (3%)	2 (9%)	0.5
Pharmacueticals			
Anti-hypertensives	4 (12%)	16 (70%)	<0.001
Diuretics	0 (0%)	2 (8%)	0.2
Anti-anginals	0 (0%)	1 (4%)	0.4
Anti-platelet medications	1 (3%)	8 (35%)	0.003
Anti-coagulants	0 (0%)	6 (26%)	0.003
Anti-arrhythmics	0 (0%)	13 (56%)	<0.001

Chapter Five

Predictors and Appropriateness of Hospitalisations in Patients with Acute Atrial Fibrillation

5.1 Introduction

The global burden of atrial fibrillation (AF) is rapidly escalating ². In Australia, a staggering 203% increase in incidence of AF hospitalisations was seen over the past 15 years. Whereas, admissions for common cardiovascular diseases (CVDs) such as congestive heart failure (CHF) and myocardial infarction (MI) have seen comparatively modest increases of 17% and 79% respectively ²⁵¹. Cost analyses from the UK ²⁴⁹ and the US ⁶⁰³ have shown that the predominant driver of AF related healthcare resource utilisations are due to hospital admissions. Indeed the National Stroke Foundation of Australia annual report estimates the annual cost of AF amounts to 1.25 billion dollars with a substantial amount attributable to in-hospital treatment costs. No dollar value can be placed on the loss of quality of life, activities of daily living and psychological effects of this arrhythmia ⁵⁷⁰.

Recent analyses of emergency physician management practices revealed a significant heterogeneity with regard to the management of acute onset AF ^{604, 605}. There is also growing evidence to suggest that a certain subset of patients; such as those who are not hemodynamically compromised, free of heart failure, with recent onset of AF (lasting 48-72 hours) can be cardioverted and initiated on anti-coagulation in the emergency department (ED) in a cost-effective manner, thus avoiding hospital admissions ^{279, 422, 606-608, 609}. Here, we sought to identify the factors that predict hospital admission for acute AF and determine the proportion of AF hospitalisations that may be avoidable in a tertiary referral hospital.

5.2 Methods

5.2.1 Sample

This was a cohort analysis of consecutive patients presenting to the Royal Adelaide Hospital (RAH), South Australia, with a primary diagnosis of AF. Patients were screened from records of the RAH that admits $\geq 83,000$ patients per annum⁶¹⁰. AF patients were identified as those with a primary ICD-10 code of I48 on discharge or a primary reason of atrial fibrillation on ED notes for non-admitted patients. The study protocol has approval from the Human Research Ethics Committee of the Royal Adelaide Hospital and the University of Adelaide.

5.2.2 Data Extraction

Admitted and non-admitted patients were differentiated as per the hospital coding system. Data for admitted patients were extracted from digital discharge summaries using the patient identifier number from the OACIS system (Version 102, DINMAR 2003, US Inc.). Data for non-admitted patients were extracted from ED separation summaries using the HASTools system, part of the EDIS (Emergency Department Information Systems, Version 8.3, 2008, iSoft).

5.2.3 Baseline Characteristics

All records were obtained and were reviewed by two investigators. Demographic information on age and gender was collected. Indication of current or pre-existing cardiac co-morbidities such as hypertension (HT), congestive heart failure (CHF), coronary artery disease (CAD), valvular heart disease (VHD, including mitral, aortic, tricuspid, pulmonary

stenosis or regurgitation), stroke and/or TIA and peripheral vascular disease (PVD) was obtained. Cardiac diagnoses were cross-referenced against discharge pharmaceuticals to confirm pathology. Current or previous diagnoses of diabetes mellitus (DM), malignancy, rheumatic fever, and prior bleeding were also recorded. CHADS₂ and CHADS₂Vasc scores were calculated to determine stroke risk^{611, 612}. Medication profiles were recorded at presentation and discharge from hospital. Medications were categorised into; rhythm control agents, rate control agents, anti-platelet agents, oral anti-coagulants (OACs), anti-hypertensives, anti-angina medications, cholesterol lowering agents and diuretics as per Table 4. Change to medication profiles (initiation of rate, rhythm control, anti-platelet and anti-coagulant therapy) during hospital or ED stay was also noted. The tests patients underwent during their stay in hospital were noted: if echocardiograms, coronary angiograms, chest x-rays (CXR), electrical cardioversion (CV) and pharmacological CV were performed.

5.2.4 Definitions

For the purpose of this investigation the following definitions were utilised:

- Out of hours presentation: before 7 am, after 6pm or on weekend days) or during hours (7am-6pm weekdays).
- Hemodynamic instability: low systolic BP at <90 mm Hg or ventricular rate of >120 bpm²⁸⁰.
- AF with concurrent infection: presence of infection such as urinary tract infection (UTI), pneumonia, gastroenteritis in conjunction with AF.

- Chronic kidney disease (CKD): categorised as present if estimated glomerular filtration rate (GFR) was $\leq 29 \text{ mL/min}$ ⁶¹³.
- Abnormal liver function tests (LFTs): if any or all the levels of gamma-glutamyl transpeptidase, alkaline phosphatase, or alkaline aminotransferase were elevated more than 3 fold beyond the normal range⁶¹⁴.
- Avoidable hospital admissions were those of 'Low risk AF' patients: AF in the absence of clinical history (or active) congestive heart failure, coronary artery disease, renal compromise, embolism (TIA or stroke), malignancy or valve disease (at least moderate). AF patients free of hemodynamic instability (heart rate >120 bpm or systolic blood pressure <90 mmHg) and associated medical reasons such as an underlying infection (i.e. pneumonia, urinary tract infection, gastroenteritis)²⁷².

5.2.5 Statistics

Normally distributed data were expressed as mean \pm standard deviation (SD). Categorical data were expressed as count and percentage. Differences between admitted and non-admitted patient groups were analysed with either a one way paired ANOVA for continuous data or chi-squared comparisons for count data. Relationships were described using odds ratio and 95% confidence intervals. Both univariate and multivariate models were considered, with only the predictors that satisfied a P-value criterion of $P < 0.05$ in univariate models included into the final multivariate model. Each variable entered into the multivariate analysis was adjusted for all other variables in the analyses to obtain the final

results. Calculations were performed using PASW (Version 21, IBM, Armonk, NY); statistical significance was set at $P < 0.05$.

5.3 Results

5.3.1 Patient Sample

A total of 858 consecutive patients with AF were screened during a 12-month period between 1st of August 2010-1st August 2011. 254 repeat presentations were removed leaving 604 unique patient presentations for AF within the year. A total of 251 patients were excluded, the exclusion criteria and detailed in Figure 1, Table 3 and Appendix 3. The diagnosis of AF was confirmed by an electrocardiogram (ECG) in all cases. The final cohort consisted of 353 patients who had presented to the hospital for the acute treatment of AF via the ED. 224 of the 353 patients were admitted to a hospital ward and the remaining 129 were treated and discharged from the ED.

5.3.2 Baseline Characteristics

The baseline characteristics are outlined in Table 1. The non-admitted patients were significantly younger than the admitted patients ($P=0.002$), with no difference in the gender distribution ($P=0.9$). Among clinical co-morbidities, HT was more prevalent in the admitted group compared to the non-admitted group ($P < 0.001$), as was CHF ($P=0.001$) and DM ($P=0.007$). However, conditions such as CAD, VHD, stroke/TIA and malignancy were present in the same proportions in both groups ($P=0.1$). The number of patients on rhythm control and rate controls medications was similar in both groups ($P=0.6$). The proportion of patients using anti-platelet and anti-coagulant medications was higher among the admitted patients

($P=0.04$). The presentation characteristics of our cohort are summarised in Table 1. The proportions of patients presenting out of hours, with a concurrent infection and with abnormal LFTs was significantly higher in the admitted patient group ($P=0.04$). The CHAD₂VaSc score was higher in the admitted group (<0.001). Hemodynamic instability was also more prevalent in admitted patient group, however this was not significant ($P=0.3$). Proportions of patients with CKD were similar in both groups ($P=0.3$). Lastly, the number of 'low risk' AF patients was significantly higher in the non-admitted patient group ($P<0.001$).

5.3.3 Avoidable Hospital Admissions

'Low risk' AF carried a 2.7 fold [1.6-4.6] increased probability for non-admission ($P<0.001$). However, 'low risk' patients contributed to 14% of admissions (31/224 admitted patients had 'low risk AF'). Admitted 'low risk' AF patients had a shorter hospital stay of 2 [1-3] days than their higher risk counterparts (4[1-5] days, $P=0.005$). Six patients were initiated on anti-platelet, 6 on anti-coagulant, 7 on rate control and 3 on rhythm control therapies. Six patients underwent echocardiograms, 11 underwent chest x-rays, 13 underwent cardioversions (CV, 11 pharmacological and 2 electrical), and 16 reverted to sinus rhythm (SR) (Table 2).

5.3.4 Predictors of Index Hospitalisation

The predictors of admission to hospital are provided in Table 2. There were eight univariate predictors of being admitted to hospital versus being treated and discharged from the ED. Age ($P=0.002$), presence of HT ($P=0.01$), CHF ($P=0.02$), and DM ($P=0.01$) were significant predictors of being admitted to hospital. Similarly, out of hours presentation

($P=0.03$) and AF with concurrent infection, abnormal LFTs and CHADS2VaSc score were also significant univariate predictors of hospital admission ($P<0.001$).

There were two significant multivariate predictors of being admitted to hospital for AF management. Presence of CHF, OR =2.3 (95% CI 1.0-5.2, $P=0.05$) and presenting with AF and a concurrent infection OR=5.2(95% CI 2.4-11.0, $P<0.001$) were predictive of this outcome.

5.4 Discussion

This snapshot of 353 AF patients presenting via the ED for treatment to an Australian tertiary care hospital presents results from patient level data analyses:

1. A significant proportion of patients with acute AF (14%) with low-risk features were admitted when outpatient treatment would have been sufficient.
2. The significant multivariate predictors of admission to hospital were presence of CHF and AF with concurrent infection, showing that more clinically complex patients were preferentially admitted to hospital for treatment of AF.

5.4.1 Avoidable Hospital Admissions for AF

The presence of 'low risk AF' was a significant multivariate predictor of non-admission to hospital. This is indicative that patients who require medical attention due to their clinical profile are being admitted to hospital over low-risk patients. However, the latter group still contributed to a substantial number of hospital admissions. In addition, this subgroup of patients also utilized hospital resources by way of ~2.2 days stay, underwent

procedures and were initiated on treatments that could have been performed in the ED or outpatient setting.

Previously, Mulcahy and co-workers found in an observation study with a new AF patient cohort (n=229), that over one third of patients did not fulfil medical criteria that justified their admission to hospital⁶¹⁵. Additionally, population level analyses of all ED admissions for all subtypes of AF from the United States concluded that although 64% of their cohort was admitted to hospital, only 30% had a high risk of thromboembolism or unstable AF that warranted admission²⁷¹. Our findings differed in number from the aforementioned studies possibly due to the variation in cohort sizes, use of patient as opposed to population level data²⁷¹ and more stringent criteria for medical justification of admission⁶¹⁵. Nevertheless, the conclusion drawn was similar, in that a substantial number of AF patients that do not medically warrant admission to hospital are being admitted for treatment.

Indeed, some interventional studies have attempted to modify the treatment of such subsets of patients in order to reduce unnecessary hospital admissions^{609, 616}. Zimentbaum et al implemented an intervention in the ED, for treating such 'low risk' patients. This involved performance of cardioversions, administration of rate control medications and referral to an outpatient clinic, which saw dramatic reductions in hospital admissions and cost savings amounting to \$1,400 per patient²⁵⁷. Indeed, two separate analyses by Conti et al revealed that it was safe and effective (~90% conversion) to perform pharmacological rhythm conversion for acute AF patients, even those with HT, SHD, mild valve disease and respiratory insufficiencies^{617, 487}. Additionally, the treatment of patients in an intensive

observational unit and their quick referral to an outpatient clinic saw a reduction in hospital admissions notwithstanding the predictors of hospital admission ⁴⁸⁷. Thus, showing that 'low-risk' patients can be treated in the ED or outpatient setting in a safe and cost-effective manner.

5.4.2 Predictors of Hospital Admission

Previous studies examining predictors of hospital admission found that co-existing factors such as age ^{281, 487, 618}, HT, DM ^{281, 487}, CHF ^{281, 487, 618, 619} and infection ⁶²⁰ were significant univariate and multivariate predictors of this outcome in patients with a history of AF ^{487, 618, 619} and recent onset AF ²⁸¹. In keeping with the findings of previous studies, we too found these abovementioned factors and others to be significant univariate predictors of being admitted to hospital for the treatment of AF. However, the multivariate adjustment attenuated the effects of many of these risk factors; with only two factors remaining predictive of hospital admission (Figure 2). This could be attributed to the larger sample sizes in the previous studies ^{487, 619}. Nevertheless, our findings affirm that the presence of CHF and concurrent infection as independent predictors of hospital admission. The co-existence of AF and CHF has been shown to complicate the management of AF patients with regard to greater number of adverse outcomes warranting hospital admission and poorer prognosis in terms of mortality and morbidity ⁶²¹.

5.5 Clinical Implications

In order to reduce the number of unwarranted hospital admissions in AF patients, preventative strategies may play a significant role. Indeed, in the case of a common cardiovascular disease such as CHF, nurse-led interventions have shown great promise

increasing patient self-awareness, and reducing admissions to hospital and improve health outcomes⁶²². Additionally, nurse-led secondary prevention clinics have also been shown to reduce hospital admissions and favourably affected health outlooks of patients with coronary heart disease⁶²³. Further, guideline based nurse-led outpatient AF clinic has been shown to improve cardiovascular outcomes including hospitalisations and mortality⁶²⁴. Further studies are needed to determine how outpatient and allied health interventional strategy can help curb the 'rising tide' of hospitalisations related to AF⁶²⁵. It is likely that implementation of a streamlined follow-up care of low-risk AF patients will help to prevent unnecessary hospitalisations.

5.6 Limitations

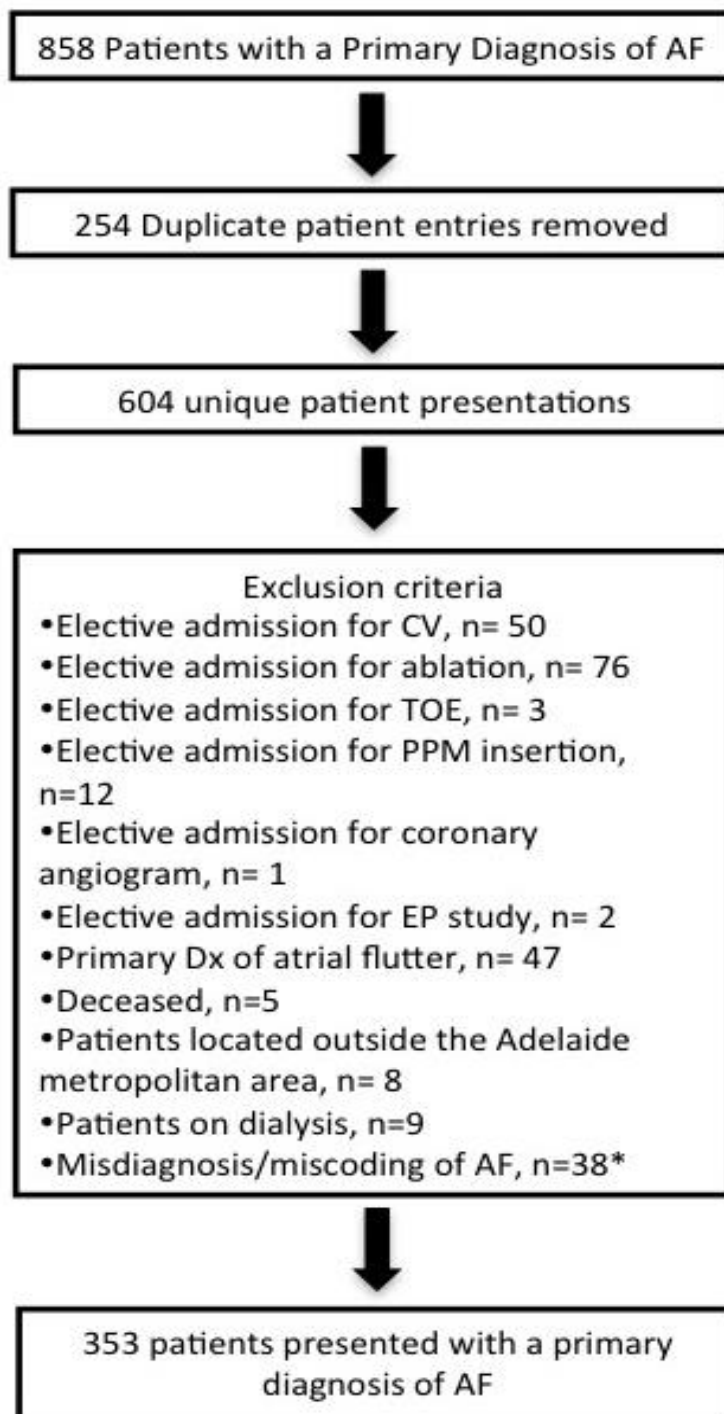
Certain limitations should be considered when interpreting the data of this study. Firstly, as this was a single centre observational study, the characteristics of the patients from our hospital may differ from those presenting and this may affect the generalizability of the results. The duration and severity of diseases, like DM, HT and CHF could not be determined from discharge summaries. This and any medication effects may have made a difference to the outcomes especially since a longer duration and poorly controlled diseases may have increased the effect of a particular disease on hospitalisations, whereas a well-controlled disease may have had less of an impact on these rates. Lastly, the type of AF was not always provided, thus it was not possible to see if perhaps a certain sub type or classification was driving the hospital admissions.

5.7 Conclusions

Majority of AF patients presenting to the ED are being admitted to hospital for treatment, however, reassuringly, most of these are clinically complex AF patients. Nevertheless, ~14% of the admitted patients, are 'low risk'. Our data strongly suggests that this remains an important group to target intervention to reduce health care utilisation. These admissions and their median 2-day bed stay could be prevented by ED management/outpatient strategies or even upstream education to limit ED presentation for these individuals in the first place. Diverting 'low risk' AF to non-hospital based therapies could significantly blunt or even halt the increase in AF hospital activity in Australia.

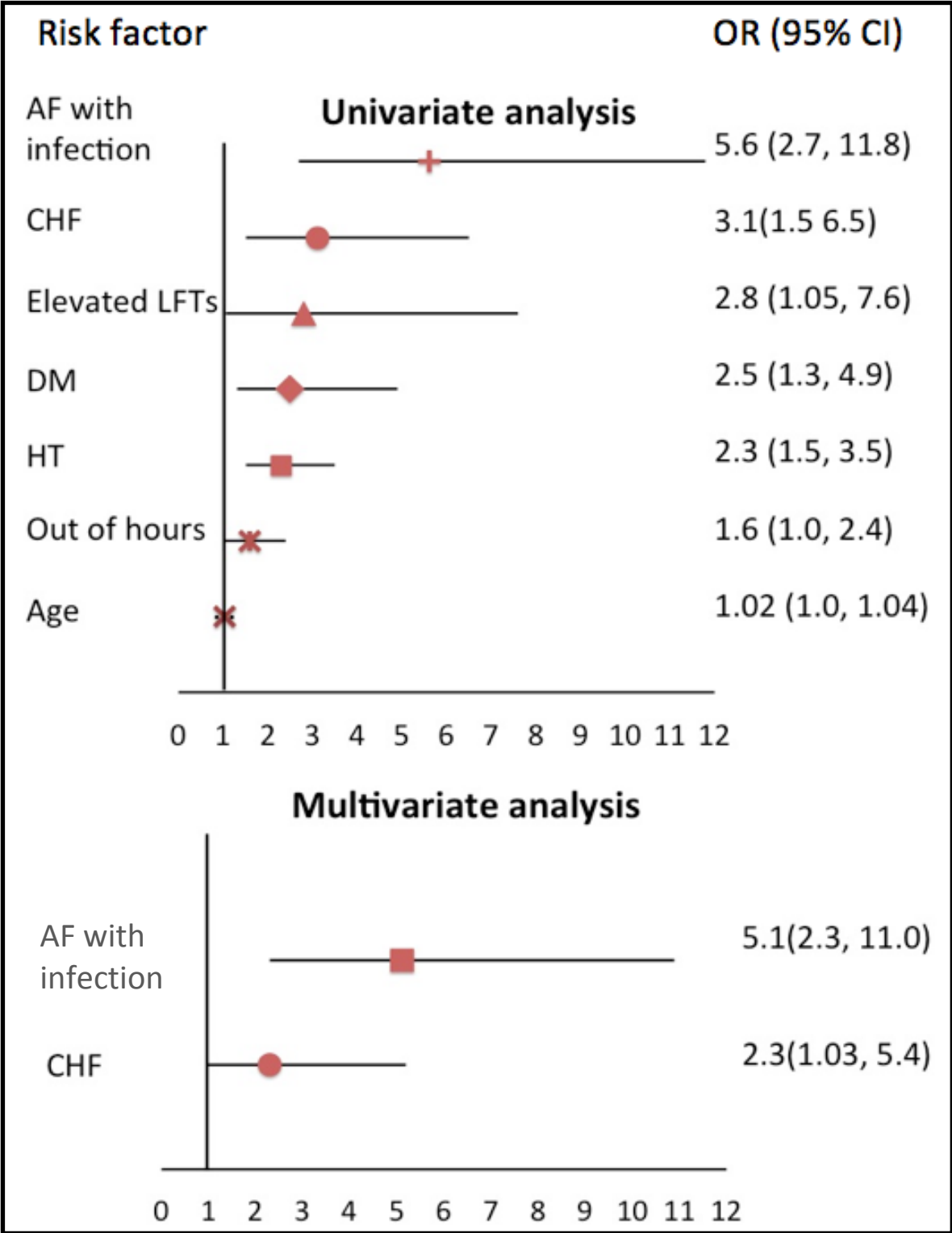
5.8 Figures

Figure 1 Exclusion criteria and patient selection



*The individual diagnoses that were mis-diagnosed as 'AF' (148) are detailed in Table 3.

Figure 2 Univariate and Multivariate Predictors of AF Hospitalization



5.9 Tables

Table 1 Baseline characteristics

	All patients, n=353	Non-admitted, n=129	Admitted, n=224	P value*
Age (years, mean±SD)	70±15	67±15	72±14	0.002
Gender (male), n (%)	163 (46%)	59 (46%)	104 (46%)	0.9
Clinical characteristics				
Hypertension, n (%)	204 (58%)	58 (45%)	146 (65%)	<0.001
Congestive heart failure, n (%)	57 (16%)	10 (8%)	47 (21%)	0.001
Coronary artery disease, n (%)	80 (23%)	27 (22%)	53 (24%)	0.3
Diabetes Mellitus, n (%)	58 (16%)	12 (10%)	46 (20%)	0.007
Valvular heart disease, n (%)	46 (13%)	12 (9%)	34 (15%)	0.1
Stroke/TIA, n (%)	39 (11%)	15 (12%)	24 (11%)	0.8
Active malignancy, n (%)	52 (15%)	14 (11%)	38 (17%)	0.1
Medication profile				
Rhythm control, n (%)	51 (14%)	17 (13%)	34 (15%)	0.6
Rate control, n (%)	113 (32%)	34 (26%)	79 (35%)	0.09
Anti-platelet agents, n (%)	84 (24%)	17 (13%)	67 (30%)	<0.001
Oral anti-coagulants n (%)	78 (22%)	21 (16%)	57 (25%)	0.04
Presentation characteristics				
Days stay	2.8±1.6	0.2±0.17	2.5±3.7	<0.001
Out of hours, n (%)	192 (54%)	61 (47%)	131 (58%)	0.04

Concurrent infection, n (%)	76 (21%)	9 (7%)	67 (30%)	<0.001
Hemodynamic instability, n (%)	90 (58%)	39 (54%)	51 (62%)	0.3
Presence of CKD, n (%)	10 (3%)	4 (3%)	6 (3%)	1.0
Elevated LFTs, n (%)	28 (8%)	5 (4%)	23 (10%)	0.04
CHADS ₂ VaSc Score (mean±SD)	2.5±1.7	1.8±1.5	2.8±1.7	<0.001
Low-risk AF, n (%)	70 (%)	39 (56%)	31 (44%)	<0.001

*P value for non-admitted vs. admitted patients

Table 2 Characteristics of ‘Low-risk’ AF patients

Demographic characteristics	Low-risk admitted patients (n=31)
Age (years, mean±SD)	63±17
Gender (male) n (%)	19 (61%)
Length of stay (days, mean±SD)	2.2±1.5
Out of hours, n (%)	17/31 (55%)
CHADS ₂ VaSc Score, (mean±SD)	1.4±1.4
Investigations	
Echocardiogram, n (%)	6/31 (19%)
Chest x-ray, n (%)	11/31 (35%)
Rhythm management	
Initiated on rhythm control, n (%)	3/31 (9%)
Pharmacological CV, n (%)	11/31 (39%)
Electrical CV, n (%)	2/31 (7%)
Spontaneous reversion to SR, n (%)	16/31 (51%)
Thromboprophylaxis	
Initiated on anti-platelet agents, n (%)	6/31 (19%)
Initiated on oral anti-coagulants, n (%)	6/31 (19%)
Other medications	
Initiated on rate control, n (%)	5/31 (16%)

Table 3 Pharmaceutical agents: drug categories and drug type

Medication category	Medication type
Rhythm Control agents	Class 1A, Class 1B, Class 1C and Class III
Rate lowering agents	Beta-blockers, calcium-channel blockers
Anti-platelet medications	Aspirin, Clopidogrel
Anti-coagulation medications	Warfarin, Dabigatran, Rivaroxaban, Apixiban

Chapter Six

Incidence and Predictors of Rehospitalisation in Patients Presenting to Hospital with Atrial Fibrillation

6.1 Introduction

The recent Global Burden of Disease study provided overwhelming evidence for the rising incidence and prevalence of atrial fibrillation (AF) ². AF patients present with a myriad of cardiac and non-cardiac co-morbidities ²¹ and are at higher risk of developing complications such as stroke/transient ischemic attack (TIA) and congestive heart failure (CHF) ⁶. This increases their mortality rate and their need for medical care, resulting in an ever-increasing economic burden on health care systems ⁶²⁶. The hospital sector bears the majority of the health care costs for AF ^{245, 253, 286}. Certainly, the prevalence of AF hospitalisations in Australia has seen a 155% increase over a 15 year period. When compared to those for myocardial infarction (MI), which increased by 50%, and those for CHF, which decreased by 2%, the figures for AF are even more alarming ²⁵¹.

The burden conferred by hospital admissions is further compounded by repeat encounters by the same individual. Only a few studies have examined the issue of re-hospitalisation, reporting substantially varying estimates of re-hospitalisation rates ^{284, 627, 628}. Additionally, while the cost of these readmissions has been quantified ^{284, 628}, it is unclear as to which patient subgroups may be driving them as these studies were restricted to medical claims data and broad demographics ^{284, 285, 628}.

This study was undertaken to explore the gap in knowledge by using patient level data to prospectively assess whether specific emergency department (ED) or hospital treatment strategies, and patient characteristics are predictive of re-presentation to hospital in patients presenting for acute treatment of AF via the ED.

6.2 Methods

6.2.1 Study Design and Sample

In this cohort study, we included patients presenting with a primary diagnosis of AF to an University teaching hospital that admits $\geq 83,000$ patients per annum⁶¹⁰. AF patients were identified as those with a primary ICD-10 code of I48 on hospital discharge summaries for admitted patients or ED notes for non-admitted patients. The study protocol has approval from the Human Research Ethics Committee of the Royal Adelaide Hospital and the University of Adelaide.

6.2.2 Data Abstraction

Admitted clinical patient data (n=224) were extracted from the individual patient records using the Open Architecture Clinical Information System (OACIS, Version 102, DINMAR 2003, US Inc.). Data for non-admitted patients (n=129) was abstracted from ED separation summaries using the HASTools system, part of the Emergency Department Information Systems (EDIS, Version 8.3, 2008, iSoft). The data extracted are presented in Table 1.

6.2.3 Medication Profile

Medication profiles were recorded at presentation and discharge from hospital. Medications were categorised as follows: rhythm control agents; rate control agents; anti-platelet agents; oral anti-coagulants (OACs); anti-hypertensives; anti-anginal agents; cholesterol lowering agents; and diuretics, detailed in Table 4.

6.2.4 Acute Presentation Characteristics and Management Strategies

For the purpose of this investigation the following definitions were utilised:

- Hemodynamic instability: low systolic BP at <90 mm Hg or ventricular rate of >120 bpm²⁸⁰.
- AF with concurrent infection: presence of infection, namely urinary tract infection (UTI), pneumonia, gastroenteritis in conjunction with AF.
- Reversion back to normal SR: either via electrical or pharmacological cardioversion or spontaneous reversion
- Chronic kidney disease (CKD): categorised as present if estimated glomerular filtration rate (GFR) was ≤ 29 mL/min⁶¹³.
- Abnormal liver function tests (LFTs): if any or all the levels of gamma glutamyltranspeptidase, alkaline phosphatase, or alkaline aminotransferase were elevated more than 3-fold beyond the normal range⁶¹⁴.

- Adherent to current oral anticoagulation (OAC) guidelines⁶²⁹: if they were on OAC and the CHADS₂ score was ≥ 1 or if they were on an anti-platelet medication with a CHADS₂ score ≤ 1 or if they had a valvular prosthesis or mitral stenosis and were on OAC.
- Non-adherent according to current guidelines⁶²⁹: if they were on OAC and the CHADS₂ score was 0, or if they had no history of CAD or PVD but were being treated with an anti-platelet agent. If they had a CHADS₂ score ≤ 1 and being treated with dual anti-platelet agent or if the CHADS₂ score was ≥ 1 and were being treated with OAC and an anti-platelet agent with no history of CAD or PVD. Also, if patients were not on OAC if their CHADS₂ was ≥ 1 , or not on an anti-platelet medication if their CHADS₂ score was ≤ 1 or if they had a valvular prosthesis or mitral stenosis and were not on OAC. Lastly, patients not on OAC for pulmonary embolism or DVT were also included in this category.

6.2.5 Follow-up

Representations to hospital were determined using the Department of Health and Ageing (Institute of Health and Welfare) state-wide patient monitoring system. This system documents every patient coded by a unique identifier across the entire state. If patients had re-presented, the reason for hospital re-admission was extracted from the primary diagnosis as per the ICD-10 coding. Readmissions were categorised into six broad criteria as follows:

- AF readmissions;

- Cardiac readmissions (other than for AF) – these included MI, chest pain, CHF, angina, other cardiac arrhythmias, valve disease, and hypotension;
- Non-cardiac readmissions – these included GI problems, respiratory problems, malignancy, infections, diabetic complications, mental/behavioural problems, OSA, and renal problems;
- Embolic events – these included stroke, transient ischemic attacks (TIAs), cerebral infarcts, and pulmonary embolisms;
- Bleeding events – these included stroke, post procedural haematomas, intracranial haemorrhages, epistaxis and peripheral haemorrhagic events; and
- Falls/syncope – these included dizziness, syncope with collapse, fractures and loss of consciousness.

In contrast to the index hospitalisation, no specific additional data were extracted from the re-hospitalisation event. Deaths and the date of their occurrence were extracted from data-linkage with Births Deaths and Marriages via the South Australian Department of Health state wide patient monitoring system.

6.2.6 Statistical Analysis

To identify predictors of cumulative all-cause and AF readmissions, negative binomial regression models (that allowed multiple readmissions per patient) were fitted. In the models the natural logarithm of follow-up for each patient was included as an offset variable. Relationships were described using rate ratios and 95%

confidence intervals. Both univariate and multivariate models were considered, with only predictors that satisfied a P-value criterion of $P < 0.05$ in univariate models included into the final multivariate model. Calculations were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). Logistic regression was used to determine the univariate predictors of death during follow-up and analyses were carried out using SPSS PASW (Version 21, IBM, Armonk, NY). A two-tailed P-value of < 0.05 was considered statistically significant.

6.3 Results

6.3.1 Patient Sample

A total of 858 AF patients were identified during a 12-month period between 1st of August 2010-1st August 2011. 254 entries were removed due to repeat presentations leaving 604 unique patient admissions for AF within the year. A total of 251 patients were excluded as detailed in Figure 1, Table 4 and Appendix 3. AF diagnosis was confirmed by an electrocardiogram (ECG) for all patients. The final cohort consisted of 353 patients who had presented to the hospital for the acute treatment of AF via the ED, 224 of which were admitted to a hospital ward and 129 who were treated and released from the ED.

6.3.2 Baseline Characteristics

Table 1 summarises the baseline characteristics of the patient cohort. The average age of the cohort was 71 ± 15 years, with slight majority being females. The average number of days of hospital stay was 2.5 ± 3.7 . Hypertension (HT) was the most common co-morbidity, present in 59% of the patients; followed by coronary artery disease (CAD), congestive heart failure (CHF), diabetes mellitus (DM), and valvular heart disease (VHD). Nearly one third of the cohort did not present with a history of any of the aforementioned co-morbidities. The numbers of patients presenting with a history of stroke/TIA, and history of or current malignancy were small. Likewise, a history of rheumatic heart disease and peripheral vascular disease (PVD) was uncommon among our patients. More than half of the cohort (54%) was hemodynamically compromised. Concurrent infection was present in 22% of our cohort while a high proportion of patients (51%) were non-adherent to their OAC medication according to their CHADS₂ score.

6.3.3 Burden of Readmissions

The sample was followed for a mean of 1.3 ± 0.4 years with a total follow-up of 475 patient years. The mean rate of all-cause readmissions per year was 1.36 (95% CI 1.07-1.66). One hundred and seventy-eight (51%) patients readmitted and were responsible for 461 unique readmissions or a mean 1.3 readmissions per patient. Forty-two patients were readmitted twice, 28 readmitted three times and 37 readmitted \geq four times.

6.3.4 Primary Reasons for Readmissions

Figure 2 demonstrates the primary reasons for readmissions to hospital. Of the total number of patients with readmissions, 73 were coded primarily for the treatment of AF. These individuals contributed to 127 (26%) readmissions, as 28 patients readmitted ≥ 2 times. This equates to 0.30 (95% CI 0.19-0.41) AF readmissions per patient per year. Cardiac readmissions, other than AF, accounted for 20%, whereas non-cardiac representations amounted to 44%. Readmissions for bleeding events (3%), embolic events (3%) and falls/syncope (4%) made up the small remainder of readmissions in this cohort.

6.3.5 Predictors of All-cause Readmissions to Hospital

Table 2 shows the univariate and multivariate predictors of readmission. The only significant univariate predictors were history of PVD ($P=0.02$), CKD ($P=0.01$), high CHADS₂ score ($P=0.003$), high CHADS₂VaSc score ($P=0.001$), and rate control medication on discharge ($P=0.02$). Reversion to sinus rhythm (SR) was a significant predictor of non readmission ($P=0.04$). On the other hand, age, male gender and co-morbidities such as history of HT, CHF, CAD, stroke/TIA, VHD, DM, and malignancy ($P>0.05$) were not predictive of all-cause readmissions. Likewise, presenting with rapid AF, low systolic BP, abnormal LFTs, being discharged on rhythm control medication and adherence to OAC guidelines were not predictive of repeat hospitalisations ($P>0.05$). The multivariate analysis showed that discharge on rate lowering medication RR=1.6,

(95% CI 1.0-2.4, P=0.02) was predictive of readmissions and reversion to SR RR=0.67, (95% CI 0.4-0.6, P=0.04) was protective against this outcome.

6.3.6 Predictors of Atrial Fibrillation Readmissions

The univariate and multivariate predictors of AF readmissions are presented in Table 3. Younger age and discharge on rhythm control medication were univariate and multivariate predictors of AF readmissions. Interestingly, male gender, cardiovascular or non-cardiovascular co-morbidities and/or presentation characteristics did not predict AF re-admission during the follow-up.

Every one year decrease in age, was associated with a 2% increase in risk of AF readmission, RR = 0.98, (95% CI 0.96-0.99, P=0.03). Patients readmitting to hospitals for AF had a lower mean age of 65 ± 15 years in contrast to those who did not (73 ± 14 years). Additionally, patients discharged on rhythm control medication were more likely to return to hospital for the treatment of AF during the follow-up period, RR=2.30 (95% CI 1.31-3.97 P=0.003).

6.3.7 Mortality Associated with Presentation with AF

Thirty-six (10.2%) patients died during the follow-up period. Twenty-four (66%) of these deaths occurred during the first 6 months. The remainder occurred over the rest of the follow-up period.

6.4 Discussion

This was a prospective medical record review of 353 patients with an index presentation of AF, who were followed up for a mean of 1.3 ± 0.4 years and we found:

1. One hundred and seventy-eight (51%) patients were responsible for 461 readmissions whereby 26% were for AF.
2. The independent predictors of readmission to hospital were discharge on rate lowering medication while reversion to sinus rhythm was protective against this outcome.
3. The independent predictors of AF-specific rehospitalisations were discharge on rhythm control medication and younger age.
4. During the follow-up period, 36 deaths (10.2% of the cohort) were recorded.

6.4.1 Predictors of All-cause Readmission to Hospital

Amin et al reported rehospitalisations rates of ~40% using pharmaceutical claims database^{284, 628} and Naccarelli et al reported rates of 38% using a hospital claims database⁶³⁰. Although similar to what we reported, these may have differed due to the use of population level data with no confirmation of AF diagnosis^{284, 628, 630}, which could have led to under representation of the actual number of AF cases and hence number of readmissions. Additionally, despite high numbers of patients readmitting, previous studies^{284, 628, 630} have not elucidated the specific predictors of rehospitalisations. We found that being discharged on rate lowering medication was associated with an increased likelihood of representation, while reversion to normal SR

was associated with a reduced likelihood of readmissions. The regulation of heart rate has been purported as a result of a variety of rate versus rhythm control trials to be equivalent to rhythm control ^{261, 413, 631, 632}. However, a recent observational study comparing the relative effectiveness of these treatments in the general population found that patients administered with rate control tended to have an over-representation of co-morbidities and were at an advanced age ⁴¹⁶. It could be speculated that these underlying diseases place these individuals at an increased risk of readmitting.

6.4.2 Atrial Fibrillation Readmissions

More than one fourth (26%) of our readmissions were due to a primary diagnosis of AF following their index presentation for the same (Figure 2). This is consistent with other studies that have studied AF specific rehospitalisation rates. Indeed, both studies conducted by Amin and co-workers found similar AF related rehospitalisation rates, making it the most common cause of rehospitalisation amongst AF patients ^{284, 628}. This was found to be the case even among patients who were newly diagnosed with AF ⁶³³.

Interestingly, our analyses revealed younger patients were more likely to return to hospital. In fact, with every one-year decrease in age of the patient the likelihood of returning to hospital for the treatment of AF was increased by 2% (Table 3). Only two other studies found a trend between age and increasing rates of AF rehospitalisation; reporting conversely, increasing age predicted representation to hospital ^{633, 634}. This observation could be due to the fact that younger patients, may be

earlier in the course of their disease progression and hence more prone to symptomatic paroxysms of AF⁶³⁵ that cause them to not only return to hospital, but to do so frequently. Certainly, Miyasaka et al found paroxysmal over persistent or permanent AF to be a significant independent predictor of rehospitalisation among newly diagnosed AF patients⁶³³; while another study found that younger patients tend to present in paroxysmal AF⁶³⁶ Also, studies looking at predictors of AF control showed that older age (≥ 75 years) and longer time since AF diagnosis (at least >12 months) were significant predictors of better rhythm control and improved symptomatic status^{637, 638}.

Patients discharged on rhythm control medication after their index hospitalisations were more likely to return to hospital with AF. This method of management is usually a first line of treatment favoured for younger, symptomatic, patients, as also for patients with recurrent AF capable of tolerating these drugs^{261, 639}. However, there can be issues with drug tolerance, toxicity and efficacy¹. Indeed, rhythm control medication was deemed to be an independent predictor of unstable AF, by way of symptomatic status, complications and need for medical interventions⁶⁴⁰.

6.4.3 Mortality

Population base-studies, including the Framingham have shown that AF independently and significantly increases the risk of mortality in its sufferers^{7, 21}. Moreover, hospital diagnosis of AF and admission for AF was also associated with a tangible risk of death^{641, 254}. Reassuringly, though, numerous studies that have

examined the temporal trends of hospital mortality in AF patients have found a significant decrease in this outcome⁶⁴¹. Indeed, a recent study of in-hospital trends in AF patients found that over the last decade, even though the hospital burden of AF grew, the in-hospital mortality dropped by nearly 30%²⁵⁵. Nevertheless, our study reported a substantial mortality of 10% at more than 1 year follow-up that may be due to advanced age and co-existing diseases²⁵⁴ such as CHF, which have been known to significantly increase the risk of death in AF patients⁶⁴².

6.5 Clinical Implications

It is evident that the hospital burden conferred by AF is on the rise²⁵¹ as is the additional burden contributed by repeat presentations and hospital readmissions^{284, 285}. This study has identified that many patients re-present for AF and has observed a potential sub-group of AF patients that are particularly vulnerable to repeat hospitalisations and hence may be targeted with interventions, which may possibly help to reduce this public health burden. Interventions such as intensive observation units, education programs and specialised personalised clinics have shown some promise in reducing hospital admissions in AF patients^{258 487}. Indeed, Inglis et al implemented a home-based, nurse-led intervention for AF patients with CHF. Patients managed with specialised post-discharge care had better event-free survival, represented to hospital less and also had fewer fatalities as opposed to those managed with usual post-discharge care⁶⁴³. If similar interventions are targeted at patient sub-groups likely to readmit to hospital, it may translate into reduced readmissions rates for AF and thus reduced unnecessary health care utilisation.

6.6 Limitations

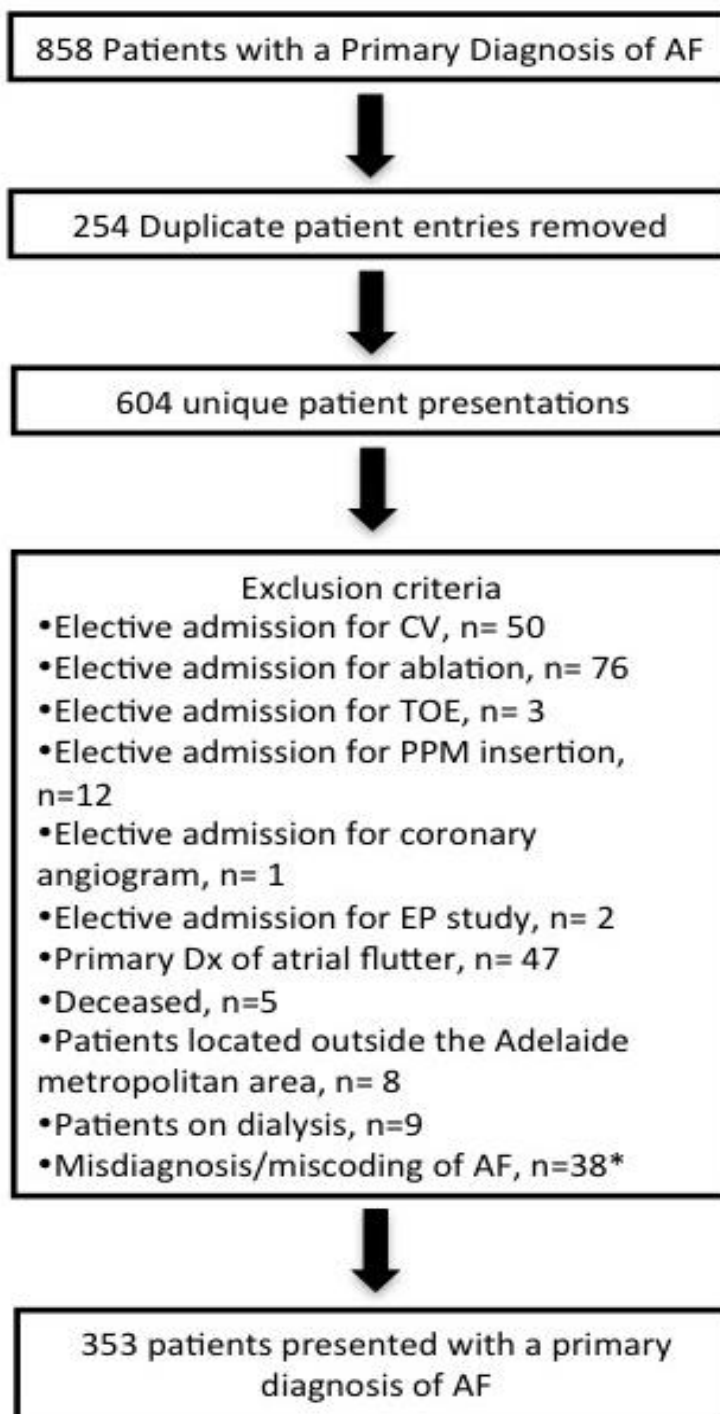
There are certain limitations that should be considered when interpreting the data of this study. Firstly, this was a single centre observational study and hence the results should be interpreted with caution, given that the characteristics of patients presenting to our centre may vary to those presenting to other centres. The specific reasons for death could not be obtained from the Births Deaths and Marriages via the SA Department of Health, and thus we could not determine how many patients in our cohort died from AF related causes or other competing risks. The type of AF, at baseline and at the time of representation could not be determined. Lastly, with regards to reasons for all-cause and AF readmissions, we used ICD-10 codes to determine these, leaving room for coding errors.

6.7 Conclusions

Following an index presentation for AF, over the following 12 months 51% of our cohort represented to hospital and 26% of these were for AF. Discharge on rhythm control medication and younger age increased likelihood of readmitting for AF. These findings highlight the urgent need for early intervention, targeted education and specialised clinics to curtail the increasing volumes of patients representing to hospital with AF.

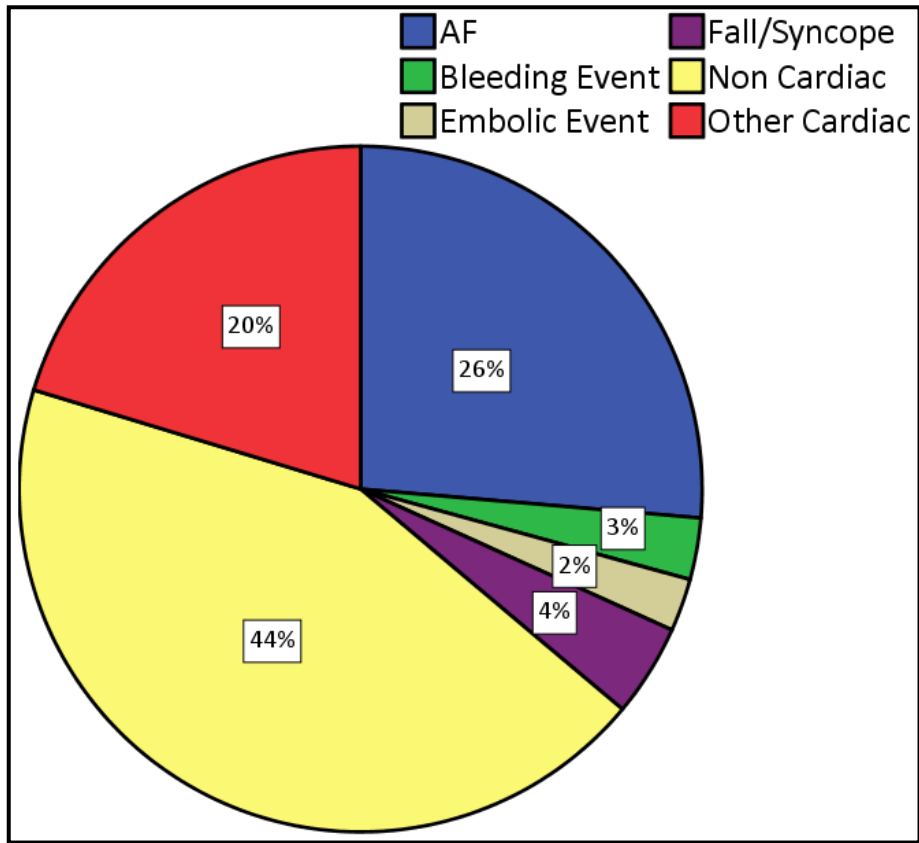
6.8 Figures

Figure 1 Exclusion criteria and patient selection



*The individual diagnoses that were mis-diagnosed as 'AF' (148) are detailed in Table 4

Figure 2 Reasons for readmissions



6.9 Tables

Table 1 Baseline characteristics: full patient cohort

Demographic Characteristics	All patients, n=353
Age (years, mean±SD)	71±15
Gender (male) n (%)	163 (46%)
Acute Presentation Characteristics	
Hospital days stay (mean±SD)	2.5±3.7
AF with concurrent infection n (%)	76 (22%)
Hemodynamic instability n (%)	192 (54%)
Non-adherent to OAC guidelines n (%)	179 (51%)
Clinical Characteristics n (%)	
Hypertension	203 (59%)
Congestive heart failure	57 (17%)
Coronary artery disease	81 (24%)
Diabetes mellitus	58 (17%)
Valvular heart disease	46 (13%)
None of the above co-morbidities	107 (30%)
History of Stroke/TIA	39 (11%)
History of Malignancy	52 (15%)
History of Rheumatic Fever	7 (2%)
Peripheral vascular disease	7 (2%)
CHADS ₂ VaSc score	2.5±1.7
Medication Profile on presentation n (%)	
Rhythm control	51 (10%)
Rate lowering	113 (32%)
Anti platelet	84 (24%)
Anti coagulant	78 (22%)
Anti hypertensive	132 (37%)
Anti anginal	26 (7%)
Cholesterol lowering	88 (25%)
Diuretic medication	55 (15%)

Table 2 Univariate and multivariate predictors of rehospitalisations

Predictor Variable	Uni-variate Analysis Rate Ratio (95% CI)	P value	Multi-variate Analysis Rate Ratio (95% CI)	P value
Demographics				
Age	1.00[0.99-1.10]	0.25	-	
Gender (Females vs Males)	1.16[0.82-1.66]	0.38	-	
Cardiovascular Risk Factors/Co-morbidities				
Hypertension	1.35[0.94-1.94]	0.10	-	
Congestive heart failure	1.28[0.79-2.06]	0.31	-	
Coronary artery disease	1.29[0.85-1.94]	0.21	-	
Stroke/ TIA	2.03[1.20-3.45]	0.44	-	
Valvular heart disease	1.16[0.71-1.89]	0.81	-	
Non-Cardiovascular Risk Factors/Co-morbidities				
Diabetes mellitus	1.36[0.86-2.15]	0.19	-	
Malignancy	1.09[0.67-1.78]	0.71	-	
Rheumatic Fever	1.34[0.44-4.13]	0.60	-	
Peripheral vascular disease	3.74[1.23-11.35]*	0.02	2.9[0.9-9.2]	0.06
Presentation Characteristics				
CHADS ₂ (score >2)	1.23[1.07-1.42]*	0.003	1.04[0.6-2.7]	0.85
CHADS ₂ VaSc (score >2)	1.18[1.06-1.30]*	0.001	1.02[0.7-1.4]	0.85
Chronic kidney disease	1.67[1.10-2.53]*	0.01	1.3[0.8-2.0]	0.20

Abnormal liver function tests (LFTs)	1.68[0.83-3.37]	0.14	-	
Rapid AF (ventricular rate >120 bpm/min)	1.32[0.90-1.92]	0.14	-	
Low systolic blood pressure (<90mmHg)	0.72[0.35-1.48]	0.38	-	
Discharge Characteristics				
Rate Control on discharge	1.72[1.16-2.52]*	0.005	1.60[1.0-2.4]†	0.02
Rhythm Control on discharge	0.87[0.57-1.34]	0.54	-	
OAC guideline adherent	1.19[0.8-1.7]	0.34	-	
Reversion to SR	0.61[0.42-0.88]*	0.008	0.67[0.4-0.9]†	0.04

CKD=chronic kidney disease, LFTs=liver function tests. CI denotes confidence interval.*Denotes variables that had P<0.05 in the univariate analysis, † Denotes variables that had P<0.05 in the multivariate analysis.

Table 3 Univariate and multivariate predictors of AF specific rehospitalisations

Predictor Variable	Univariate Analysis Rate Ratio (95% CI)	P-value	Multi-variate Analysis Rate Ratio (95% CI)	P value
Demographics				
Age	0.97[0.96-0.99]*	0.01	0.98[0.96-0.99]†	0.03
Gender (Females vs Males)	0.89[0.53-1.48]	0.66	-	
Cardiovascular Risk Factors/Co-morbidities				
Hypertension	0.94[0.55-1.58]	0.82	-	
Congestive Heart Failure	0.79[0.37-1.69]	0.55	-	
Coronary Artery Disease	1.17[0.64-2.13]	0.59	-	
Stroke/ TIA	0.69[0.28-1.73]	0.44	-	
Valvular Disease	1.60[0.78-3.28]	0.19	-	
Non-Cardiovascular Risk Factors/Co-morbidities				
Diabetes Mellitus	1.06[0.53-2.10]	0.86	-	
Malignancy	1.02[0.49-2.08]	0.95	-	
Rheumatic Fever	1.16[0.20-6.55]	0.86	-	
Peripheral Vascular Disease	1.18[0.15-8.93]	0.87	-	
Presentation Characteristics				
CHADS ₂	0.81[0.66-1.01]	0.06	-	
CHADS ₂ Vasc	0.88[0.75-1.03]	0.11	-	
CKD	0.88[0.45-1.72]	0.72	-	
LFTs	1.63[0.60-4.41]	0.33	-	

Creatinine	0.62[0.24-1.55]	0.30	-	
Rapid AF (ventricular rate >120 bpm/min)	1.04[0.59-1.82]	0.89	-	
Low systolic blood pressure (<90mmHg)	0.43[0.12-1.51]	0.19	-	
Discharge Characteristics				
Rate Control on Discharge	1.68[0.93-3.03]	0.07	-	
Rhythm Control on Discharge	2.69[1.55-4.64]*	0.0004	2.30[1.31-3.97]†	0.003
OAC guideline adherent	1.15[0.66-1.99]	0.60	-	
Reversion to Sinus Rhythm	0.84[0.47-1.47]	0.54	-	

CKD=chronic kidney disease, LFTs=liver function tests. CI denotes confidence interval. *Denotes variables that had P<0.05 in the univariate analysis, † Denotes variables that had P<0.05 in the multivariate analysis.

Table 4: Pharmaceutical agents: drug categories and drug type

Medication category	Medication type
Rhythm Control agents	Class 1A, Class 1B, Class 1C and Class III
Rate lowering agents	Beta-blockers, calcium-channel blockers
Anti-platelet medications	Aspirin, Clopidogrel
Anti-coagulation medications	Warfarin, Dabigatran, Rivaroxaban, Apixiban
Anti-hypertensive medications	Beta blockers, calcium-channel blockers, Alpha blockers, Alpha and beta blockers, Angiotensin-converting enzyme (ACE) inhibitors, Angiotensin II blockers, Antiadrenergic agents, vasodilators
Anti-anginal agents	Beta blockers, nitrates and calcium channel blockers
Cholesterol lowering agents	Statins, cholesterol absorption inhibitors, bile-acid-binding resins and fibrates
Diuretics	Thiazide diuretics, potassium-sparing diuretics, loop diuretics

Chapter Seven

Final Discussions

This thesis presents the differential impact of the main risk factors on the probability of developing atrial fibrillation (AF). It provides novel insights into the levels and types of substrate modification that are present at the onset of the arrhythmia. Lastly, it identifies the discreet AF patient subgroups that significantly burden the hospital system. Understanding how, and to what extent each risk factor impacts the likelihood of developing AF and what derails normal sinus rhythm into AF at the outset of disease evolution may help improve management of this arrhythmia. This may play an important role in reducing the incidence and prevalence of this burgeoning epidemic and in turn reduce health care utilisation.

The systematic review and meta-analysis surrounding the literature on ten key risk factors for AF showed that congestive heart failure (CHF) exerted the greatest quantitative impact on the risk of developing incident AF. Nevertheless, when this effect was put into context in terms of the proportion of AF cases that could be prevented if a modifiable risk factor was to be eliminated; hypertension was shown to have the greatest impact due to its high prevalence in the Australian population. Thus, Chapter 2 acknowledged that AF is a complex arrhythmia affected by numerous factors, which, if modified could potentially reduce the cases of incident AF and the severity of existing arrhythmia.

The characterisation of the substrate levels in new onset AF is presented in Chapter 3. The larger proportion of new AF patients that presented with paroxysmal AF were found to have more frequent ectopic activity and more closely coupled atrial premature beats compared to age and gender matched arrhythmia free controls. Whereas, the smaller proportion of patients that presented with persistent AF showed evidence of structural remodelling in the form of left atrial dilatation and reduced left ventricular systolic function compared to controls. This indicated that newly diagnosed paroxysmal AF may be ‘trigger fibrillators’, while newly diagnosed persistent AF may be ‘substrate fibrillators’⁶⁴⁴. Furthermore, Chapter 4 examined the potential risk of thromboembolic events that may exist in the newly diagnosed AF patients. We found elevated levels of biomarkers that suggested existence of localised and systemic inflammation, endothelial dysfunction and abnormal levels of extracellular matrix remodelling compared to normal control subjects. This was indicative of an increased risk of stroke at an early stage of the arrhythmia disease process. These findings revolving around the various detrimental changes that are present at the onset of AF may help treat and manage this arrhythmia more effectively.

Improved management of AF could in turn reduce the burden it confers on the hospital system. Indeed, Chapter 5 examined the proportion of AF hospital admissions that could be avoided and identified the patient characteristics that increased likelihood of admission to hospital. Fourteen per cent of the cohort of 353 (patients with a primary index presentation for AF) were ‘low- risk AF’ and did not medically warrant hospital admission. Additionally, patients with concurrent congestive heart

failure and infection were significantly more likely to be admitted to hospital for treatment. These data highlighted a need for new management strategies to avoid admitting patients that could safely and effectively be managed in the emergency department or outpatient setting; which could in turn potentially curb the rising AF hospitalisation rates in Australia.

While the rates of hospital admission for AF are rising, this burden is further compounded by repeat admissions by patients. Chapter 6 attempted to identify discreet sub-categories of patients that were more prone to burdening the hospital system with readmissions. We found that 51% of the cohort of 353 patients with an index presentation for AF represented over a ~1 year follow-up period. Moreover, 26% of these representations were for the treatment of AF. Younger patients and those discharged on rhythm control medication were the significant drivers of this outcome. This patient level data provides an impetus for early intervention and specialised clinics targeted at the vulnerable patients in order to curtail the rising numbers of repeat admissions to hospital for AF treatment.

Chapter Eight

Future Directions

Enhancing the understanding of the differential impact that the main risk factors exert on the likelihood of developing AF is important. The data underscore the importance of risk factor modification as a key to managing this multi-faceted arrhythmia. Recent interventions in obesity⁵¹⁹, hypertension⁵¹⁵ and left ventricular hypertrophy⁶⁴⁵ have shown great promise towards the benefits of implementing risk factor modification. There was reversal/reduction of the extent of atrial remodelling⁶⁴⁵, improved patient outcomes⁵¹⁹ and even a reduced incidence of AF⁵¹⁵. If the main risk factors are managed appropriately, this could have a substantially favourable impact on the risk of developing incident AF. Additionally, once the arrhythmia has developed, it is essential to treat it appropriately so as to reduce the burden on the individual sufferer and on health care usage. Since our study showed evidence of electrical abnormalities in new paroxysmal AF and structural anomalies in the new persistent AF; employing targeted therapies for the different subtypes of AF may lead to improved outcomes. Individualised therapies such as pulmonary vein isolation (PVI) to eliminate ectopic triggers in paroxysmal AF patients may reduce AF inducibility. Substrate modification by treating risk factors such as hypertension and congestive heart failure, diseases known to induce detrimental structural changes in persistent AF patients may help prevent further remodelling. In addition, there is also a very tangible elevated stroke risk that exists in the newly diagnosed AF patients due to abnormal

markers of inflammation, endothelial dysfunction and extracellular matrix remodelling at this early stage of their disease. Thus, the aforementioned strategies should be incorporated in conjunction with appropriate stroke prophylaxis. If this sub-group of newly diagnosed AF patients are not managed appropriately at this nascent stage of their arrhythmia evolution, they are likely to go on to burden the health care system. Thus, our data also highlight the need to re-examine and perhaps re-think the existing management practices for AF especially due to the current rising trends in AF hospital admissions²⁵¹ and readmissions²⁸⁴. For instance, the use of observational units⁴⁸⁷ and ED interventions²⁵⁷ have been shown to expedite treatment of AF patients by circumventing already burdened hospitals. Additionally, educational nurse-led interventions for patients suffering from common cardiovascular illness such as congestive heart failure^{258, 643}, are breaking new ground and making considerable positive changes to the way this cardiovascular disease is managed by reducing tertiary health care utilisation. Such similar approaches could be adopted for AF patient care in order to curb the high burden on hospital systems and curtail the public health epidemic of this arrhythmia.

Appendix 1

Structured interview: AF patients

1. When were you diagnosed with atrial fibrillation?

Date

2. Is this your first episode of atrial fibrillation?

Yes/No

2. Have you been diagnosed with atrial flutter?

Yes/No

3. Have you been diagnosed with other heart rhythm disorders?

Yes/No

What heart rhythm disorder was it (eg. SVT)

3. Have you had a heart attack?

Yes/No

4. Have you ever had a stent?

Yes/No

5. Have you had CABG?

Yes/No

6. Have you suffered from angina – sporadic chest pain that requires medication to treat?

Yes/No

7. Have you been diagnosed with heart failure?

Yes/No

8. Have you had you ever had a stroke?

Yes/No

Do you know what kind?

Hemorrhagic (bleeding)/ Embolic (occlusive/clot)

7. Have you been had you ever had a TIA or a mini-stroke?

Yes/No

8. Have you been diagnosed with another thrombo-embolic (ie blood clotting) complication?

Yes/No

(Deep vein thrombosis/Pulmonary embolism/ Peripheral embolism/ Other embolism location)

9. Have you been diagnosed as having high blood pressure?

Yes/No

10. Have you been diagnosed as having high cholesterol?

Yes/No

11. Have you been diagnosed with diabetes?

Yes/No

Type I/Type II

12. Have you been had an abnormal thyroid function test? (Hypo/Hyper)

Yes/No

13. Have you been had you ever suffered from rheumatic fever?

Yes/No

14. Have you been had you ever undergone any cardiac valve replacements?

Yes/No

Which valve has been replaced?

Mitral valve/Tricuspid valve/Aortic valve/Pulmonary valve

15. Have you been had you ever undergone general cardiac surgery?

Yes/No

Why?

16. Have you been had you ever undergone a heart pacing device implantation?

Yes/No

What kind?

Pacemaker/ICD – defibrillator/Cardiac resynchronisation

17. Have you been diagnosed with a malignancy (cancer)?

Yes/No

Are you currently in remission?

Yes/No

Have you/Will you ever undergo chemotherapy?

Yes/No

Have you/Will you ever undergo radiotherapy?

Yes/No

18. Have you been diagnosed with renal failure/impairment?

Yes/No

Renal Failure or CKD?

19. Have you been had you ever smoked cigarettes/cigars/pipes?

Yes/No

Current smoker/Ex-smoker

20. Have you been diagnosed with sleep apnea?

Yes/No

Are you using CPAP?

Yes/No

21. Are you on any cardiac medications at the present time?

List:

Structured interview: Community Controls

1. Have you been diagnosed with atrial flutter?

Yes/No

2. Have you been diagnosed with other heart rhythm disorders?

Yes/No

What heart rhythm disorder was it (eg. SVT)

3. Have you had a heart attack?

Yes/No

4. Have you ever had a stent?

Yes/No

5. Have you had CABG?

Yes/No

6. Have you suffered from angina – sporadic chest pain that requires medication to treat?

Yes/No

7. Have you been diagnosed with heart failure?

Yes/No

8. Have you had you ever had a stroke?

Yes/No

Do you know what kind?

Hemorrhagic (bleeding)/ Embolic (occlusive/clot)

7. Have you been had you ever had a TIA or a mini-stroke?

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8. Have you been diagnosed with another thrombo-embolic (ie blood clotting) complication?

Yes/No

(Deep vein thrombosis/Pulmonary embolism/ Peripheral embolism/ Other embolism location)

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18. Have you been diagnosed with renal failure/impairment?

Yes/No

Renal Failure or CKD?

19. Have you been had you ever smoked cigarettes/cigars/pipes?

Yes/No

Current smoker/Ex-smoker

20. Have you been diagnosed with sleep apnea?

Yes/No

Are you using CPAP?

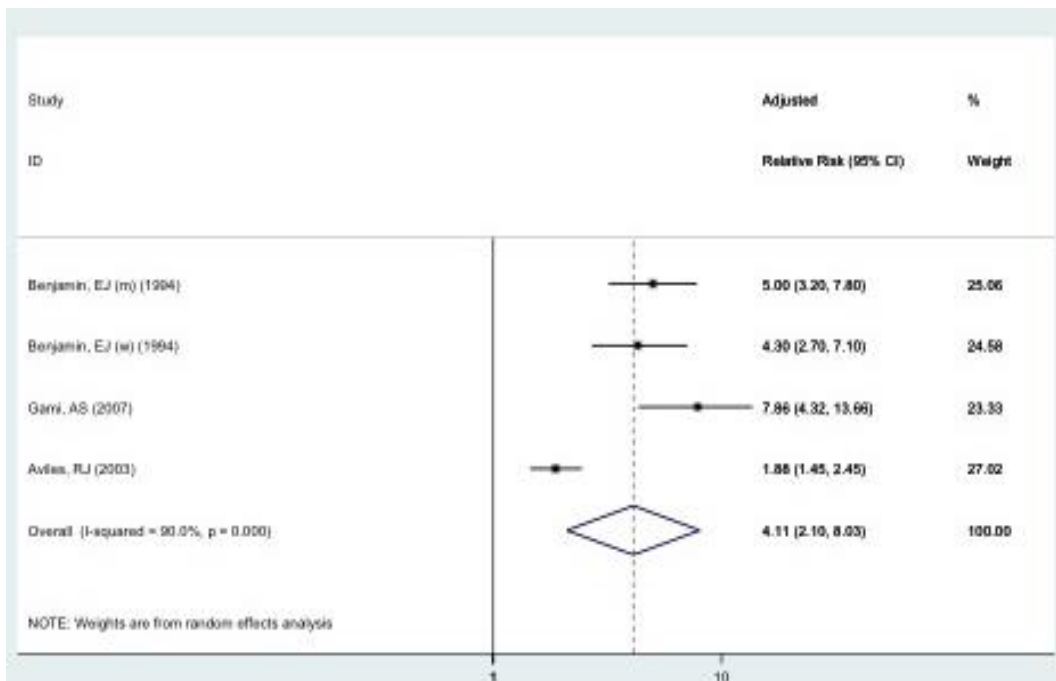
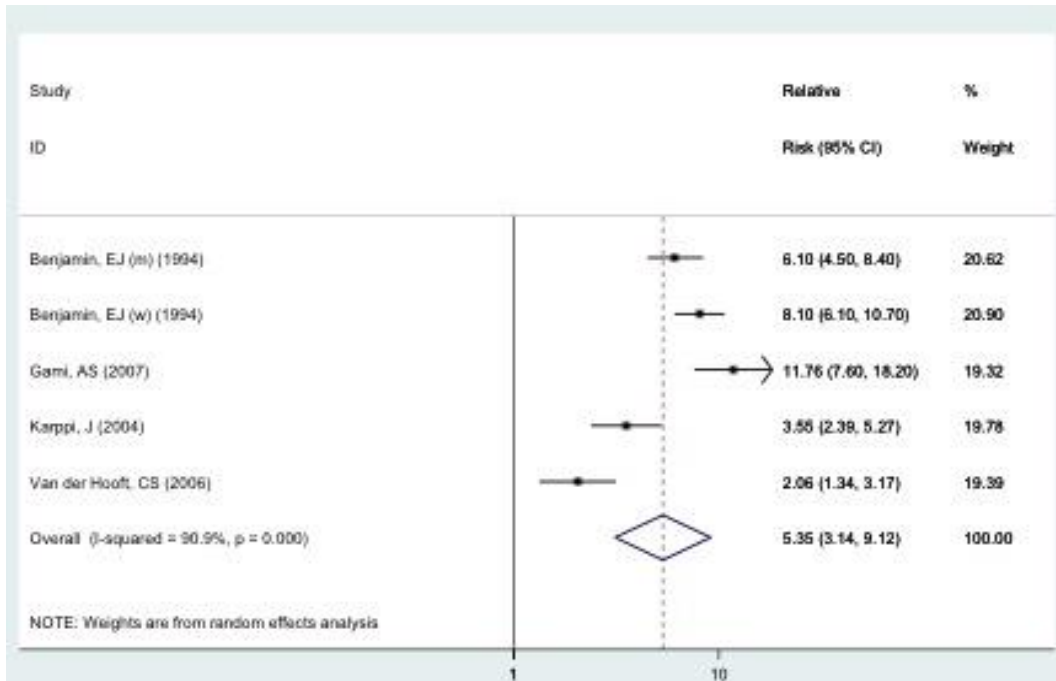
Yes/No

21. *Are you on any cardiac medications at the present time?*

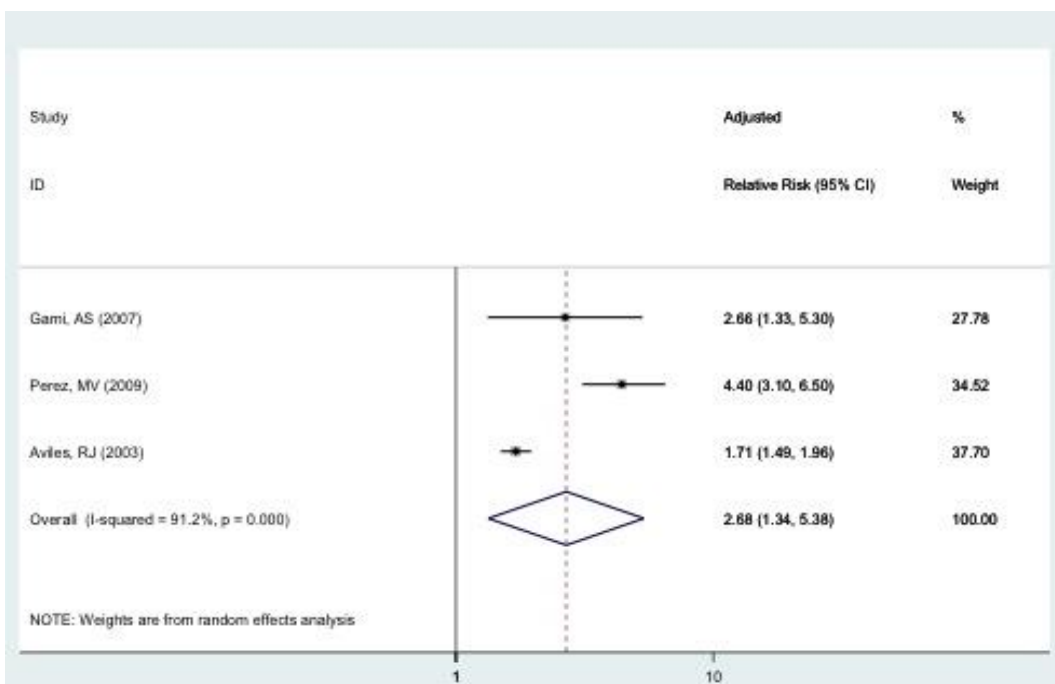
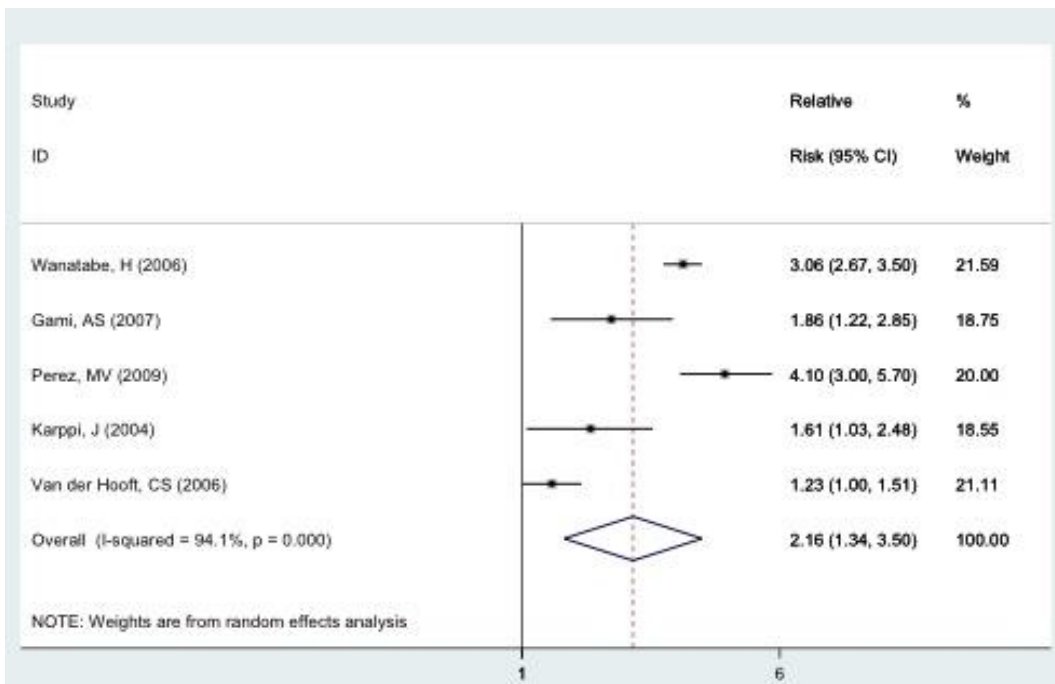
List:

Appendix 2

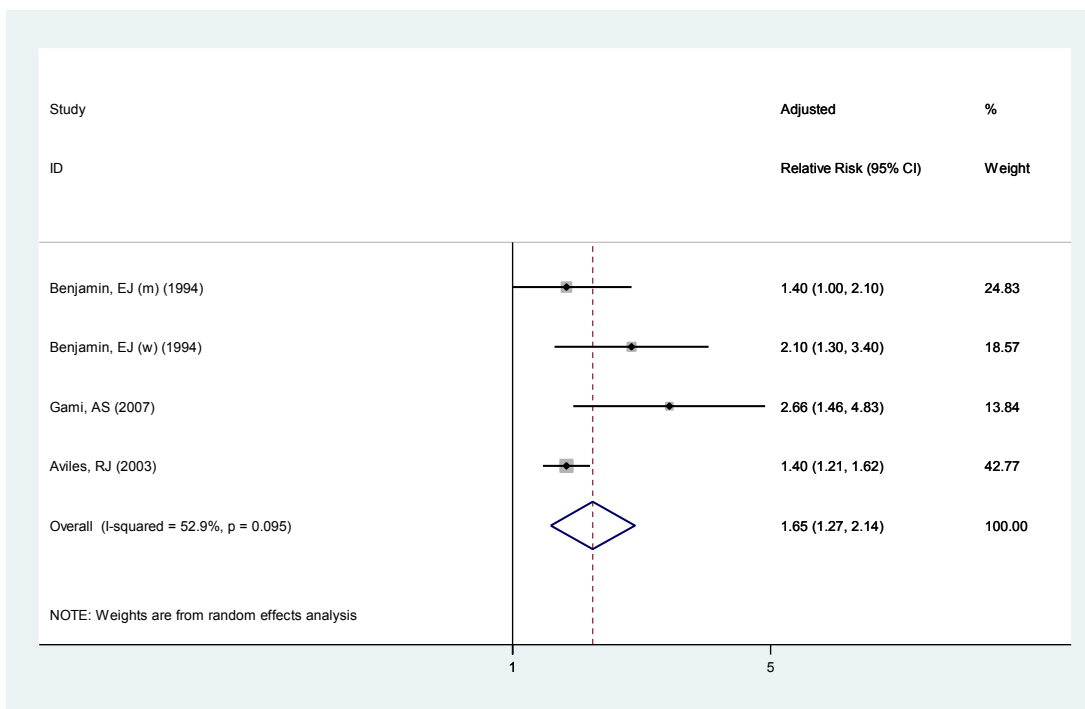
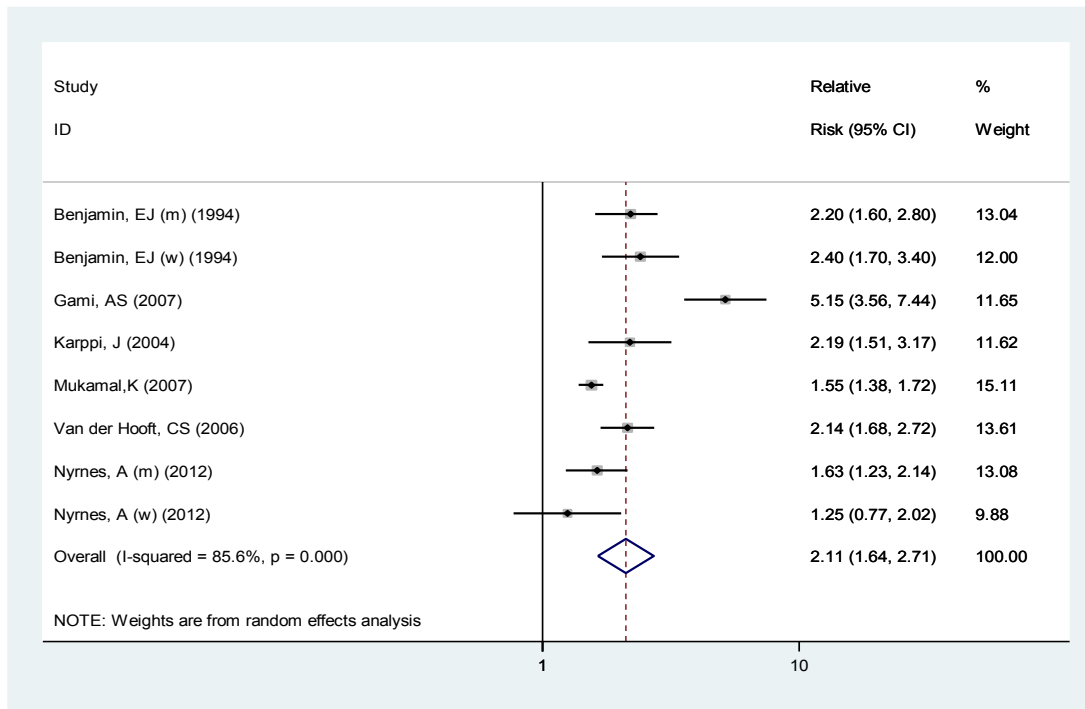
Congestive heart failure: univariate and multivariate statistical outputs



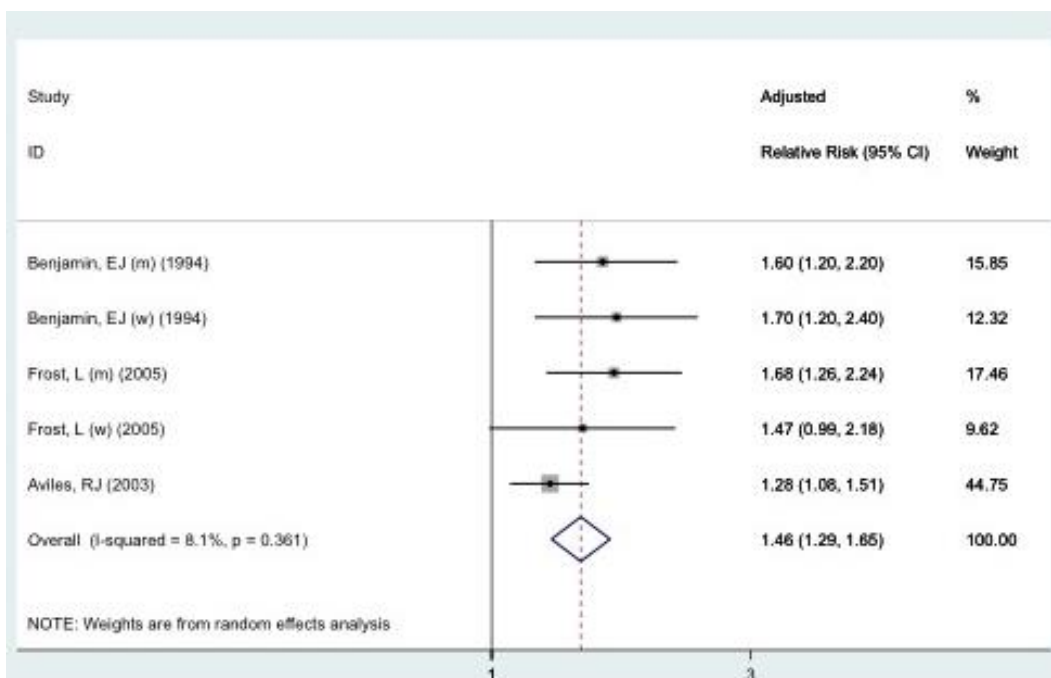
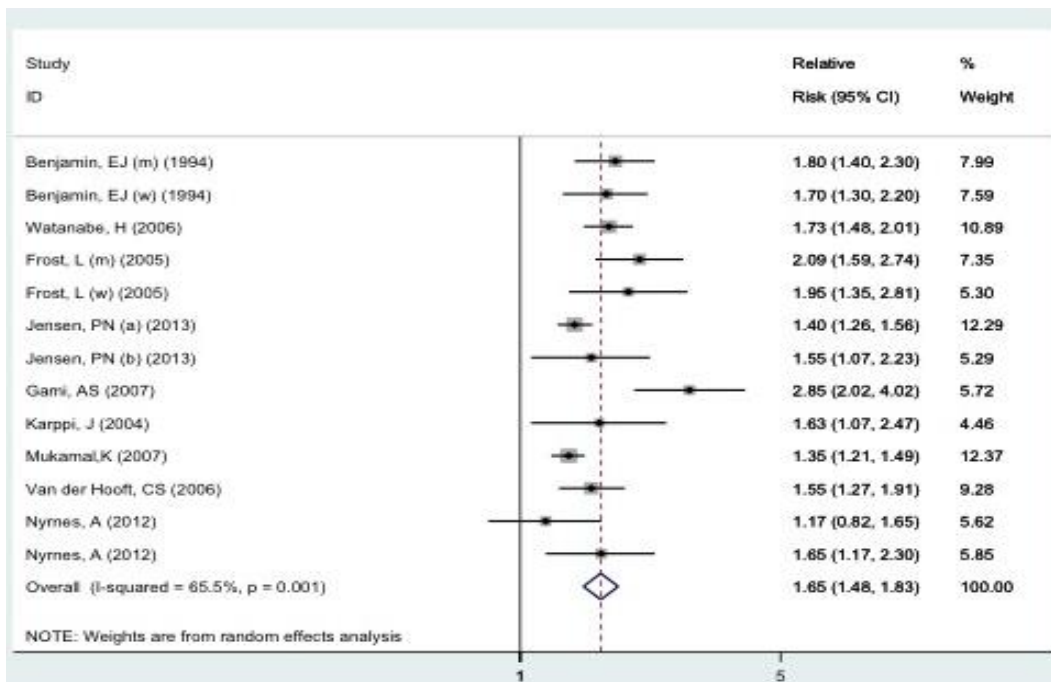
Male gender: univariate and multivariate statistical outputs



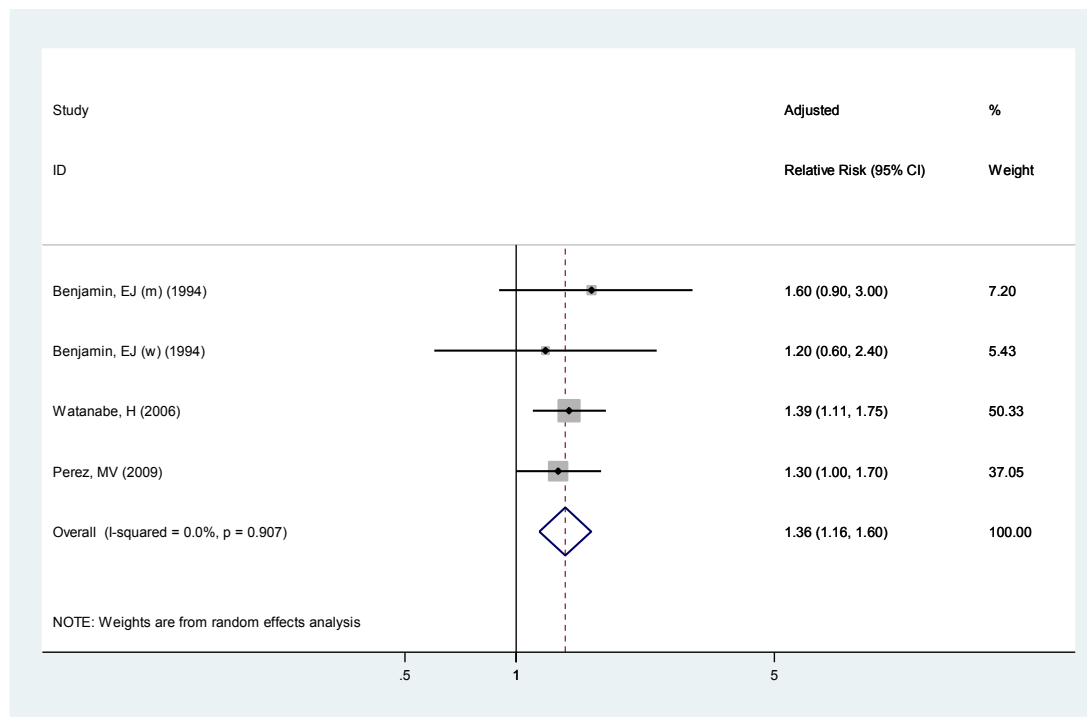
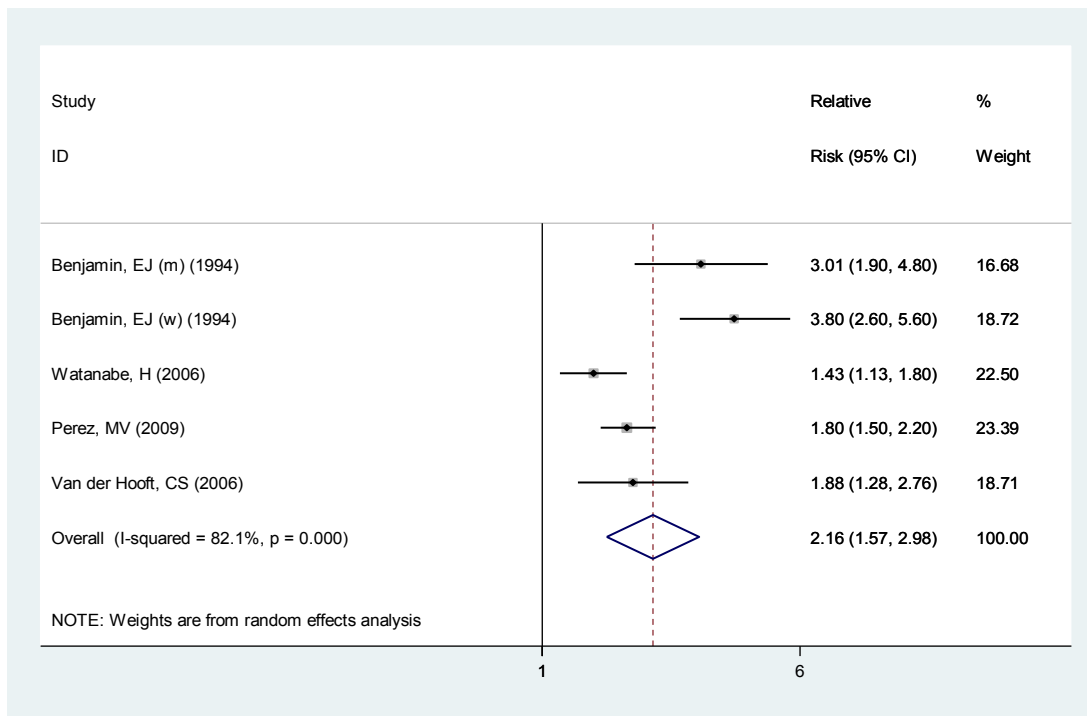
Coronary artery disease: univariate and multivariate statistical outputs



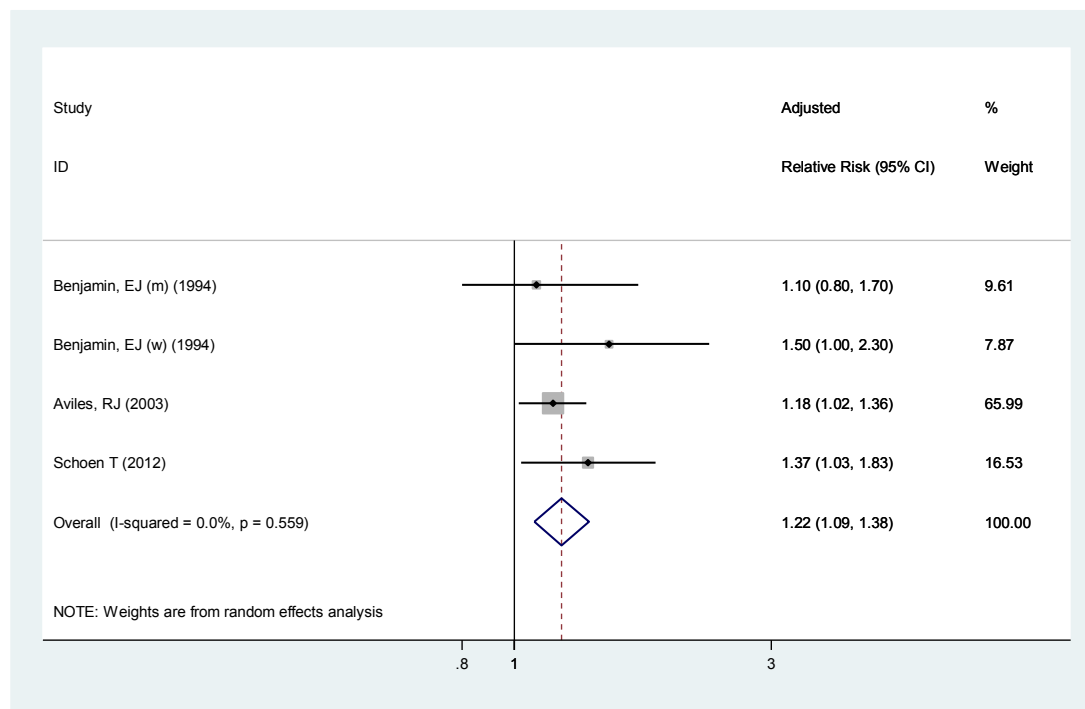
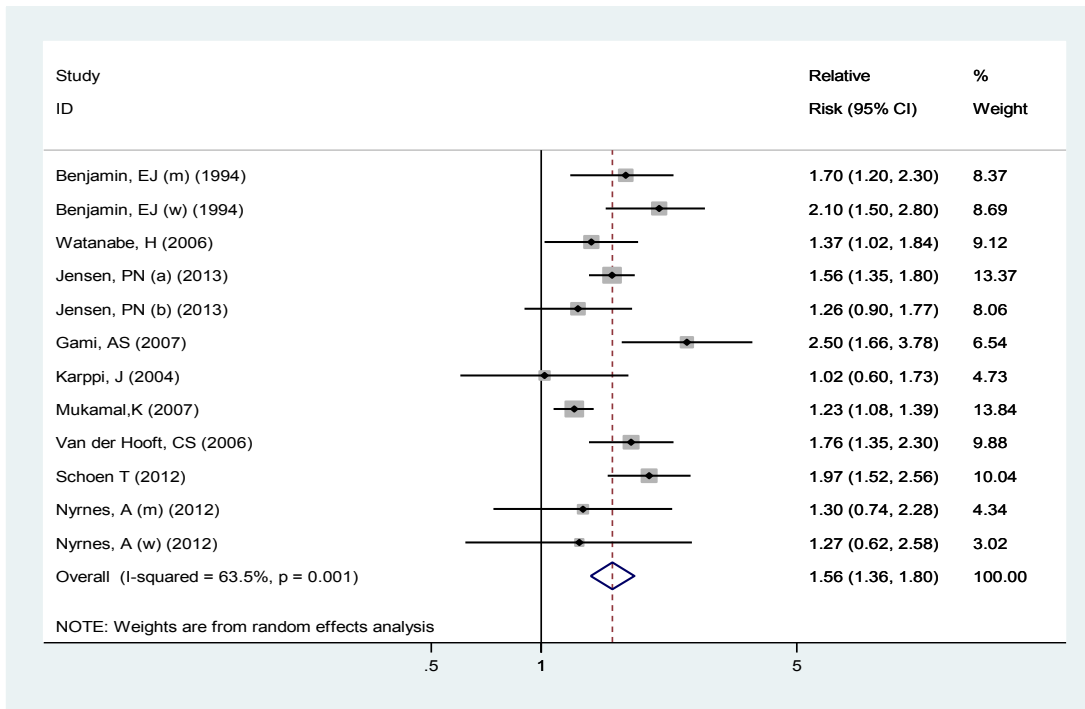
Hypertension: univariate and multivariate statistical outputs



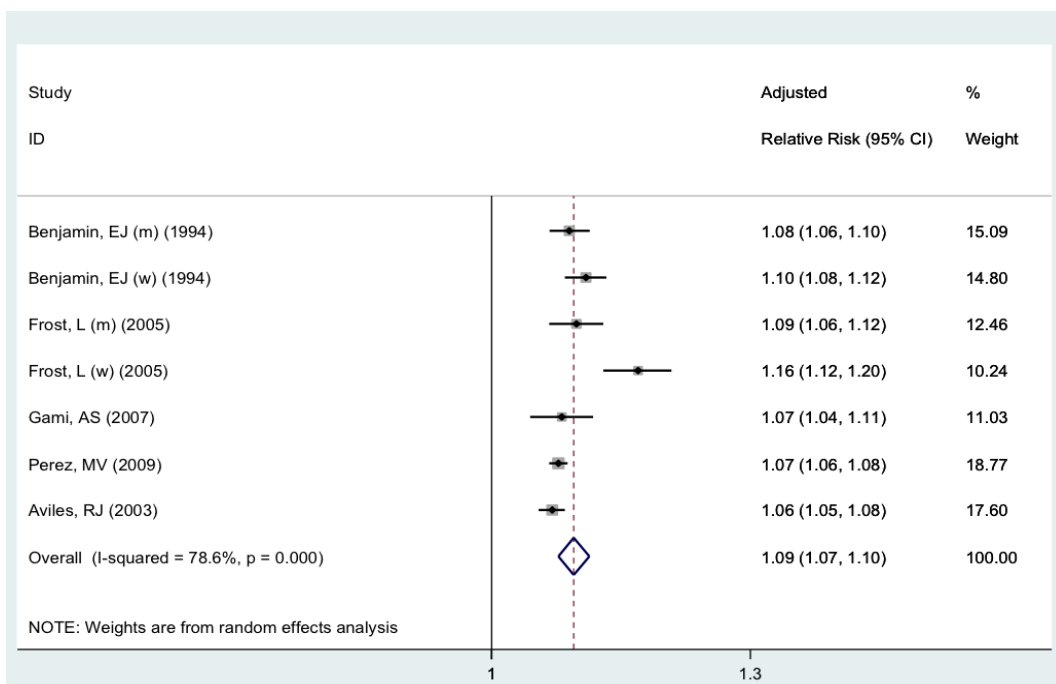
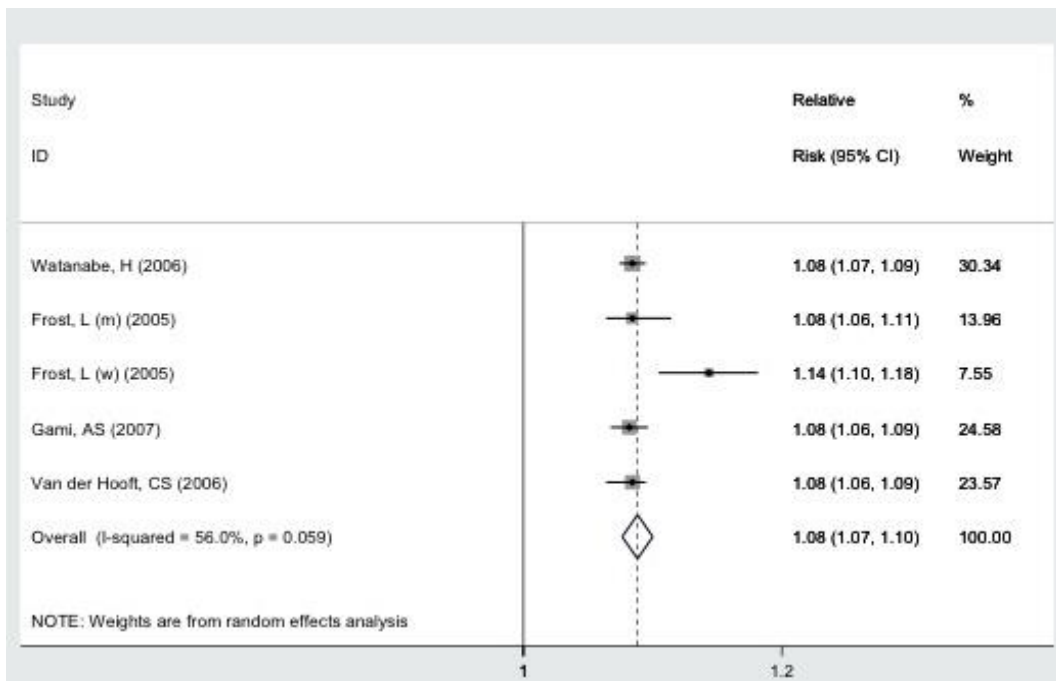
Left ventricular hypertrophy: univariate and multivariate statistical outputs



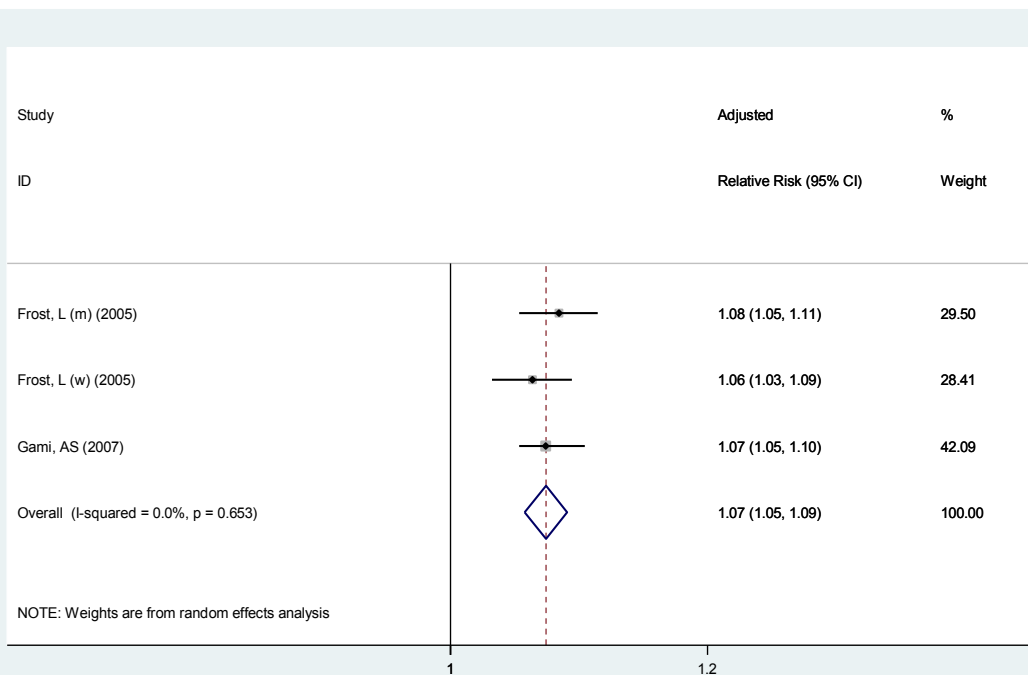
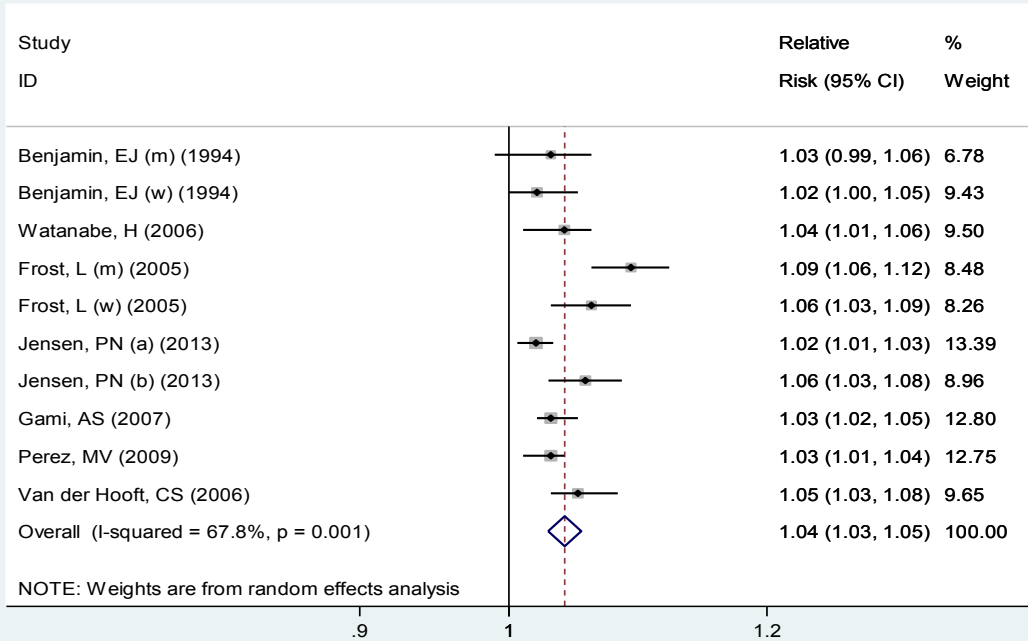
Diabetes mellitus: univariate and multivariate statistical outputs



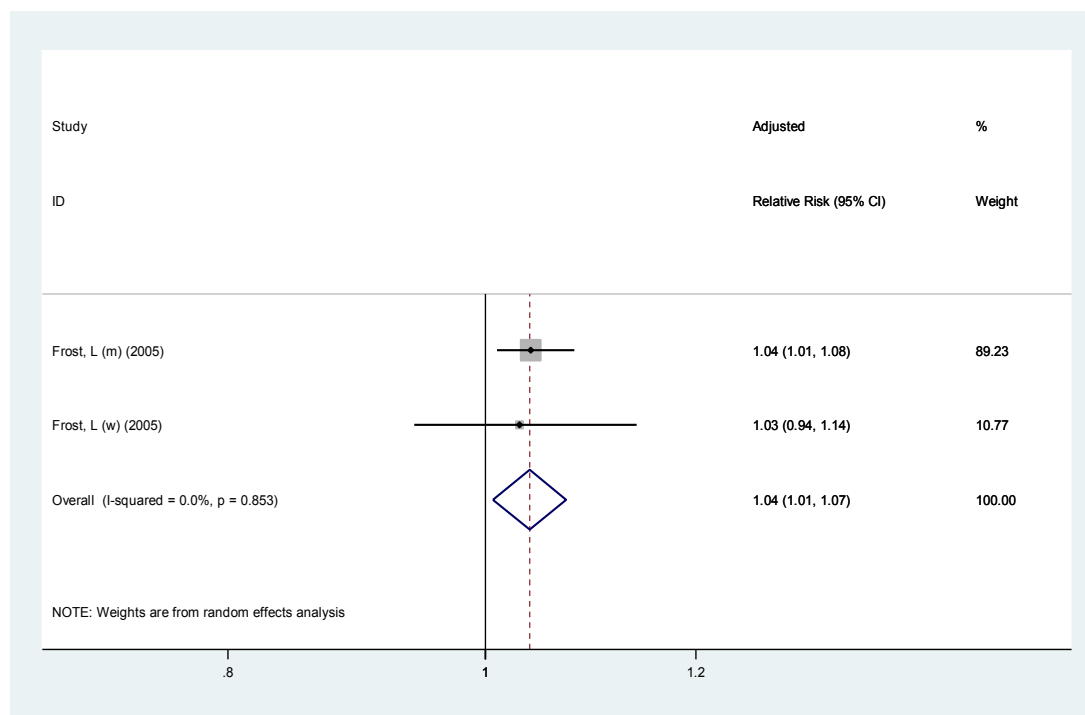
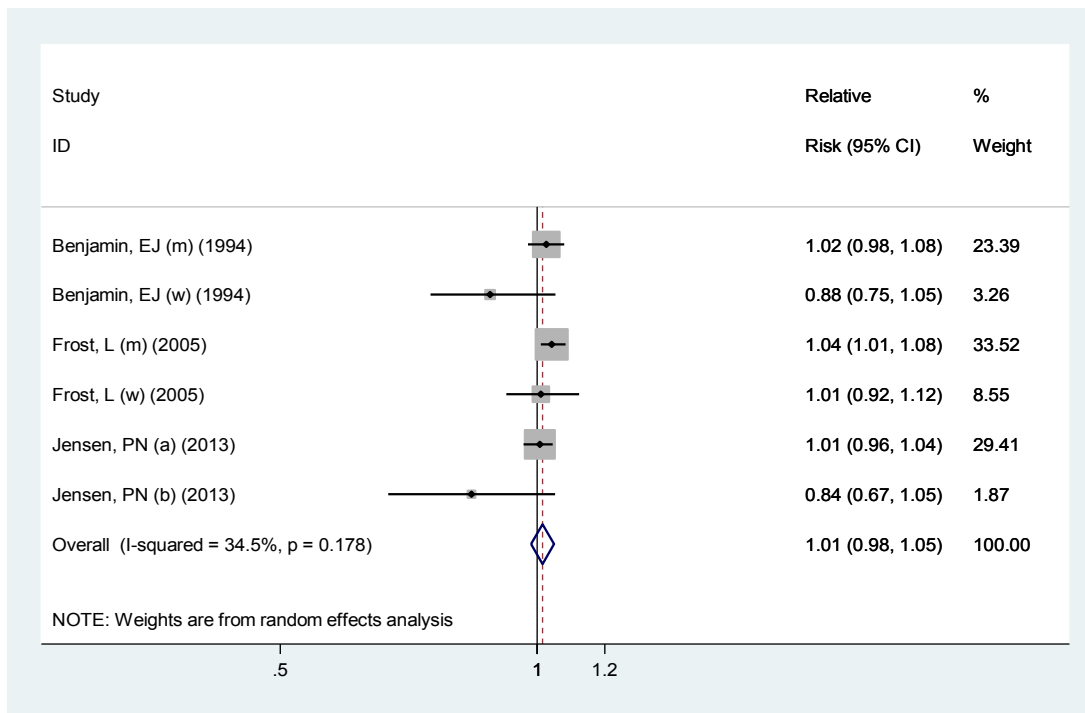
Age: univariate and multivariate statistical outputs



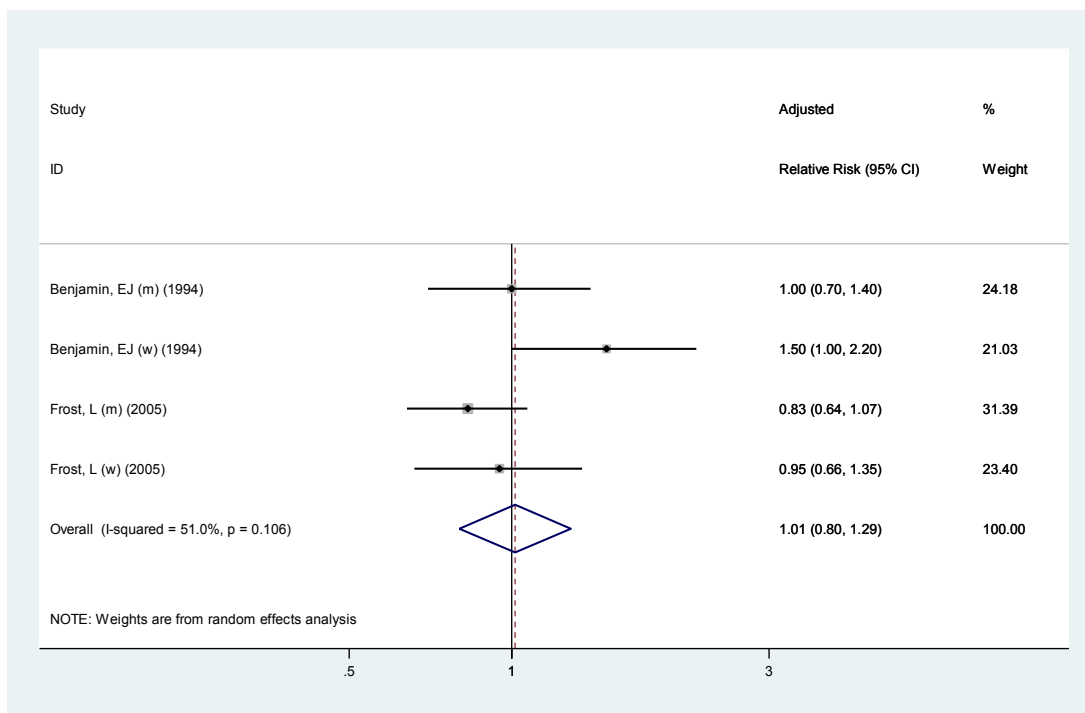
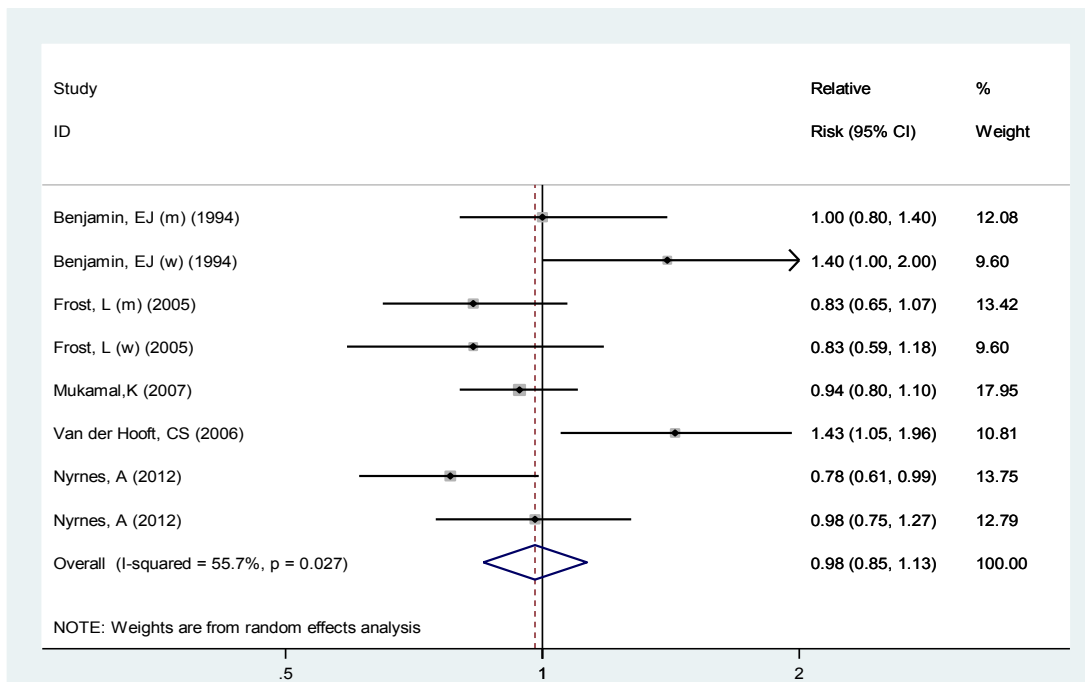
BMI: univariate and multivariate statistical outputs



Alcohol consumption: univariate and multivariate statistical outputs



Cigarette smoking: univariate and multivariate statistical outputs



Appendix 3

Exclusion due to mis-coding of atrial fibrillation (I48) from total patient sample (n=858)

Malignancy n (%)	5 (0.6)
SVT n (%)	5 (0.6)
Post procedure AF n (%)	4 (0.4)
Pneumonia n (%)	3 (0.3)
GI problems n (%)	3 (0.3)
Whooping cough n (%)	2 (0.2)
Syncope n (%)	2 (0.2)
Palpitations n (%)	2 (0.2)
Asystole n (%)	2 (0.2)
Myocardial infarction n (%)	1 (0.1)
Tachy-brady syndrome n (%)	1 (0.1)
Femoral artery occlusion n (%)	1 (0.1)
COPD n (%)	1 (0.1)
Knee replacement n (%)	1 (0.1)
AVNRT n (%)	1 (0.1)
Adrenalin-flecainide challenge n (%)	1 (0.1)
Total n (%)	38 (4.4)

Appendix 4

Output table for univariate and multivariate analysis of predictors of hospital admission

	Uni-variate Analysis Odds Ratio (95% CI)	P-value	Multi-variate Analysis Odds Ratio (95% CI)	P-value
Demographics				
Age (yrs)	1.02[1.0-1.04]*	0.002	1.0[0.9-1.02]	0.9
Gender (Male)	1.0[0.6-1.5]	0.9		
Clinical characteristics				
Hx of HT	2.3[1.5-3.5]*	0.001	1.4[0.7-2.6]	0.3
Hx of CHF	3.1[1.5-6.5]*	0.003	2.3[1.03-5.4]†	0.04
Hx of CAD	1.0[0.6-1.7]	0.9		
Hx of DM	2.3[1.2-4.6]*	0.01	1.4[0.6-3.1]	0.4
Hx of VHD	1.8[0.9-3.4]*	0.05	1.3[1.2-4.7]	
Hx of Stroke/TIA	1.9[0.8-4.2]	0.1		
Presentation characteristics				
Out of hours	1.6 [1.0-2.4]*	0.04	1.4[0.8-2.3]	0.1
Rapid AF	1.5 [0.9-2.4]	0.08		
Elevated liver function tests	2.8 [1.05-7.6]*	0.02		
AF with infection	5.6 [2.7-11.8]*	<0.001	5.1[2.3-11.0]†	<0.001
Low systolic blood pressure <90mmHg	0.9 [0.4-2.2]	0.9		
High systolic blood pressure >160mmHg	0.4[0.1-1.2]	0.1		

Appendix 5

Ethics approvals for chapters 3 & 4

18 August 2010

Prof Prash Sanders
Director
Cardiac Electrophysiology
ROYAL ADELAIDE HOSPITAL

Dear Prof Sanders,

Re: "Quantification of cardiac substrate preceding the onset of new AF – a case control study."

RAH PROTOCOL NO: 100804.

Researcher: Ms Geetanjali Rangnekar

I am pleased to advise that Research Ethics Committee EXPEDITED APPROVAL is granted to the above project on the above date.

The following have been reviewed and approved:

- **Protocol**
- **Participant Information Sheet & Consent Form – Non-AF Patients, Version 1, 29 June 2010**
- **Participant Information Sheet & Consent Form – AF Patients, Version 1, 29 June 2010**

Please quote the RAH Protocol Number allocated to your study on all future correspondence. Research Ethics Committee deliberations are guided by the NHMRC National Statement on Ethical Conduct in Human Research 2007.


GENERAL TERMS AND CONDITIONS OF ETHICAL APPROVAL:

- Adequate record-keeping is important. If the project involves signed consent, you should retain the completed consent forms which relate to this project and a list of all those participating in the project, to enable contact with them in the future if necessary. The duration of record retention for all clinical research data is 15 years.
- You must notify the Research Ethics Committee of any events which might warrant review of the approval or which warrant new information being presented to research participants, including:
 - (a) serious or unexpected adverse events which warrant protocol change or notification to research participants,
 - (b) changes to the protocol,
 - (c) premature termination of the study,
 - (d) a study completion report within 3 months of the project completion.
- The Committee must be notified within 72 hours of any serious adverse event occurring at this site.
- Approval is **ongoing**, subject to satisfactory annual review. Investigators are responsible for providing an annual review to the RAH REC Executive Officer each anniversary of the final approval date using the Annual Review Form available at: <http://www.rah.sa.gov.au/rec/index.php> The REC must be advised with a report or in writing when this study approval is complete so that the file can be closed.

Yours sincerely,

Dr A Thornton
CHAIRMAN
RESEARCH ETHICS COMMITTEE

Ethics approval for chapters 5 & 6

 **Government of South Australia**
SA Health

3 April 2012

Dr Anthony Brooks
Centre for Heart Rhythm Disorders
Department of Cardiology
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Research Ethics Committee
Level 3, Hanson Institute
Tel: (08) 8222 4139
Fax: (08) 8222 3035
Email: Heather.O'Dea@health.sa.gov.au

Dear Dr Brooks,

Re: An audit of acute management for atrial fibrillation at the Royal Adelaide Hospital.
RAH PROTOCOL NO: 120401.

I am pleased to advise that Research Ethics Committee APPROVAL is granted to the above project on the above date. The following have been reviewed and approved:

- **Protocol, Version 1 (27 March 2012)**


Please quote the RAH Protocol Number allocated to your study on all future correspondence.

Research Ethics Committee deliberations are guided by the NHMRC National Statement on Ethical Conduct in Human Research (2007).

GENERAL TERMS AND CONDITIONS OF APPROVAL OF AUDIT:

- Adequate record-keeping and data security is important. The duration of record retention for all clinical research data is 15 years.
- Confidentiality is important. The data collected should as much as possible protect the identity of individuals. Where this is not possible, a separate file of subject identifiers should be maintained such that clinical information is kept separately from subject identifiers.
- You must notify the Research Ethics Committee of any changes which might warrant review of the approval.
- The REC must be advised when this study is complete so that the file can be closed.
- Approval is ongoing. Annual reports are *not* required.

Yours sincerely,



Dr A Thornton
CHAIRMAN
RESEARCH ETHICS COMMITTEE

Ethical issues:

There were no anticipated ethical concerns associated with the enrolment of patients in the new AF studies, included in chapters 3 & 4. The procedures used in these studies such as Holter monitoring, echocardiography and blood tests are established non-invasive medical procedures and have been used in many previous studies. None of the non-invasive measures of cardiac function, structure, electrical assessment and inflammatory blood profile involve ionising radiation.

There were also no anticipated ethical concerns associated with the enrolment of patients in studies included in chapters 5 & 6. These studies only required information regarding patient characteristics and experiences, which will be obtained from case notes and a clinical interview.

The funds for all these studies, including the clinical tests came from the research funds of the Centre for Heart Rhythm Disorders. The results of all the studies are presented in a de-identified manner and when published in the future will not identify any participant.

Chapter Nine

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