EPIDEMIOLOGY, PATHOGENESIS AND MANAGEMENT OF ATRIAL FIBRILLATION

A thesis submitted for the degree of Doctor of Philosophy

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Dr Christopher Xin Jie Wong MBBS

Centre for Heart Rhythm Disorders

South Australian Health and Medical Research Institute

University of Adelaide and Royal Adelaide Hospital

"If I have seen further, it is by standing on the shoulders of giants."

Sir Isaac Newton

DEDICATION

To my parents, Charles and Siew Jee, and my wife Michelle.

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ABSTRACT

Atrial fibrillation is the most common heart rhythm disorder. Once considered to be a benign condition, it is now known to be associated with significant morbidity and mortality. The rising incidence and prevalence of atrial fibrillation has thus led to growing concern by clinicians and policymakers. In recent years, there have been marked strides in our mechanistic understanding of atrial fibrillation that, coupled with technological advances, have allowed for many new therapies. Despite the resultant explosion in research on atrial fibrillation, however, innumerable uncertainties regarding this intriguing arrhythmia still remain. This has provided fertile ground for the work undertaken as part of this thesis and future research on this condition.

Previous studies contributing to our current understanding of atrial fibrillation are first reviewed in Chapter 1. Chapter 2 subsequently characterises the population burden of atrial fibrillation on the Australian healthcare system by analysing nationwide trends in hospitalisations. To provide some insight into the determinants of such healthcare utilisation, and how they may potentially be modified, Chapter 3 analyses relevant patient- and management-specific factors as they pertain to these trends. Data on two other cardiovascular conditions, myocardial infarction and heart failure, are contrasted with those for atrial fibrillation to provide context and insight into these trends.

Given the emerging epidemic of obesity, Chapter 4 characterises the contribution of obesity to the risk of atrial fibrillation in various clinical situations by undertaking

comprehensive systematic reviews and meta-analyses. In Chapter 5, the possible contribution of pericardial fat in mediating the the relationship between obesity and atrial fibrillation is further studied.

In Chapter 6, race-specific differences in atrial fibrillation are explored by analysing differences in the prevalence of atrial fibrilllation between Indigenous and non-Indigenous Australians. An insight into possible mechanisms underlying these differences are subequently provided by studying cardiac structural characteristics. Given the greater prevalence of atrial fibrillation and burden of stroke experienced by Indigenous Australians, in Chapter 7 the race-specific management of atrial fibrilation is characterised with regards to anticoagulation practices.

Finally, insights into the epidemiology, pathogenesis and management of atrial fibrillation from the research presented in this thesis are placed in the context of the previous literature in Chapter 8, before possible directions for future studies on atrial fibrillation are discussed in Chapter 9.

DECLARATION

I certify that this work contains no material which has been accepted for the award of any other degree of diploma in my name in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint award of this degree.

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Dr Christopher Xin Jie Wong

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PUBLICATIONS AND COMMUNICATIONS TO LEARNED SOCIETIES

Chapter One

1. <u>Editorial</u>: Wong CX, Lau DH, Sanders P. Atrial Fibrillation Epidemic and Hospitalizations: How to Turn the Rising Tide? *Circulation 2014; 129(23):2361-3*

2. <u>Manuscript</u>: Wong CX, Mahajan R, Pathak R, Sanders P. Pericardial and Epicardial Fat: Role in Atrial Fibrillation Pathophysiology and Ablation Outcomes. *Journal of Atrial Fibrillation 2013; 5(5):37-43*

Chapter Two

1. <u>Manuscript</u>: Wong CX, Brooks AG, Leong DP, Roberts-Thomson KC, Sanders P. The Increasing Burden of Atrial Fibrillation Compared to Heart Failure and Myocardial Infarction: A 15 Year Study of All Hospitalizations in Australia. *Archives of Internal Medicine 2012*; 172(9):739-741

2. <u>Letter</u>: Wong CX, Roberts-Thomson KC, Sanders P. The Burden of Hospitalizations for Atrial Fibrillation. *Archives of Internal Medicine 2012*; 172(22):1770

3. <u>Editorial</u>: Wong CX, Lau DH, Sanders P. Atrial Fibrillation Epidemic and Hospitalizations: How to Turn the Rising Tide? *Circulation 2014; 129(23):2361-3*

4. <u>Presentation</u>: Wong CX, Sun MT, Lau DH, Brooks AG, Leong DP, Shipp NJ, Alasady M, Lim HS, Abed HS, Sanders P. Increases in Atrial Fibrillation Hospitalization Rates are Greater than Myocardial Infarction or Heart Failure: A 15-Year Nationwide Study. ***Heart Rhythm 2011***

Chapter Three

1. <u>Manuscript</u>: Wong CX, Brooks AG, Lau DH, Leong DP, Sun MT, Sullivan T, Roberts-Thomson KC, Sanders P. Factors Associated With the Epidemic of Hospitalizations Due to Atrial Fibrillation. ***American Journal of Cardiology 2012;*** 110(10):1496-9

2. <u>Manuscript</u>: Wong CX, Sun MT, Lau DH, Leong DP, Brooks AG, Sullivan T, Worthley MI, Roberts-Thomson KC, Sanders P. Nationwide Trends in the Incidence of Acute Myocardial Infarction in Australia, 1993-2010. ***American Journal of Cardiology 2013****; 112(2):169-73*

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Chapter Four

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2. Presentation: Wong CX, Sun MT, Mahajan R, Pathak R, Leong DP, Lau DH, Roberts-Thomson KC, Sanders P. Obesity and the Risk of Atrial Fibrillation: A Systematic Review and Meta-Analysis. *Circulation 2012*

3. Presentation: Wong CX, Sun MT, Pathak R, Mahajan R, Lau DH, Roberts-Thomson KC, Sanders P. Body Mass Index Predicts Postoperative Atrial Fibrillation: Results of a Contemporary Meta-Analysis. *Circulation 2012*

4. Presentation: Wong CX, Brooks AG, Sun MT, Sullivan T, Lau DH, Leong DP, Ganesan AN, Roberts-Thomson KC, Sanders P. Obesity and Risk of Atrial Fibrillation: A Systematic Review and Meta-Analysis. *Heart, Lung and Circulation 2012*

5. Presentation: Wong CX, Brooks AG, Sun MT, Lau DH, Sullivan T, Leong DP, Roberts-Thomson KC, Sanders P. Body Mass Index Predicts Postoperative Atrial Fibrillation: Results of a Contemporary Meta-Analysis. *Heart, Lung and Circulation 2012*

6. <u>Presentation</u>: Wong CX, Sullivan T, Sun MT, Mahajan R, Pathak RK, Middeldorp M, Twomey D, Ganesan AN, Rangnekar G, Roberts-Thomson KC, Lau DH, Sanders P. Obesity and Post-Ablation Atrial Fibrillation. ***Heart Rhythm 2015***

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Chapter Five

1. <u>Manuscript</u>: Wong CX, Abed HS, Molaee P, Nelson AJ, Brooks AG, Sharma G, Leong DP, Lau DH, Middeldorp ME, Roberts-Thomson KC, Wittert GA, Abhayaratna W, Worthley SG, Sanders P. Pericardial Fat is Associated with Atrial Fibrillation Severity and Ablation Outcome. ***Journal of the American College of Cardiology 2011;*** 57(17):1745-1751

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3. <u>Letter</u>: Wong CX, Abed HS, Molaee P, Sanders P. Distinction of 'Fat Around the Heart'. ***Journal of the American College of Cardiology 2011;*** 58(15)1640-1641

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5. <u>Presentation</u>: Wong CX, Abed HS, Molaee P, Nelson AJ, Brooks AG, Leong DP, Lau DH, Roberts-Thomson K, Abhayaratna WP, Worthley SG, Selvanayagam JB, Sanders P. Pericardial Fat is Associated with Left Atrial Structure and Function: Implications for Atrial Fibrillation. ***Heart, Lung and Circulation 2012***

6. <u>Presentation</u>: Wong CX, Abed HS, Molaee P, Mahajan R, Nelson AJ, Roberts-Thomson KC, Wittert GA, Abhayaratna WP, Worthley SG, Selvanayagam JB, Sanders P. Pericardial Fat is Associated with Left Atrial Structure and Function: Implications for Atrial Fibrillation. ***Heart Rhythm 2012***

7. <u>Presentation</u>: Wong CX, Sun MT, Mahajan R, Pathak R, Brooks AG, Lau DH, Roberts-Thomson KC, Abhayaratna WP, Worthley SG, Selvanayagam JB, Sanders P. Pericardial Fat Predicts Reverse Remodeling of the Left Atrium Following Atrial Fibrillation Ablation. ***European Heart Journal 2013***

8. <u>Presentation</u>: Wong CX, Sun MT, Mahajan R, Pathak R, Brooks AG, Lau DH, Roberts-Thomson KC, Abhayaratna WP, Worthley SG, Selvanayagam JB, Sanders P. Pericardial Fat Reduction and Reverse Remodeling Following Atrial Fibrillation Ablation. ***Heart, Lung and Circulation 2013***

Chapter Six

1. Manuscript: Wong CX, Brooks AG, Cheng Y, Lau DH, Rangnekar G, Roberts-Thomson KC, Kalman JM, Brown A, Sanders P. Atrial Fibrillation in Indigenous and Non-Indigenous Australians: A Cross-Sectional Study. *BMJ Open 2014; 4(10):6242*

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1. Manuscript: Wong CX, Lee SW, Gan S, Mahajan R, Rangnekar G, Pathak RK, Twomey D, Schultz C, Ganesan AN, Brooks AG, Roberts-Thomson KC, Brown A, Lau DH, Sanders P. Underuse and Overuse of Anticoagulation for Atrial Fibrillation: A Study in Indigenous and Non-Indigenous Australians. *International Journal of Cardiology (in press)*

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1. Royal Adelaide Hospital Nimmo Professorial Prize, 2011

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CHAPTER 1: LITERATURE REVIEW

1.1 Epidemiology of atrial fibrillation

1.1.1 Incidence of atrial fibrillation

Atrial fibrillation is the most common heart rhythm encountered in clinical medical practice. The frequent incidence of this condition in the community is significant as it is associated with considerable morbidity and mortality for patients, as will be discussed in more detail later in this Chapter, including that due to stroke, congestive cardiac failure and cardiovascular mortality.

The majority of large epidemiological studies describing the incidence of atrial fibrillation have been in predominantly Caucasian cohorts from the developed world, particularly North America and Europe.[1] In a report from the Framingham Study investigators, individuals 30 to 62 years of age were followed for a period of 22 years, with routine electrocardiograms revealing an overall atrial fibrillation incidence of two per thousand in each biennium.[2] The cumulative incidence over the 22 year study period rose sharply with age, ranging from 2.6 and 2.2 per 1000 for men and women 24 to 34 years of age respectively, to 37.9 and 29.9 per 1000 for men and women 55 to 64 years of age respectively. In a later Framingham Study report including individuals up to 94 years of age at baseline, incidence continued to rise with age, ranging from 6.2 and 3.8 cases per 1000 person-examinations (approximately 2000 person-years) in men and women aged 55 to 64 years of age respectively, to 75.9 and 62.8 cases per 1000 person-examinations in men and

women aged 85 to 94 years of age respectively.[3] The overall age- and sex-adjusted estimated incidence of atrial fibrillation in Olmsted County, Minnesota, has been reported as being 3.40 (95% confidence interval 3.30 to 3.50) per 1000 person-years.[4] In those under 55 years of age, this age-adjusted incidence rates were 0.62 and 0.19 in men and women respectively; this rose in those greater than or equal to 85 years of age to 39.66 and 27.69 in men and women respectively. In the Cardiovascular Health Study, there was a comparatively higher overall incidence rate of 19.2 per 1000 person-years given the greater than 65 years of age cohort.[5] However, age-specific incidence rates were more similar; men and women aged 65 to 74 years of age had incidence rates of 17.6 and 10.1 per 1000 person-years respectively, and those aged 75 to 84 years of age had incidence rates of 42.7 and 21.6 per 1000 person-years respectively.

Comparable findings have been reported in other developed countries. The Manitoba Follow-Up Study described an overall atrial fibrillation incidence of 2 per 1000 person-years in Canadians, with age-specific incidence rates ranging from 0.5 per 1000 person-years for those under 50 years of age to 16.9 per 1000 person-years for those greater than 85 years of age.[6] In Scotland, the incidence of atrial fibrillation in the Renfrew/Paisley study was 0.54 cases per 1000 person-years.[7] From the General Practice Research Database in the United Kingdom, the overall incidence of atrial fibrillation was 1.7 per 1000 person-years.[8] These two studies similarly described increasing atrial fibrillation incidence rates with age.

In contrast, there is a relative paucity of population data on atrial fibrillation outside North America and Europe and from less developed countries. Reported incidence rates of atrial fibrillation from Asian cohorts tend to be lower than in predominantly Caucasian studies from other regions. For example, a Japanese cohort described an overall incidence of atrial fibrillation of 2.2 per 1000 person-years.[9] In Taiwan, incidence rates ranged from 0.76-1.16 per 1000 person-years in women to 1.37-1.68 per 1000 person-years in men.[10, 11] The best available data from the Global Burden of Disease 2010 Study suggest there is an approximately 2-fold greater incidence of atrial fibrillation in developed regions compared with developing countries.[1] In North Africa and the Middle East, there is an estimated incidence rate of 0.62 per 1000 in men and 0.42 per 1000 women respectively.[1] Similar estimates have been reported for Sub-Saharan Africa, ranging from 0.49-0.61 per 1000 in men and from 0.38-0.51 per 1000 in women respectively.[1]

Two important characteristics of atrial fibrillation are relevant to interpreting these incidence data, which likely renders the above figures underestimates of the true incidence of atrial fibrillation. Firstly, atrial fibrillation is often asymptomatic and many individuals may go undiagnosed unless they have a screening electrocardiogram or an electrocardiogram for another clinical indication.[12] Indeed, approximately thirty and forty-five percent of individuals in the Cardiovascular Health Study and SPAF-III Trial respectively had atrial fibrillation detected incidentally on an electrocardiogram for an unrelated reason.[13, 14] Secondly, a significant proportion of individuals has paroxysmal atrial fibrillation and may thus remain undiagnosed if a screening electrocardiogram is undertaken during a period of sinus rhythm. The latter fact is

evidenced by the difference in incidence rates across studies depending on the diagnostic frequency, with more frequent electrocardiograms being increasingly likely to diagnose paroxysmal atrial fibrillation. Furthermore, differing rates are also somewhat dependent on the approach used to identify atrial fibrillation; methodology varies considerably across studies, including medical record review, hospitalisation databases, patient survey and screening electrocardiograms. The availability of atrial fibrillation diagnosis via other technologies, such as 24 hour or longer Holter monitors and implantable cardiac devices, can also result in even greater rates of atrial fibrillation diagnosis by capturing increasingly infrequent episodes of paroxysmal atrial fibrillation.[15]

1.1.2 Prevalence of atrial fibrillation

As of 2010, it is estimated that there are 33.5 million men and 12.6 million women with atrial fibrillation globally.[1] The prevalence of atrial fibrillation in the unselected adult population is approximately 2%, though this figure rises significantly with age and can exceed 10% in those over 80 years of age.[16] Given the morbidity and mortality associated with atrial fibrillation, it is concerning that the global prevalence of atrial fibrillation appears to be increasing. These trends have been consistently reported in a number of studies. The Framingham investigators examined the prevalence of atrial fibrillation in persons aged 65 to 84 years of age from 1968 to 1989 in their study.[17] They found that the prevalence of atrial fibrillation appeared to increase from 2% to 5.3% over the study period in men but not women. In a cohort of Medicare beneficiaries 65 years or older with atrial fibrillation in the United States,

the prevalence of atrial fibrillation appeared to increase by a mean of 5% each year from 1993 to 2007.[18] This increasing prevalence was seen in all age groups, though the magnitude was greater in older age groups, and similar in both men and women. In the Copenhagen City Heart Study, the age-standardised prevalence of atrial fibrillation increased from 1.4% to 3.3% in men from 1976 to 1994, though no significant change was seen in women.[19] Again, there is much less data on the prevalence of atrial fibrillation from less developed regions. The Global Burden of Disease 2010 Study reported prevalence rates ranging from 250-325 per 100 000 population in China, 400-475 per 100 000 population in South East Asia and 475-625 in Africa, the Middle East and South America.[1] Other epidemiologic investigations have individually reported a lower prevalence of atrial fibrillation in these regions compared to North American and European populations.[20, 21]

A number of studies have also made predictions regarding the future prevalence of atrial fibrillation based on current figures. Using cohort data assembled from 1996 to 1997 in the Kaiser Permanente of North California organisation, another report reported an overall 0.95% diagnosed prevalence of atrial fibrillation.[22] By applying prevalence data to the United States census population statistics, they estimated that the 2.3 million United States adults with atrial fibrillation would rise to 5.6 million by the year 2050. From a claims database, the United States prevalence of atrial fibrillation was estimated to be 3.03 million and forecast to rise to 7.56 by the year 2050.[23] In a subsequent study, Olmsted County data was developed to similarly estimate the prevalence of atrial fibrillation in the year 2050.[4] These estimates were even greater than those from the previous reports, with the projected number of

people with atrial fibrillation in the United States being potentially 15.9 million.

Regions with lower prevalence rates but larger populations may also have

significantly more people with atrial fibrillation.[24] In China, for example, it was

estimated that the prevalence of atrial fibrillation was 5.26 million in 2010 alone.[25]

Furthermore, it is predicted that a more rapid increase in the prevalence and burden

of atrial fibrillation will be seen these regions compared to the United States in the

next 50 years.[24]

There are numerous factors that are likely to be contributing to these increasing

prevalence trends. The most important factor is likely to be age given the changing

population structures evident in developed countries. As described above, the

prevalence of atrial fibrillation rises with increasing age and ageing populations are

thus a significant driver of increasing overall atrial fibrillation prevalence. Similarly, a

portion of the change in prevalence can also be attributed to increasing population

size. The atrial fibrillation epidemic, however, is not entirely explained on the basis of

an ageing population alone.[26] Despite changing population structures and gross

population numbers, the age-specific incidence of atrial fibrillation appears to be also

increasing. In the Olmsted County data, for example, investigators described a

relative 12.6% (95% confidence interval 2.1 to 23.1) increase in age- and sex-

adjusted atrial fibrillation incidence over a 21 year period, with incidence estimates

rising from 3.04 (95% confidence interval 2.78 to 3.31) in 1980 to 3.68 (95

confidence interval 3.42 to 3.95) in 2000 per 1000 person-years.[4] Overall, from 1990

to 2010, the global incidence in both developed and developing countries is

estimated to have risen from 0.61 to 0.78 per 1000 person-years in men and from

0.44 to 0.60 per 1000 person-years in women, as reported in the Global Burden of Disease 2010 Study.[1] It is likely that changing risk factor profiles is also in-part responsible for these trends. A number of risk factors are associated with atrial fibrillation, including hypertension, congestive cardiac failure, myocardial infarction, valvular heart disease, diabetes and obesity; the relationship of these to atrial fibrillation is outlined in further detail later.[3, 27] Rates of obesity are rising and are of particular relevance; the estimated change in obesity over the period observed in the Olmsted County data, for example, was reported to potentially account for 60% of the estimated increase in age- and sex-adjusted atrial fibrillation incidence.[4] Finally, increasingly sensitive diagnostic practices, for example the use of electrocardiographic monitoring, Holter monitors and other technologies, may be contributing in-part to some of these trends. It may be possible that these prevalence estimates are also underestimates of the true figures if some patients with asymptomatic and paroxysmal atrial fibrillation remain undiagnosed for reasons discussed above.

1.1.3 Traditional risk factors for atrial fibrillation

As referenced to above, age is a significant, non-modifiable risk factor for atrial fibrillation. In addition, gender has similarly been recognised for some time as another non-modifiable risk factor for atrial fibrillation. In the Framingham Heart Study, for example, men were 1.5 times more likely to develop atrial fibrillation than women, even after adjusting for other studied risk factors.[3] In a subsequent report,

the lifetime risk for the development of atrial fibrillation was reported as being 26% for men and 23% for women.[28]

Because of its frequency in the general population, hypertension is the most common underlying risk factor in patients with atrial fibrillation.[2] In a longitudinal study of routinely evaluated military personnel, a history of hypertension was associated with a 1.42-fold increased risk of developing atrial fibrillation.[6] Similar risk estimates have also been reported in other studies.[29]

Both stenotic and regurgitant valvular lesions are also associated with the development of atrial fibrillation. While now uncommon in developed countries, the prevalence of atrial fibrillation associated with varying combinations of valve lesions in with rheumatic heart disease, for example, is particularly striking, ranging from 16 to 70%.[30]

Cardiac failure often coexists with atrial fibrillation, and the presence of one condition increases the likelihood of the other developing.[31] In those with congestive cardiac failure, an atrial fibrillation incidence rate of 5.4% per year has been described.[32] Both left ventricular systolic and diastolic dysfunction are associated with the development of atrial fibrillation.[33, 34]

Coronary artery disease also increases the risk of developing atrial fibrillation, particularly in the setting of myocardial infarction. In those with an acute myocardial infarction, rates of atrial fibrillation have been reported to exceed 10% in some series.[35, 36] While a higher incidence is seen in the post-infarction period, the

development of later atrial fibrillation following discharge is also not insignificant and associated with worse outcomes.[37]

Patients with hyperthyroidism have also been long recognised to be at increased risk of developing atrial fibrillation.[38] In one population based study, atrial fibrillation was described in 8.3% of patients with diagnosed hyperthyroidism.[39] Notably, the incidence of atrial fibrillation is also higher in those with subclinical hyperthyroidism compared to those with normal thyroid stimulating hormone concentrations.[40]

Episodes of atrial fibrillation are also well described in the setting of heavy alcohol consumption and binge drinking, a phenomenon that has been termed "the holiday heart syndrome". Atrial fibrillation can be triggered in up to 60% of binge drinkers, and heavy alcohol consumption associated a hazard ratio for incident atrial fibrillation of 1.45. [41, 42] A recent dose-response meta-analysis, however, suggested that even moderate alcohol consumption as low as one drink per day increased the risk of atrial fibrillation by 8%.[43]

Atrial fibrillation also occurs in relation to surgery, particularly in patients undergoing coronary artery bypass graft or cardiac valve surgery. Series have described an incidence up to 40% following coronary artery bypass graft surgery, up to 50% following cardiac valve surgery, and even higher in those undergoing both types of surgery concurrently.[44] Atrial fibrillation is less common after non-cardiac surgery, though the risk is also not insignificant, with a prevalence of 4.1%.[45]

1.1.4 Emerging risk factors for atrial fibrillation

In addition to the above traditionally recognised risk factors for atrial fibrillation, data on a number of other risk factors have emerged in recent years.

The most significant of these is undoubtedly obesity, which, while controversial in the past, has now become convincing as an important and influential risk factor for atrial fibrillation.[4] This is discussed in more detail later in this Chapter.

Diabetes has also been postulated to be a possible risk factor for atrial fibrillation. A meta-analysis of cohort and case-control studies suggested that there may be a 34% greater risk of atrial fibrillation in the presence of diabetes.[46] However, a later cohort study has suggested that further multivariable adjustment for not only baseline confounders, but also, changes in atrial fibrillation risk factors and intercurrent cardiovascular events, attenuated the relationship and rendered it nonsignificant.[47]

Given many risk factors implicated in atrial fibrillation are part of the metabolic syndrome, the relationship of the metabolic syndrome to atrial fibrillation has also been studied. In a Japanese cohort study, the metabolic syndrome and its components, with the exception of elevated triglycerides, was found to be associated with an increased risk of atrial fibrillation.[48]

Emerging data also show that obstructive sleep apnoea appears to a risk factor for incident atrial fibrillation.[49] In univariate models, obstructive sleep apnoea (as defined by an apnoea-hypopnoea index≥5) was associated with a doubling in risk of

atrial fibrillation. The degree of nocturnal oxygen desaturation remained an independent predict tor in multivariable analyses that included body mass index and other risk factors.

The risk of atrial fibrillation is also greater in patients with chronic kidney disease. Indeed, a bidirectional relationship between chronic kidney disease and atrial fibrillation has been observed.[50] In multivariable models, there was a 2% increased risk of atrial fibrillation for every 10ml/min per 1.73m^2 decline in glomerular filtration rate. Reduced glomerular filtration rate and albuminuria has also shown to be associated with atrial fibrillation independent of other risk factors elsewhere.[51, 52]

Inflammatory processes have also been hypothesised to have a role in the pathogenesis of atrial fibrillation. Patients with atrial fibrillation have been shown to have higher levels of serum C-reactive protein, an acute phase reactant.[53, 54] However, this association may not be causal. In a Mendelian randomisation study, while elevated C-reactive proteins were associated with an increased risk of atrial fibrillation, C-reactive protein gene polymorphisms were not.[55] Thus, inflammation, as determined by C-reactive protein, may be a marker for other confounding factors as opposed to being a direct cause or perpetuating agent.

That the incidence of atrial fibrillation may vary by race, family history and genetic factors has also become increasingly recognised in recent years. This is discussed further in subsequent sections of this Chapter. Other miscellaneous factors that have also been reported to be associated with atrial fibrillation but are not discussed in detail here include other cardiopulmonary diseases (such as hypertrophic

cardiomyopathy, pericardial disease, congenital heart disease, chronic obstructive pulmonary disease and other cardiac conduction disorders), low serum magnesium, low birth weight and exercise.[29, 56, 57 58]

1.1.5 Racial differences in atrial fibrillation

A number of studies from North America have highlighted the different rates of atrial fibrillation in African Americans compared to white Americans.[5, 22, 59-64] Cross-sectional analyses have described a prevalence of 1.0% to 2.5% in African Americans compared to 2.2% to 7.8% in white Americans.[22, 62, 64] Similarly, a lower incidence of atrial fibrillation in African Americans has also been reported compared to white Americans.[5, 59, 60] These differences have been observed in spite of the higher burden of traditional atrial fibrillation risk factors seen in African Americans. Even after adjusting for these confounders, however, studies have reported a lower risk of atrial fibrillation ranging from 16% to 41%.[60] At least some of this decreased risk is thought to be due to genetic factors. In a report pooling data from multiple, prospective cohort studies using protocol-driven electrocardiograms to diagnose atrial fibrillation, thus avoiding potential bias from differential ascertainment of atrial fibrillation, African Americans were found to less atrial fibrillation and smaller left atrial diameters compared to Caucasians.[62] Using ancestry informative markers to quantify genetic ancestry in two large cohort studies, investigators have also shown that for every 10% increase in European ancestry there was a 13% increased risk of incident atrial fibrillation.[61]

Given the dichotomy between white and black Americans in previous reports, it remained previously uncertain whether African American race afforded protection against atrial fibrillation or white race conferred increased risk. Analyses of atrial fibrillation in other datasets have subsequently shown that Asians and Hispanics also have a reduced incidence of atrial fibrillation compared to white Americans.[60] In one report, data from a large trial of implantable cardiac devices provided another opportunity to describe ethnic differences in atrial fibrillation without ascertainment bias.[65] In this substudy, multiple non-European ethnic groups, including Africans, Chinese and Japanese, had comparably lower incidence of atrial fibrillation compared to patients of European race. Given the consistency of elevated risk compared to other ethnic groups, these studies further support the notion that Caucasian ancestry increases the risk of atrial fibrillation.

To the best of our knowledge, atrial fibrillation has not been previously studied in Indigenous Australians. Based on studies in other ethnicities, such as those discussed above, it might be expected that they would have a lower incidence of atrial fibrillation compared to Caucasian Australians predominantly of European ancestry. Given the frequency of risk factors in this population, however, a high prevalence of atrial fibrillation would not be unexpected.[66] Supporting this hypothesis is the well-established disproportionate burden of stroke morbidity and mortality that Indigenous Australians face.[67] Data show that the age-adjusted incidence rate of stroke in Indigenous people is approximately three-times that of other Australians.[67] National hospitalisation rates for stroke are subsequently two-times greater than in non-Indigenous Australians.[67, 68] As a result, death attributable

to stroke in Indigenous Australians is two-times greater, and up to five-times greater in younger age groups, than in non-Indigenous Australians.[68] Overall, Indigenous Australians have an excess burden of overall cardiovascular disease and 11-year lower life expectancy compared to other Australians.[69, 70] Given its associated morbidity and mortality, as discussed above, the prevention and management of atrial fibrillation in Indigenous Australians might be an opportunity to reduce this disparity if it is shown to be a possible contributor in this population.

1.1.6 Genetic differences in atrial fibrillation

Consistent with the above discussion on racial variation in atrial fibrillation being at least in-part attributable to genetic factors is its recognised hereditability. There are reports of familial atrial fibrillation, for example, from the 1930s and 1940s.[71] The aggregation of atrial fibrillation in families was subsequently recognised more frequently and noted in multiple other studies.[72, 73] Consistent with this is the fact that a parental history of atrial fibrillation has been shown to increase the risk of atrial fibrillation independent of traditional risk factors.[74] Another report also showed that a familial history predicted new-onset atrial fibrillation, having a 40% increased risk, even after adjusting for traditional risk factors and known atrial fibrillation-related genetic factors.[75]

As genetic techniques have advanced, our understanding of the genetics of atrial fibrillation has also advanced.[76] Typical Mendelian inheritance has been identified in some families, consistent with single, disease-causing genes, and genetic linkage analyses were first used to identify responsible loci.[77, 78] Brugada and colleagues

first identified a genetic locus for atrial fibrillation in 1997 in a series of related families with early onset disease.[77] In 2003, Chen and investigators identified a gain-of-function mutation in the KVLQT1 (KCNQ1) gene, which encodes a subunit of the slowly repolarising potassium channel current, in a Chinese kindred with autosomal dominant atrial fibrillation.[73] A range of other potassium channel variants have also been described.[76] Variation in sodium channel subunits have also been identified in familial atrial fibrillation – for example, variants in the major cardiac sodium channel SCN5A.[74] From these multiple reports of ion channel variation, it seems that both loss-of-function and gain-of-function variations can be associated with the develpoment of atrial fibrillation.[76]

Subsequently, genome wide association studies have been used to identify disease associations at single nucleotide polymorphisms. For example, single nucleotide polymorphisms associated with atrial fibrillation have been reported on chromosome 4q25.[79] Other reports, and particularly analyses with data from multiple cohorts, have identified single nucleotide polymorphisms associated with atrial fibrillation on other loci, including 16q22, 1q21, 1q24, 7q31, 14q23, 9q22, 15q24 and 10q22.[80] As the fields of genetics advances, it is likely that further contributing genes will subsequently be identified.

1.2 Morbidity and mortality associated with atrial fibrillation

1.2.1 Thromboembolism associated with atrial fibrillation

The most serious and common complication associated with atrial fibrillation is arterial thromboembolism, of which the most concerning is ischaemic stroke; peripheral thromboembolism accounts for less than 10 percent of thromboembolic events.[81] Atrial fibrillation causes up to one-quarter of all ischaemic strokes, and these are often more severe and disabling than ischaemic strokes from other causes.[82, 83] The incidence of stroke and peripheral thromboembolism in patients with atrial fibrillation depends on the baseline characteristics of the population studied. Large cohort studies have suggested an unselected stroke risk of approximately 4% per year in the absence of anticoagulation.[84] This risk varies considerably based on clinical risk factors, however, as will be discussed below.

The risk of thromboembolism in patients with atrial fibrillation and either moderate-to-severe mitral stenosis or mechanical prosthetic valves is significantly higher than in patients with atrial fibrillation without these conditions.[85] This is in-part related to the high risk of baseline stroke in the absence of atrial fibrillation. For example, mitral stenosis patients have been described to have a stroke risk of as high as 7 to 15% per year.[86] In those with mitral stenosis, atrial fibrillation and prior embolism, embolic rates range from 15 to 40% per year.[87] Similarly, mechanical prosthetic valves have a baseline risk of approximately 4% per year, with mitral valve prostheses having approximately twice the risk of those with aortic valve prostheses.[88] When these patients have coexistent atrial fibrillation, they have been historically, and still

commonly, termed as having 'valvular' atrial fibrillation, and patients with atrial fibrillation but without these conditions termed 'non-valvular' atrial fibrillation, though the interpretation of these terms is not without variation and clinical confusion.[85] The remainder of this section will restrict discussion to studies of thromboembolic risk factors in patients with 'non-valvular' atrial fibrillation.

The incidence of stroke associated with atrial fibrillation increases significantly with age. This is demonstrated in one large study in patients with atrial fibrillation that described a stroke rate of 0.23%, 2.05% and 3.99% per year in those aged less than 65, between 65-74, and over 75 years of age respectively.[89] For every increasing decade of age, there is a relative risk increase of 1.5.[90] Another powerful predictor of stroke is a history of prior stroke or transient ischaemic attack; this is associated with a relative risk increase of 2.5.[90] Other traditional risk factors for stroke in patients with atrial fibrillation include hypertension, diabetes mellitus and heart failure.[90, 91]

A number of risk models have been derived from analyses studying these traditional risk factors in patients with atrial fibrillation in an attempt to predict thromboembolic risk. One of the most common is the $CHADS_2$ score. The $CHADS_2$ score was based upon independent clinical predictors of thromboembolism from early studies and then validated in other cohorts.[84, 92] One point is ascribed for heart failure, hypertension, age≥75 years and diabetes, and two points for prior stroke or transient ischaemic attack. Increasing scores are associated with greater risk of events: 0.49%, 1.52%, 2.50%, 5.27%, 6.02% and 6.88% per year for $CHADS_2$ scores of 0, 1, 2, 3, 4 and 5 or 6 respectively in the absence of anticoagulation.[92]

In addition to the traditional risk factors discussed above, other factors associated with greater thromboembolic risk have since become more established in recent years. Female sex is associated with modestly increased risk; after multivariable adjustment in one cohort study, female sex was still predictive of increased stroke risk with a hazard ratio of 1.18.[93] Peripheral arterial disease, vascular disease and prior myocardial infarction have also been reported as independently associated with higher thromboembolic risk in atrial fibrillation.[94] Aortic plaque as seen on imaging studies is correlated with thromboembolic rates.[95] Chronic kidney disease has also been associated with higher rates of thromboembolism.[96] As a result, other risk models have been developed in an attempt to better improve risk stratification. The CHA_2DS_2VASc score, for example, refines the $CHADS_2$ score by ascribing one additional point for arterial vascular disease (prior myocardial infarction, peripheral arterial disease, or aortic plaque), female gender and age between 65 and 74 years, and two points instead of one point for age≥75 years.[97] These changes recognise that stroke risk increases with age, and that female sex and vascular disease have also been shown to be stroke risk factors in atrial fibrillation. A key advantage of the CHA_2DS_2VASc score is that risk stratification is improved at the lower end of the risk stratum of the $CHADS_2$ score. Other risk scores exist to predict thromboembolism in atrial fibrillation (for example, SPAF III, AFI, Framingham, R2CHADS2 and ATRIA scores) but the $CHADS_2$ and CHA_2DS_2VASc score discussed above are best known and referred to consensus guidelines.

1.2.2 Congestive cardiac failure associated with atrial fibrillation

There is a bi-directional relationship between atrial fibrillation and heart failure, and the two conditions often coexist.[31] In those with atrial fibrillation, the incidence of heart failure is 3.3% per year; conversely, in those with heart failure, the incidence of atrial fibrillation is 5.4% per year.[32] Patients with both left ventricular systolic and diastolic dysfunction are associated with atrial fibrillation.[33, 34] There are multiple mechanisms by which the presence of atrial fibrillation can cause or exacerbate heart failure. Firstly, changes in rate (both bradycardia and tachycardia) and rhythm may decrease cardiac output. Secondly, persistent tachycardia can lead to a tachycardia mediated cardiomyopathy.[98] Thirdly, a loss of atrial systole in atrial fibrillation (referred to as the atrial 'kick') results in suboptimal ventricular filling, a situation which is particularly deleterious in diastolic heart failure where filling is most dependent on atrial contraction. Finally, atrial fibrillation may activate neurohumoral vasoconstrictors, including angiotensin II and norepinephrine, in addition to other maladalptive biochemical mechanisms. As a result, considerable data suggest that the presence of atrial fibrillation is independently associated with all-cause mortality in patients with heart failure.[99]

1.2.3 Sinus node disease and syncope associated with atrial fibrillation

In addition to sinus node disease often being associated with atrial fibrillation, forming the basis for what is sometimes termed the "tachycardia-bradycardia syndrome", atrial fibrillation can itself lead to sinus node remodelling and

dysfunction. This is supported by experimental and clinical studies showing that sinus node dysfunction and remodelling occurs even after short periods of atrial tachyarrhythmias.[100, 101] Similarly, patients with atrial fibrillation not infrequently have sinus pauses on termination of atrial fibrillation, and with curative ablation can exhibit reverse remodelling of sinus node function.[102] Clinically, electrocardiographic abnormalities (bradycardia, sinus pauses and sinus arrest), can lead to symptoms of light-headedness, presyncope and syncope.[103]

1.2.4 Other cardiovascular diseases associated with atrial fibrillation

There is some data to suggest that atrial fibrillation may be associated with other cardiovascular events, such as myocardial infarction. In the Women's Health Study, for example, women with incident atrial fibrillation had a significantly greater hazard for myocardial infarction.[104] However, this relationship was driven by events in the first 30 days following atrial fibrillation diagnosis, raising the possibility that the relationship may be due to concomitant processes. Independent associations between atrial fibrillation and incident myocardial infarction have also been observed in other study cohorts.[105, 106]

1.2.5 Cognitive impairment associated with atrial fibrillation

Given atrial fibrillation is a risk factor for cerebrovascular disease, studies have subsequently assessed its relationship to cognitive impairment and dementia. In a study in elderly men, for example, an association between atrial fibrillation and low cognitive function was described, independent of stroke and other cardiovascular

risk factors.[107] Imaging studies have also shown that atrial fibrillation is associated

with hippocampal atrophy, in addition to cognitive impairment.[108] Atrial fibrillation has

also been shown to correlate with subtypes of Alzheimer's disease and vascular

dementia that could not be accounted for by clinical stroke history.[109] Brain damage

secondary to microembolism is a one hypothesis for such impairment which seems

particularly plausible given the not insignificant rates of silent cerebral infarction seen

in asymptomatic patients with atrial fibrillation.[110]

1.2.6 Mortality associated with atrial fibrillation

Atrial fibrillation is associated with an increased risk of all-cause mortality in

observational studies independent of other risk factors, though it is still considered

controversial by some as to whether this truly represents a causal relationship.[111]

After adjusting for potential confounders, the relative risk of all-cause mortality in

patients with atrial fibrillation has been reported to be approximately between 1.5

and 2.[104, 112-117] This increase in mortality is due not only to an increase in occlusive

vascular events (such as those due to coronary artery disease and stroke), but also,

an increase in rates of sudden cardiac death.[118] Furthermore, adjusting for nonfatal

cardiovascular events potentially on the causal pathway seems to attenuate but

does not render risk of death associated with atrial fibrillation nonsignificant.[104] There

is also evidence to suggest that mortality associated with atrial fibrillation is

increasing. The Global Burden of Disease 2010 Study reported that the age-

adjusted mortality rate for men and women was 0.8 and 0.9 per 100 000 population

in 1990 respectively; this increased to 1.6 and 1.7 per 100 000 in 2010 respectively.[1]

1.3 Management strategies for atrial fibrillation

1.3.1 Acute management of atrial fibrillation

Atrial fibrillation is a complex and multifaceted condition which, in addition to the heterogeneous population in which it manifests, creates a number of management issues to consider, particularly in the acute setting.[119] In patients who are haemodynamically compromised from acute atrial fibrillation, urgent electrical cardioversion is mandated; if the situation permits, peri-cardioversion bridging anticoagulation should be administered. In those who are haemodynamically stable, the initial step should be rate control aiming for a target resting heart rate below 100 beats per minute. Pharmacologic agents often employed include beta-blockers and non-dihydropyridine calcium channel blockers; less commonly, digoxin and magnesium are used though these are not recommended as first-line. If suboptimal rate control or symptoms persist after this initial step, patients who have acute atrial fibrillation with onset less than 48 hours ago have traditionally undergone cardioversion without anticoagulation. This practice of no anticoagulation has recently been called into question, however, particularly in patients with comorbidities such as heart failure and diabetes in whom the risk of thromboembolism may be as high as 9.8% despite atrial fibrillation onset less than 48 hours ago.[120, 121] As a result, recent guidelines now recommend anticoagulation during and after cardioversion in patients with acute atrial fibrillation <48 hours and with risk factors. [111, 122] In those with acute atrial fibrillation with onset more than 48 hours ago or of unknown duration, there is an increased risk of left atrial thrombus.

Cardioversion in this setting should thus only be attempted after 3 weeks of anticoagulation or after transoesophageal echocardiography to rule out left atrial thrombus. Patients who have recurrent episodes of haemodynamically stable atrial fibrillation may be candidates for an outpatient 'pill in the pocket' strategy. However, this strategy is only suitable in clinically stable individuals. A more detailed discussion on rate and rhythm control management strategies, not restricted to acute episodes of atrial fibrillation, will be discussed below. Importantly, separate to that discussed above, all patients should also have an assessment of their thromboembolic risk to determine whether they would benefit from long-term anticoagulation. This is also discussed in greater detail below. Finally, any associated medical problems, including those that may have precipitated atrial fibrillation (such as infection, inflammation, thyrotoxicosis, alcohol ingestion, electrolyte disturbances, pulmonary embolism or heart failure) should also be treated; a discussion on the management of these issues is beyond the scope of this thesis.

1.3.2 Thromboembolic risk reduction in atrial fibrillation

1.3.2.1 Anticoagulation in atrial fibrillation

Due to the significant risk of thromboembolic events, most patients with atrial fibrillation should be considered for long-term anticoagulation therapy.

Patients with valvular atrial fibrillation have sufficiently high risk of thromboembolism that anticoagulation is of definite net benefit. While anticoagulation has not been

specifically tested in comparison to placebo in this population via formal randomised trials, retrospective studies show a 4- to 15-fold decrease in thromboembolic events with anticoagulation.[88, 123, 124]

In patients with non-valvular atrial fibrillation, stroke risk varies according to the presence of clinical risk factors, and thus a balance of the thromboembolic benefits and haemorrhagic hazards of anticoagulation must be weighed, taking absolute baseline risks into consideration.

Anticoagulation with warfarin results in a two-thirds relative reduction in stroke, as shown in a meta-analysis of randomised trials in patients with atrial fibrillation and at least moderate stroke risk (relative risk reduction 64% [95% confidence interval 49-74]).[125] In comparison, the effects of anticoagulation in lower risk individuals have not been well studied in trials. There is little evidence to suggest that this relative risk reduction varies across stroke risk strata, however; in an observational study, even patients with low $CHADS_2$ scores had comparable relative risk reductions compared to higher risk categories.[92] Thus, given the reasonable evidence of homogeneity of relative benefits from anticoagulation, an assessment of absolute benefit in any patient depends on baseline stroke risk. This is commonly predicted using $CHADS_2$ or CHA_2DS_2VASc scores as discussed above. On the other hand, bleeding hazards, including intracranial haemorrhage and major extracranial bleeding, are at least doubled by anticoagulation with warfarin, though the absolute risks were very low in trials (≤0.3% per year); as a result, in the at least moderate risk patients studied in the trials included in the above meta-analysis, all-cause mortality was significantly

reduced (relative risk reduction 26% [95% confidence interval 3-43], absolute risk

reduction 1.6% per year).[125] Recent guidelines have highlighted the importance of

concurrent formal bleeding risk assessment alongside thromboembolic risk

assessment.[122, 126] Bleeding risk scores such as the $HEMORR_2HAGES$, ATRIA,

RIETE and HAS-BLED scores have been proposed to quantify haemorrhage risk. It

is important to emphasise, however, that bleeding risk scores should not be used to

exclude anticoagulation. This is because many factors that increase stroke risk also

increase bleeding risk, as evidenced by commonalities between the above-

discussed thromboembolic and bleeding risk scores. As a result, absolute

thromboembolic benefits may still outweigh absolute bleeding hazards in patients

with high thromboembolic and bleeding risk scores. This has been demonstrated in

analyses of net clinical benefit where anticoagulation is preferable in all but very low

thromboembolic risk patients with atrial fibrillation.[127]

Individuals with $CHADS_2$ scores ≥2 have an annual risk of stroke ranging from 4.0%

to 18.2%, and those with CHA_2DS_2VASc scores ≥2 with annual risk of stroke ranging

from 2.2% to 15.3%.[122] Based on these risks and the above trial evidence, at these

moderate to high levels of thromboembolic risk, anticoagulation has definite and

significant net clinical benefit; guidelines thus recommend anticoagulation in these

individuals.[122, 126] In patients at lower risk of stroke, the risk-benefit ratio becomes

less certain. Patients with $CHADS_2$ scores of 0 and 1 have approximate annual

ischaemic stroke risks of 0.6-1.0% and 3.4-3.9%, and those with CHA_2DS_2VASc

scores of 0 and 1 have approximate annual stroke risks of 0.2-0.4% and 0.6-0.9%.[94,

127] The most recent guidelines now suggest the use of CHA_2DS_2VASc scores over

CHADS$_2$ scores. For CHA$_2$DS$_2$VASc scores of 0, it is considered reasonable to omit any antithrombotic therapy. [113, 117] In those with a CHA$_2$DS$_2$VASc scores of 1, guidelines vary with suggested options including anticoagulation, aspirin or no antithrombotic therapy (Class IIa in the European Society of Cardiology guidelines, and Class IIb in the American Heart Association guidelines).[122, 126] An exception is those females with CHA$_2$DS$_2$VASc scores of 1 based only on their gender; in these individuals, the European Society of Cardiology guidelines suggest no antithrombotic therapy can be considered.[126] There remains considerable debate, however, as to what is the optimum antithrombotic therapy in patients with CHA$_2$DS$_2$VASc scores of 1. As an example, the Canadian Cardiovascular Society Guidelines suggest anticoagulation for most patients 65 years of age and greater.[128] These controversies are further fueled by the more favourable risk-benefit ratio of novel anticoagulants, discussed further in the subsequent section.

1.3.2.2 Novel anticoagulants in atrial fibrillation

In recent years, novel anticoagulants that inhibit thrombin (dabigatran) or Factor Xa (rivaroxaban, apixaban and edoxaban) have emerged as alternatives to warfarin for thromboembolic risk reduction in patients with atrial fibrillation. A meta-analysis pooled the results of the four main phase III trials assessing these novel anticoagulants compared to warfarin in atrial fibrillation.[129] Treatment with novel anticoagulants were associated with non-significantly fewer ischaemic strokes (relative risk 0.92, 95% confidence interval 0.83-1.02), a relative halving of haemorrhagic strokes (relative risk 0.49, 95% confidence interval 0.38-0.64) and

resultant decrease in any stroke or systemic embolisation (relative risk 0.81, 95%

confidence interval 0.73-0.91). There was a relative increase in gastrointestinal

bleeding by one-quarter (relative risk 1.25, 95% confidence interval 1.01-1.55). As a

result, all-cause mortality was reduced by 10% in patients treated with novel

anticoagulants compared to warfarin therapy (relative risk 0.90, 95% confidence

interval 0.85-0.95).

There are many advantages to the use of novel anticoagulants. Firstly, they would

appear to have better efficacy and safety profile compared to warfarin amongst

people similar to those in randomised trials, as discussed above. Secondly, novel

anticoagulants are not associated with dietary limitations seen with vitamin K

antagonists such as warfarin. Thirdly, repeated international normalised ratio testing

is not required as is the case in patients on warfarin therapy. Finally, they have more

predictable pharmacological profiles (including fewer drug interactions and rapid

onset/offset).

There are, however, important limitations to their use. Patients with valvular atrial

fibrillation were not included in the above trials, and they have been demonstrated to

be harmful in patients with mechanical heart valves.[130] They have also not been

studied in patients with severe or end-stage chronic kidney disease, or in patients

with significant liver disease. As a result, careful monitoring of both kidney and liver

function is required. Following on from this point is the fact that lower doses may be

more appropriate in some patient populations, including those with chronic kidney

disease, advanced age or low body weight, though the data supporting their use in

these subgroups are not as robust. There is also evidence to suggest that tailoring of dose to plasma drug concentrations might improve the risk-benefit of novel anticoagulants, though such a strategy was not tested in trials and is not currently possible in clinical practice.[131] As described above, novel anticoagulants are associated with higher rates of extracranial bleeding, though this is offset by reductions in intracranial bleeding. Similarly, a consequence of more rapid onset and offset can be that non-compliance increases the risk of thromboembolism following premature discontinuation. There has also been controversy as to whether dabigatran is associated with an increased risk of myocardial infarction as compared to warfarin therapy.[132] While they have fewer drug interactions, drugs that inhibit cytochrome P450 3A4, or are P-glycoprotein inhibitors or inducers, are either contraindicated or should be used with caution when prescribing novel anticoagulants. Finally, reversal agents are not presently available, though some are under development. This has somewhat deterred the uptake of novel anticoagulants thus far given the greater rates of major extracranial bleeding with novel anticoagulants and availability of reversal agents for vitamin K antagonists.

1.3.2.3 Antiplatelet therapy in atrial fibrillation

In comparison to anticoagulants, the evidence supporting antiplatelet therapy for thromboembolic risk reduction in atrial fibrillation is relatively modest. Only one trial has reported a significant benefit for aspirin on stroke prevention, and in totality, meta-analyses have shown there is a non-significant 19% relative risk reduction with aspirin (relative risk 0.81, 95% confidence interval 0.65-1.01).[125] Combination

antiplatelet therapy with aspirin and clopidogrel has been compared to single-agent

aspirin; while combination therapy was more effective at stroke prevention, bleeding

rates were comparable with anticoagulation.[133] Furthermore, both aspirin and

combination aspirin/clopidogrel have been shown to be substantially less effective

than warfarin.[134, 135] As a result, guidelines have de-emphasised the role of

antiplatelet therapy in recent years; the European Society of Cardiology has a Class

IIa recommendation for antiplatelet therapy if patients refuse anticoagulants, and the

American Heart Association has a Class IIb recommendation for it as an alternative

to anticoagulation or no antithrombotic agents in those with a CHA_2DS_2VASc-score

of 1.[122, 126]

1.3.2.4 Nonpharmacologic strategies

The left atrial appendage is the dominant location of thrombus formation in patients

with non-valvular atrial fibrillation.[136, 137] The importance of this location has led to

the strategy of left atrial appendage ligation, amputation or occlusion as an

alternative to antithrombotic therapy, primarily in those patients who cannot receive

long-term anticoagulation. Overall, however, the exact role of these

nonpharmacologic strategies remains uncertain and studies are ongoing.

A number of percutaneous, catheter-based methods have been developed. The best

studied so far is the WATCHMAN device, an expandable device deployed via

transeptal puncture into the left atrial appendage. Initial trial results showed non-

inferiority to warfarin for a composite endpoint of stroke, systemic embolisation and

cardiovascular death, though there higher safety events particularly due to early,

periprocedural complications.[138] While later follow-up from this trial suggested continued non-inferiority,[139] a subsequent trial did not reach the pre-specified criteria for non-inferiority with regards to its co-primary efficacy endpoint of stroke, systemic embolism and cardiovascular/unexplained death.[140] Other percutaneous, catheter-based methods include the Amplatzer Cardiac Plug[141] and the PLAATO device, the latter of which has been discontinued for safety reasons.[142] Percutaneous surgical approaches have also been studied, in particular, the LARIAT system. This system places a lasso around the left atrial appendage, tying it off from inside the pericardial space.[143] The current role for these devices is as an alternative to patients with non-valvular atrial fibrillation who have contraindications to anticoagulants. The role of such devices in all patients requiring anticoagulants continues to be debated.

1.3.3 Rate control for atrial fibrillation

Once therapy is initiated as appropriate in the acute setting in patients with atrial fibrillation, a decision will need to be made between a long-term strategy of rate control or a rhythm control. Irrespectively of the chosen strategy, however, it needs to be acknowledged that a) thromboembolic risk reduction is required regardless of this decision; b) rate control may still be necessary even in those managed with a rhythm-control strategy due to recurrent episodes of atrial fibrillation; and c) that the alternative rate or rhythm control strategy may need to be re-considered later due to the possibility of short- and long-term failure of either approach.

Randomised trials comparing rate and rhythm control strategies have demonstrated comparable outcomes with regards to thromboembolism and death.[144, 145 146-148] The

largest randomised patients aged 65 years or older to rate control (using digoxin, beta blockers and/or calcium channel blockers) or rhythm control (most commonly amiodarone and sotalol).[144] After a mean follow-up of 3.5 years, there was a non-significant increase in all-cause mortality with rhythm control that has been suggested to be due to the adverse effects of antiarrhythmic drug use.[149] Similar findings were found in a meta-analysis of all rate and rhythm control strategy trials.[150] In addition to the above findings, the frequency of recurrent atrial fibrillation and the not insignificant need to cross over to a rate control strategy are cited as reasons that a rate control strategy may be somewhat more preferable than a rhythm control strategy. For example, circumstances in which there may be a low likelihood of maintaining sinus rhythm after cardioversion include the continuous presence of atrial fibrillation for more than one year, a markedly dilated left atrium and an uncorrected underlying cause (e.g. mitral valve disease).[151-153] Other factors favouring an initial rate control strategy include a relative lack of symptoms and older age.

Once a rate control strategy has been chosen, pharmacologic therapies that block atrioventricular conduction are most often used, such as beta blockers or non-dihydropyridine calcium channel blockers. For asymptomatic patients with permanent atrial fibrillation, a relatively lenient rate control strategy targeting a resting heart rate of less than 110 beats per minute may be reasonable, though symptomatic patients may require more stringent targets.[154] In patients in whom rapid ventricular responses persist on pharmacologic therapy, or are intolerant of

such therapy, atrioventricular nodal ablation with subsequent implantation of a permanent pacemaker is also an option.[155]

1.3.4 Rhythm control for atrial fibrillation

In contrast to that discussed above, there are multiple reasons why rhythm control for atrial fibrillation may be preferable. In the rate versus rhythm control strategy trial referred to above, for example, subsequent analyses[149, 156] demonstrated that the presence of sinus rhythm regardless of strategy was associated with a significant halving in mortality (hazard ratio 0.53); a similar finding has been observed in another trial.[157] This has led to the suggestion that the maintenance of sinus rhythm may be beneficial if safer antiarrhythmic medications, or non-pharmacologic measures, were available.[158] Other patients remain persistently symptomatic while in atrial fibrillation despite adequate rate control, or are unable to attain adequate rate control, and in these individuals rhythm control may also be preferable. In others, the relation of subtle, nonspecific symptoms to atrial fibrillation may be only distinguishable by a trial of cardioversion. In general, rhythm control is also often favoured in younger patients in whom optimal cardiac performance from sinus rhythm is desirable. Finally, patients with new onset or newly recognised atrial fibrillation who are symptomatic, not very elderly, and do not have multiple comorbidities should have at least one cardioversion attempt; the likelihood of success if often high and sinus rhythm may be maintained for a relatively long period of time.

If the patient is in atrial fibrillation, cardioversion to sinus rhythm is required when a rhythm control strategy is chosen. As discussed above, careful consideration of thromboembolic and management risk should be first considered in the peri-cardioversion period as well as the longer term. The two subsequent cardioversion strategies are direct current and pharmacologic. Direct current cardioversion has an immediate success rate greater than 90% and low rate of complications.[159] While later recurrence following direct current cardioversion by itself is not uncommon, as evidenced by a report describing a 57% recurrence rate within one month in patients with chronic atrial fibrillation, there are advantages compared to pharmacologic conversion.[160] The immediate success rate of pharmacologic agents is significantly lower.[152] There is also a need for electrocardiographic monitoring to screen for proarrhythmic effects with pharmacologic agents and the possibility that atrial fibrillation may be converted to atrial flutter. Pharmacologic conversion does obviate the need for the sedation and anaesthesia required with direct current cardioversion, however, and may be thus preferable in those in whom procedural sedation risks are higher.

A number of antiarrhthythmic drugs have documented efficacy for pharmacologic conversion; these include flecianide, propafenone, ibutilide, dofetilide and, to a lesser degree, amiodarone. Vernakalant is a relatively new antiarrhythmic drug, available in intravenous form.[161] Other antiarrhythmic agents, such as sotalol and dronaderone, and rate control agents, such as digoxin, calcium channel blockers and beta blockers, are less or not effective in restoring sinus rhythm.[126] In addition to the use of antiarrhythmic drugs alone for pharmacologic conversion, they can also

be used as pre-treatment to facilitate the success of direct current cardioversion.[126] Finally, antiarrhythmic agents can be used to maintain sinus rhythm, particularly in patients in whom atrial fibrillation has either recurred or are at higher risk of recurrence (for example, due to a longer duration of atrial fibrillation, dilated left atria, left ventricular dysfunction or valvular disease).[126]

1.3.5 Other therapies for atrial fibrillation

As mentioned above, one interpretation from rate versus rhythm control strategy trials is that the findings may be due to the adverse effects of antiarrhythmic agents, rather than the equivalence of atrial fibrillation and sinus rhythm. Nonpharmacologic approaches to promote sinus rhythm are thus attractive options to avoid the potentially harmful side effects of pharmacologic therapy.

A number of surgical techniques have been developed. The original MAZE procedure and its subsequent modifications were developed first in the 1990s; these techniques surgically created a "maze" of functional atrial myocardium that reduced the likelihood of re-entry.[162] Radiofrequency energy or cryoablation techniques can also been employed during cardiac surgery, mimicking the "cut and sew" maze procedure.[163]

Percutaneous catheter ablation techniques have also been developed and are an increasingly used therapeutic approach.[164] The evolution of these procedures have been aided by an increasingly sophisticated understanding of the mechanisms underlying atrial fibrillation, as is outlined below.[165] Using either radiofrequency

energy or cryoablation, these techniques focus on isolating electrical triggers in the pulmonary veins and electrically modifying the underlying atrial substrate perpetuating atrial fibrillation. Arrhythmia free survival following ablation procedures has been demonstrated to be superior to antiarrhythmic drug therapy and with a low rate of periprocedural complications.[166, 167] Indeed, some guidelines have advocated for the use of ablation as first-line in adequately experienced centres.

1.4 Public health and economic burden of atrial fibrillation

1.4.1 Hospitalisations for atrial fibrillation

There are multiple reasons for patients with atrial fibrillation to require management within an acute-care facility or hospital. Complications from atrial fibrillation or its treatment often require inpatient management, for example due to heart failure, hypotension or thromboembolism. Treatment of associated comorbidities that may have precipitated atrial fibrillation is another reason for hospitalisation, including infection, hypertension, chronic obstructive pulmonary disease, pulmonary embolism, myocardial ischaemia and pericarditis. As discussed above, electrocardiographic monitoring while antiarrhythmic agents are initiated is an additional cause. Elderly patients may also require hospitalisation due to comorbidities that complicate pharmacologic management. Finally, nonpharmacologic therapies, such as direct current cardioversion and ablation procedures, can be additional indications for acute-care facility admission.

As a result of the above, there is considerable evidence that hospitalisations for atrial fibrillation are increasing. The majority of such studies are again from North American and European healthcare systems. A Scottish study on atrial fibrillation-related hospital activity found that, from 1986 through 1996, the number of hospitalisations for atrial fibrillation had increased three-fold from 1,869 to 5,757.[168] This was accompanied by an 80% increase in bed days utilised each year, despite a decreasing median length of stay (6 to 3 days). An analysis of Danish data additionally revealed that atrial fibrillation hospitalisations had increased by 60%

over a similar period, from 163 to 216 cases.[169] Another report utilised survey data to estimate hospitalisations in the entire United States.[170] From 1985 to 1999, these investigators estimated that hospitalisations for atrial fibrillation had increased from 154,086 to 376,487 in the United States.[170] Similarly, Canadian investigators have also described a rise in atrial fibrillation hospitalisations between 1997 and 2000.[171] The rise in the number of hospitalisations has been speculated to be due to not only ageing of the general population, but also, the greater prevalence of risk factors driving increases in atrial fibrillation incidence and, possibly also, symptomatology. Changing physician management strategies may also be affecting hospitalisations; for example, there has been a growth in admissions for ablation procedures, a concurrent decline in admissions for direct current cardioversion procedures in recent years, and clear temporal change in hospitalisation trends following the publication of major rate versus rhythm control strategy trials.[172]

1.4.2 Emergency department visits for atrial fibrillation

Emergency department visits for atrial fibrillation are also important to quantify as not all patients who present to emergency departments are subsequently admitted to hospital as inpatients. In similarity to hospitalisation data, reports suggest that emergency department visits for atrial fibrillation are also rising. In the United States, for example, between 1993 and 2004 there was an 88% increase in the absolute number of visits, from 300,000 to 564,000 per year; the admission rate remained approximately constant.[173]

1.4.3 Outpatient services for atrial fibrillation

The increasing incidence and prevalence of atrial fibrillation is also likely to have subsequent effects on outpatient management services. This is evidenced by the increasing prevalence of atrial fibrillation in patients from general practice databases.[174] Studies suggest that patients with atrial fibrillation visit general practitioners once per year.[175] This does not encapsulate hospital or specialist outpatient visits, however, and together with increasing rates of atrial fibrillation results in significant burden. In the United States alone, it has been estimated that there are 5.0 million atrial fibrillation-related office visits and 234,000 atrial fibrillation-related outpatient visits in 2001.[176] Furthermore, these patients often have a number of comorbidities and are more complex to manage as a result.[177]

1.4.4 Economic costs associated with atrial fibrillation

As a result of healthcare utilisation, there is a significant economic burden from atrial fibrillation.[176, 178-181] The total cost of direct healthcare associated with non-valvular atrial fibrillation in the United States has been recently estimated to be 6.7 billion Untied States dollars per year.[176] In the United Kingdom, direct health care costs of atrial fibrillation alone have been estimated to be 459 million pounds.[179] When indirect costs are also considered, these figures become even greater. In Greece, the annual cost is 6.2 billion euros and in Italy 3.3 billion euros.[180] Given the trends in individual components of healthcare utilisation described above, total healthcare costs are also continuing to rise over time.[179] It is possible that these figures are

also underestimates of the true cost to society as they are unlikely to adequately account for reduced society productivity, cost attributable to pain and suffering, unpaid caregivers and the burden on people with undiagnosed atrial fibrillation.

The vast majority of the economic costs associated with atrial fibrillation-related healthcare are due to hospitalisations. From the Nationwide Inpatient Survey, three-quarters of atrial fibrillation-related costs in the United States are attributable to hospitalisations.[176] Similarly, in the United Kingdom, hospitalisations accounted for half of all costs.[179] It is clear that atrial fibrillation leads to substantial public health and economic burden worldwide, and a better understanding of atrial fibrillation-related healthcare utilisation is required for appropriate healthcare planning and for interventions to reduce system demands.

1.5 Pathogenesis of atrial fibrillation

1.5.1 Electrophysiological basis of atrial fibrillation

Over there last century, there has been significant progress in understanding the electrical mechanisms underlying atrial fibrillation. While this has allowed for an evolution in management strategies, there is still significant and limiting mechanistic uncertainty.

For many years, the prevailing school of thought was that of the multiple wavelet hypothesis, as initially purported by Gordon Moe.[182, 183] According to this mechanistic theory, multiple meandering wavelets coexisted independently in the fibrillating atria. Mapping studies in the experimental setting suggested that at least 4-6 wavelets were required to maintain atrial fibrillation, and that antiarrhythmic drug therapies could decrease the number of wavelets and terminate atrial fibrillation.[184, 185] Clinical studies in the surgical setting also demonstrated multiple wavefronts, non-uniform conduction, uni-directional block and macroreentrant circuits.[186] These observations led to the MAZE procedure in which surgical compartmentalisation of the atria could interrupt the multiple wavelets maintaining atrial fibrillation, and later earlier efforts at mimicking the MAZE procedure using percutaneous radiofrequency catheter ablation.[162]

The seminal observation regarding the importance of the pulmonary veins by Haïssaguerre and colleagues was a momentous advance in our understanding of atrial arrhythmogenesis.[165] This demonstration, that focal electrical triggers are

frequently discharged from the pulmonary veins and initiate atrial fibrillation, provided the basis for pulmonary vein isolation that underlies modern radiofrequency ablation techniques. Multiple possibilities have been speculated to explain their particular importance in arrhythmogenesis. Muscular fibres at the atriovenous junction are heterogeneously arranged, supporting anisotropic conduction and micro-re-entry.[187-189] Cardiac conduction tissue in embryonic pulmonary veins and abnormal automaticity in isolated cardiomyocytes suggest that automaticity might be a mechanism.[190, 191] Early and delayed after-depolarisations from pulmonary vein cardiomyocytes have also been demonstrated following rapid atrial pacing. [192]

Localised re-entry with fibrillatory conduction as a mechanism underlying atrial fibrillation has also been observed in the pulmonary veins and left atrium. There are three requirements for re-entry to occur: 1) a central core of non-excitable tissue (anatomical, functional or mixed) around which re-entrant waves can circulate; 2) a uni-directional conduction block in along the pathway of one re-entrant wave; and 3) an "excitable gap" that is maintained ahead of the re-entrant wavefront.[193] As discussed above, the pulmonary veins and the left atrium have distinctive anatomic and subsequent electrophysiological properties that can facilitate local re-entry leading to fibrillatory conduction and arrhythmogenesis.

Finally, localised regions of high-frequency and spatio-temporal periodicity have been described as "drivers" of atrial fibrillation.[194-196] These "rotors" result in fibrillatory conduction and arrhythmogenesis when adjacent atrial myocardium is unable to maintain 1:1 conduction, and are often found in regions of anatomic

heterogeneity, such as in the pulmonary vein ostia, posterior left atrium or in more diverse atrial locations particularly in persistent atrial fibrillation.[197-199]

1.5.2 Rate-related remodelling of the atria

One method by which atrial fibrillation continues to be classified reflects its often progressive nature, transitioning from initially paroxysmal atrial fibrillation to more chronic forms including persistent atrial fibrillation, long-lasting persistent atrial fibrillation and permanent atrial fibrillation. In an attempt to explain this natural history, early studies characterised the effect that atrial fibrillation itself has on the electrical properties of the atria.

The "electrical remodelling" that takes place in the presence of atrial fibrillation was described in two seminal reports.[200] [201] In a canine model, Morillo and colleagues described reductions in effective refractory periods after six weeks of continuous atrial pacing, and this was highly predictive of atrial fibrillation inducibility.[200] In a study that popularised the phrase "atrial fibrillation begets atrial fibrillation", Wijffels and investigators similarly observed that with progressively longer intervals of atrial fibrillation there was a concurrent shortening of the fibrillatory interval; after cardioversion, these electrophysiological changes reversed within a week.[201] Subsequently, comparable tachycardia-related shortening of the effective refractory period was also demonstrated in humans.[202] Other studies have also shown that, in addition to decreasing refractory periods, there is also greater heterogeneity of refractoriness and a loss of normal rate adaptation of refractoriness which also facilitates arrhythmogenesis.[203, 204]

It has been shown that fibrillatory intervals are correlated with atrial effective refractory periods and functional refractory periods, allowing their use in the study of electrical remodelling when direct measurement is not available.[205, 206] Fibrillatory intervals have been shown to shorten, become more disorganised, and also less disperse as atrial fibrillation progresses from paroxysmal to more chronic forms.[207, 208] Comparing fibrillatory interval characteristics between the left and right atria also suggests greater electrical remodelling in the left compared to right atrium, with shorter fibrillatory intervals and greater disorganisation in the former.[209]

Conduction velocity remains largely unchanged, or even increases, during initial periods of atrial arrhythmias, in contrast to early decreasing refractoriness.[203] With increasingly longer durations of atrial arrhythmias, however, there is a gradual slowing in atrial conduction velocities.[201] In an experimental model of sustained atrial flutter, for example, atrial conduction velocity slowed from day 0 to day 28, though these changes occurred more gradually than those of atrial refractoriness.[210] Clinical studies have more often used surrogate measures of conduction velocity, including P wave duration indices, linear conduction between two points, the presence of fractionated electrograms and, more recently, electroanatomical mapping wavefront propagation.[211]

Electrical remodelling of the atria in response to tachycardia is also associated with sinus node dysfunction. In experimental models, rapid atrial pacing has been shown to be followed by prolongation of corrected sinus node recovery times and sinus cycle lengths.[100] Similar prolongation of sinus node recovery time, sinus cycle length

and sinoatrial conduction time has also been demonstrated in humans following rapid atrial pacing.[101] Bradycardia from sinus node dysfunction increases the time window which, via greater atrial ectopy and dispersion of refractoriness, can contribute to arrhythmogenesis.[212]

The potential mechanisms responsible for the electrical changes described above are many. Atrial ion currents have been well studied, and abnormalities in calcium, potassium and sodium currents documented.[213] It is likely that other factors separate to electrical remodelling must also be involved in the development of the substrate supporting atrial fibrillation. This is suggested by cumulative atrial fibrillation stability with repeated episodes despite reversal of electrical remodelling between episodes.[214] Supporting this theory of a 'second factor' independent of electrical remodelling is the demonstration of significant electrophysiologic and electroanatomic abnormalities in patients with lone atrial fibrillation.[215]

1.5.3 Atrial substrates in predisposing conditions

As described earlier in this Chapter, there are a number of conditions shown to be associated with the development of atrial fibrillation in epidemiologic reports. Experimental and clinical studies have demonstrated abnormalities of the atrial substrate underlying these conditions that contribute to arrhythmogenesis.

In a preclinical study, Li et al described the electrophysiological and histological characteristics seen in congestive heart failure.[216] A dog model of congestive heart failure induced by rapid ventricular pacing was compared to control dogs and those

receiving only rapid atrial pacing. Congestive heart failure dogs did not exhibit any changes in atrial effective refractory periods in contrast to rapid atrial pacing dogs. There was, however, increasing conduction heterogeneity which histological examination suggested was due to extensive interstitial fibrosis.

In the clinical setting, Sanders and colleagues studied the electrophysiological and electroanatomic atrial substrate in patients with symptomatic congestive heart failure.[217] Compared to controls, patients with congestive heart failure demonstrated increases in effective refractory period, slowing in conduction velocities, evidence of conduction heterogeneity, sinus node dysfunction and areas of low voltage.

Comparable reports have similarly studied other predisposing substrates in preclinical and clinical models. Ageing has been shown to result in widespread electrophysiological abnormalities and increased interstitial fibrosis.[218, 219] Hypertension similarly results in electrical changes, left atrial dilation, interstitial fibrosis and inflammatory infiltrates.[220-222] Electrophysiologic, electroanatomic and histological changes have also been seen in other predisposing conditions, including valvular disease, atrial septal defects, sinus node dysfunction, myocardial ischaemia and obstructive sleep apnoea.[223-228] In contrast, the effects of obesity on atrial remodelling have not been as well studied, despite its increasing importance as a risk factor. Potential mechanisms underlying the atrial substrate in obesity are discussed in greater detail later in this Chapter.

1.6 Obesity and atrial fibrillation

1.6.1 Population studies in obesity and atrial fibrillation

Obesity is a risk factor with increasingly broad implications for health, not only in developed countries, but increasingly also in developing countries undergoing epidemiologic transition.[229]

While initially controversial as a potential risk factor for atrial fibrillation, data supporting the relationship between obesity and atrial fibrillation are now convincing. In the Framingham Heart Study, obesity was associated with a 40-50% increased risk of incident atrial fibrillation.[27] Comparable data have been reported in a number of other cohort studies. [49, 230-235] One previous meta-analysis pooling data from a number of cohort studies concluded that obese individuals have a 49% increased risk of developing atrial fibrillation compared to non-obese individuals.[236] Based on post-cardiac surgery studies, this report also concluded that there was no increased risk of post-operative atrial fibrillation with obesity. One limitation of this report, however, is that it only included studies reporting risk estimates within body mass index categories and thus was not able to take into account the totality of available evidence regarding obesity and atrial fibrillation.

Obesity may also influence the progression of existing atrial fibrillation. In a longitudinal cohort study, for example, obesity was associated with at least a 1.5 fold increase in the risk of progressing from paroxysmal to permanent atrial fibrillation in adjusted models.[237] The association between body mass index and atrial fibrillation

was also stronger for sustained atrial fibrillation compared to transitory or intermittent atrial fibrillation in one case-control analysis.[238]

Of all atrial fibrillation risk factors, obesity is one of the most important and influential. It has been estimated that obesity accounts for one-fifth of all atrial fibrillation cases.[239] This is partly as a result of the significant population prevalence of obesity. In the United States, the adult prevalence of obesity is 34.9%.[240] In Australia, 62% of the adult population is either overweight or obese.[241] Furthermore, rising obesity rates has increased the proportion of atrial fibrillation attributable to obesity; data suggests that obesity could account for approximately 60% of the rising age- and sex-adjusted incidence of atrial fibrillation.[4] From these data, it is clear that any preventative and therapeutic efforts to slow the increasing burden of atrial fibrillation must address obesity as a key risk factor.

1.6.2 Mechanistic studies in obesity and atrial fibrillation

1.6.2.1 Structural remodelling in obesity

The mechanisms underlying the promotion of atrial fibrillation by obesity remain poorly understood. Obese patients have been shown to have higher mean left atrial pressures, volumes and strain.[242] Similarly, however, investigators elsewhere have also highlighted the role that impaired diastolic dysfunction may have in mediating the relationship between obesity and atrial fibrillation.[243] Population studies have shown that obesity is a powerful determinant of left atrial enlargement, an important risk factor for atrial fibrillation, as evidenced by left atrial size attenuating the

epidemiologic relationship between obesity and atrial fibrillation in one study.[27]

Furthermore, weight loss may also promote favourable reverse remodelling of the

left atrium, supporting the important role that left atrial size may play in mediating

this relationship.[244] In experimental studies, progressive weight gain has also

resulted in increasing left atrial volume and pressure.[245] This was accompanied by

interstitial fibrosis, inflammation and lipidosis.

1.6.2.2 Electrical abnormalities in obesity

As discussed above, shorter effective refractory periods can sustain or perpetuate

atrial fibrillation. Given the critical nature of the pulmonary veins in initiating and

maintaining atrial fibrillation, Munger and colleagues studied effective refractory

periods in the pulmonary veins of obese patients and found that these were

substantially shorter than in non-obese individuals.[242] These individuals could not

demonstrate a difference in left atrial conduction velocities and scar between obese

and non-obese individuals. This is in contrast to other data suggesting that

conduction is affected in obese individuals, as suggested by P wave indices,

independent of other factors.[246]

Experimental models have provided more detail into resultant atrial electrical

abnormalities from obesity. In contrast to the above clinical study, progressive

weight gain in an ovine model was associated with no change in effective refractory

period, a decrease in conduction velocity and increase in conduction

heterogeneity.[245] Zucker rats were used to study the interaction between obesity,

obstructive sleep apnoea and atrial fibrillation in another study; apnoea caused

acute left atrial dilation significantly more in obese rats due to left ventricular diastolic dysfunction, promoting greater atrial fibrillation.[247]

1.6.2.3 Pericardial and epicardial fat

The terms epicardial fat, paracardial and pericardial fat, have been used interchangeably throughout the literature, despite differences in location and function. They are often collectively referred to as cardiac ectopic fat or cardiac adipose tissue. Pericardial fat consists of two layers: the visceral, epicardial fat layer and the parietal, paracardial fat layer. Epicardial fat is adipose tissue layer situated between the myocardium and visceral pericardium. Paracardial fat is the adipose tissue layer located external to the parietal pericardium. Given the different embryological origins and vascular supply of these two fat depots, there is reason to suspect they may have distinct biochemical properties. However, there is a lack of standardised nomenclature and few reports have individually studied each depot in relation to metabolic parameters and outcomes. Keeping this in mind, subsequent discussion refers to individual fat depots as defined by the authors of each study.

Cardiac ectopic fat has been suspected to be associated with atrial arrhythmias since the 1960s. [248-251] Without the availability of modern imaging techniques, it was recognised in necropsy observations that some individuals demonstrated prominent amounts of fatty deposits both in the interatrial septum and in the epicardial space. It was hypothesised that 'lipomatous hypertrophy' of the interatrial septum might interrupt electrical pathways to facilitate atrial arrhythmogenesis.[252] In recent years, a number of studies have able to accurately quantify cardiac ectopic fat using

modern imaging techniques. These described similar associations between fat

layers surrounding the heart and the presence and chronicity of atrial fibrillation and,

taken together, have provided suggestive evidence supporting a relationship

between the two entities. [253, 254] [255-257]

The potentially arrhythmogenic mechanisms of cardiac ectopic fat are debated and

the subject of ongoing study. Visceral ectopic fat depots are thought to exert

systemic and local effects.[258] Fat depots such as visceral adipose tissue,

intrahepatic fat/fatty liver and intramuscular fat have been shown to be associated

with a number of systemic metabolic derangements, supporting the theory of their

systemic pathological effect.[259, 260] The proximity of these fat depots to organs

involved in insulin, glucose and lipid metabolism are speculated to facilitate these

derangements. In contrast, fat depots such as epicardial fat, pericardial fat,

perivascular fat and renal sinus fat are thought to have local toxic effects.[258] With

regards to investigations pertaining to epicardial and pericardial fat, a number of

studies provide increasing mechanistic evidence. Epicardial fat is a source of various

inflammatory mediators and other bioactive molecules. [261] As an endocrine and

paracrine organ, in this way it has been hypothesised that released adipokines and

free fatty acids could directly influence the adjacent myocardium and coronary

arteries. Similarly, epicardial fat has been demonstrated to have significant

elevations in inflammatory infiltrates, and the presence of lymphocytes,

macrophages and mast cells, compared to subcutaneous fat,. [262] Epicardial fat also

demonstrates greater expression of key inflammatory signaling molecules such as

inflammatory-nuclear factor kappaB and c-Jun N-terminal kinase activity compared

to subcutaneous fat.[263] Others have also shown via proteomic analysis higher levels of reactive oxygen species and lower levels of catalase in epicardial fat compared to subcutaneous fat.[264] In an ex vivo model of rat atrial organoculture, the effects of adipose tissue secretomes on myocardium were studied.[265] Conditioned medium from human epicardial adipose tissue, but not subcutaneous adipose tissue, was shown to induce fibrosis of atrial myocardium. The adipokine Activin A also showed a marked fibrotic effect which could be blocked with a neutralising antibody.

It has been previously suggested by epidemiologic studies that the relationship between body mass index and atrial fibrillation may be mediated by changes in cardiac structure, as discussed above.[27] However, there is also growing evidence linking epicardial and pericardial fat with cardiac structure. Pericardial fat volumes have shown to be independent predictors of left atrial diameter and volume. [256, 266] Others have described infiltration of fat into the atria and ventricles and a correlation between epicardial fat and myocardial fat content by magnetic resonance spectroscopic.[267-269] Such structural lipid remodelling could lead to heterogenous conduction and non-uniform anisotropy, predisposing to arrhythmogenesis.[270-273]

Since the relationship between cardiac ectopic fat and atrial fibrillation has become apparent, a few investigators have studied the relationship between epicardial or pericardial fat and atrial fibrillation ablation outcomes. Tsao studied 68 patients with paroxysmal and persistent atrial fibrillation and found that computed tomography measured epicardial fat volume surrounding the left atrium was associated with atrial fibrillation recurrence. [35] Similarly, Nagashima reported that computed tomography

measured epicardial fat volume surrounding the left atrium was associated with atrial fibrillation recurrence in a cohort of 40 patients with paroxysmal and persistent atrial fibrillation.

In addition to those discussed in the preceding section, the findings of the above studies provide further insight into possible mechanisms underlying the relationship between epicardial fat, pericardial fat and atrial fibrlilation. Cardiac ectopic fat contain numerous ganglionated plexi that have long been hypothesised to facilitate the occurrence of atrial fibrillation via their role in the cardiac autonomic nervous system.[274] Studies have shown, albeit variably, that ablation of ganglionated plexi may potentially reduce atrial fibrillation inducibility.[275, 276] Consistent with this, one recent report described how epicardial fat correlated anatomically with endocardial sites of high dominant frequency, suggesting a potential role in supporting atrial fibrillation drivers.[277] Another recent study found that obese patients had significantly shorter effective refractory periods in the left atrium and pulmonary veins than normal weight individuals, though epicardial or pericardial fat was not measured.[242] Put together, these lines of evidence suggest additional neural mechanisms may link pericardial/epicardial fat and atrial fibrillation; patients with greater amounts of ectopic cardiac fat may have increased intrinsic adrenergic and cholinergic nerve structures within ganglionated plexi.[278]

To date, there are also few studies assessing the effect of weight loss on epicardial or pericardial fat. A well-conducted recent study in bariatric surgery patients provides key initial information. In this study, investigators used measured epicardial fat

volumes using magnetic resonance imaging, in addition to computed tomography measured visceral abdominal fat and standard body mass index.[279] They found that bariatric surgery significantly reduced epicardial fat volumes. Interestingly, the decrease in epicardial fat volumes was not correlated with the decrease in visceral abdominal fat or body mass index, suggesting heterogenous effects of weight loss on differing fat depots. Whilst no published reports exist on weight loss and cardiac ectopic fat in patients with atrial fibrillation yet to the best of our knowledge, preliminary data from our group suggests that weight loss may potentially reverse obesity-related electrical and structural remodelling, and improve atrial fibrillation symptoms.[280, 281]

CHAPTER 2: TRENDS IN HOSPITALISATIONS FOR ATRIAL FIBRILLATION

2.1 Introduction

Atrial fibrillation is the most common sustained heart rhythm disorder.[4] Though initially thought to be a benign condition, it is now well appreciated that atrial fibrillation is associated with significant morbidity and mortality.[22, 282] As a result, atrial fibrillation represents a considerable economic and public health burden.

A number of studies suggest that the prevalence of atrial fibrillation and subsequent utilisation of health care services is increasing.[17, 22, 168, 169, 171, 173, 283-286] From a sample of hospitals in the United States, it has been estimated that atrial fibrillation hospitalisations have increased 2- to 3-fold from 1985 to 1999, and that these have been increasing more so than any other arrhythmia.[170, 283] European reports have likewise shown dramatic increases in the atrial fibrillation hospitalisations, with Scotland also demonstrating a 2- to 3-fold increase between 1986 and 1996.[168, 284, 286] The reasons underlying these trends are numerous, but are at least in-part due to ageing populations and prolonged exposure to predisposing conditions as a result of improving medical care.

Given the vast majority of the economic cost associated with atrial fibrillation is borne by hospital systems, trends in hospitalisations for this common condition are of paramount public health and clinical importance.[176, 179, 287] As such, we sought to examine nationwide trends in atrial fibrillation hospitalisations across the entirety of Australia over a 15-year period. In this report, we also compared these trends to

those for two other common cardiovascular conditions, myocardial infarction and

heart failure. Our reports presents a recent update on atrial fibrillation

hospitalisations trends compared to these two other conditions and also, to the best

of our knowledge, represents the first nationwide data on hospitalisations for atrial

fibrillation outside North America and Europe.

2.2 Methods

2.2.1 Data source

Data were obtained from the National Hospital Morbidity Dataset, a source maintained by the Australian Institute of Health and Welfare that includes inpatient information at every hospital in Australia. The proportion of missing data is negligible, representing less than 0.004% of cases per year.

We identified hospitalisations with a principal diagnosis of atrial fibrillation across a 15-year period from 1993 through to 2007 inclusive. The *International Classification of Diseases 9th Rev, Clinical Modification* (ICD-9-CM) and *ICD 10th Rev, Australian Modification* (ICD-10-AM), were used for coding hospitalisation diagnoses between 1993-1997 and 1998-2007 respectively. Atrial fibrillation was defined for patients with ICD-9-CM 4273, and ICD-10-AM I48, codes that include both atrial fibrillation and atrial flutter. Myocardial infarction was defined for patients with ICD-9-CM 410, and ICD-10-AM I21. Heart failure was defined for patients with ICD-9-CM 428, and ICD-10-AM I50. We also calculated the total number of all hospitalisations for any diagnosis to characterise the relative burden of atrial fibrillation, myocardial infarction and heart failure. Hospitalisation data are presented for the number of hospitalisations, age grouping, length of stay and total hospital bed utlisation. The prevalence of hospitalisations are expressed per 10 000 population, and Australian Bureau of Statistics population estimates utilised.[288]

We additionally reviewed hospitalisations with atrial fibrillation and heart failure as principal and secondary diagnoses, as an increased awareness of and/or emphasis on atrial fibrillation in recent years may have influenced coding practices such that hospitalisations attributed to heart failure in the past might be increasingly attributed to atrial fibrillation.

2.2.2 Statistical analysis

Time trends in the yearly number of hospitalisations were assessed using negative binomial regression models. Comparisons were made both within and between conditions, and by age group and sex. Time trends in the yearly prevalence of hospitalisations, defined as the number of hospitalisations in a calendar year divided by midyear population estimates, were analysed as above but with the logarithm of the population size included as an offset variable in the models. Prevalence rates were also investigated by directly standardising yearly hospitalisation counts to the 2007 Australian population age/sex structure. Finally, time trends in length of stay and bed days utilised were assessed using negative binomial regression models. All analyses were performed using SAS Version 9.2 (SAS Institute Inc., Cary, NC, USA), and statistical significance was set at $p<0.05$.

2.3 Results

2.3.1 Total hospitalisations

Over a 15-year period from 1993 to 2007, there were a total of 93,029,656 hospitalisations for any diagnosis in Australia (representing a follow-up period of almost 300 million person-years). We identified a total of 473,501 atrial fibrillation hospitalisations, 208,305 myocardial infarction hospitalisations and 622,082 heart failure hospitalisations. Annual hospitalisations for each condition are shown in Figure 2.1. There was a relative increase in number of hospitalisations for atrial fibrillation of 203% from 1993 to 2007. Negative binomial regression analysis revealed a relative annual increase of 7.9% (rate ratio 1.079, 95% confidence interval 1.069-1.088, p<0.001). This was in contrast to a relative increase in the number of all hospitalisations of only 71%, or an estimated 3.7% annually (rate ratio 1.037, 95% confidence interval 1.036-1.039, p<0.001). As a result, atrial fibrillation as a percentage of all hospitalisations increased by an estimated 4.0% annually (rate ratio 1.040, 95% confidence interval 1.031-1.050, P<0.001; see Figure 2.2).

In contrast, the number of hospitalisations for myocardial infarction and heart failure only demonstrated relative increases of 79% and 17%, or an estimated 4.5% (rate ratio 1.045, 95% confidence interval 1.040-1.050, p<0.001) and 0.7% (rate ratio 1.007, 95% confidence interval 1.004-1.009, p<0.001) annually respectively. There was a significant interaction between year and condition (p<0.001), with a greater increasing trend in the number of hospitalisations for atrial fibrillation compared to myocardial infarction and heart failure (p<0.001 for both). Similarly, atrial fibrillation

and myocardial infarction as a rate of total hospitalisations increased by 4.0% (rate ratio 1.040, 95% confidence interval 1.031-1.048, p<0.001) and 0.7% (rate ratio 1.007, 95% confidence interval 1.001-1.013, p=0.014) annually respectively, compared to heart failure which decreased by 3.0% annually (rate ratio 0.970, 95% confidence interval 0.968-0.973, p<0.001).

2.3.2 Prevalence of hospitalisations

After accounting for annual population estimates, the prevalence of atrial fibrillation hospitalisations increased by 155%, or an estimated relative increase of 6.5% annually (rate ratio 1.065, 95% confidence interval 1.056-1.075, p<0.001; Table 2.1). The prevalence of myocardial infarction hospitalisations only increased by 50% (3.2% relative annual increase, rate ratio 1.032, 95% confidence interval 1.027-1.037, p<0.001) and the prevalence of heart failure hospitalisations decreased by 2% (3.0% relative annual decrease, rate ratio 0.970, 95% confidence interval 0.968-0.973, p<0.001).

When standardised to the age and sex structure of the population in 2007, the differences between conditions became even more pronounced (Figure 2.3). Whilst the rate of atrial fibrillation hospitalisations showed a relative annual increase of 4.9% (rate ratio 1.049, 95% confidence interval 1.041-1.058, p<0.001), myocardial infarction hospitalisations only increased annually by 2.0% (rate ratio 1.020, 95% confidence interval 1.016-1.025, p<0.001) and heart failure hospitalisations decreased annually by 2.2% (rate ratio 0.978, 95% confidence interval 0.976--0.981, p<0.001).

2.3.3 Length of stay and total bed days utlised

The average length of stay of hospitalisations for atrial fibrillation fell from 4.0 to 3.1 days (1.8% relative annual decrease, rate ratio 0.982, 95% confidence interval 0.978-0.987, p<0.001; Table 2.2). Similarly, the average length of stay for myocardial infarction and heart failure fell from 8.2 to 5.4 days (2.7% relative annual decrease, rate ratio 0.974, 95% confidence interval 0.971-0.976, p<0.001) and 10.4 to 7.8 days (1.8% relative annual decrease, rate ratio 0.982, 95% confidence interval 0.978-0.987, p<0.001) respectively. Despite this decrease in average length of stay, the increase in atrial fibrillation hospitalisations resulted in a 125% increase in the total bed days utilised for atrial fibrillation hospitalisations (5.9% relative annual increase, rate ratio 1.059, 95% confidence interval 1.055-1.063, p<0.001). In contrast, there was only an 18% increase in bed days utilised for myocardial infarction hospitalisations (1.7% relative annual increase, rate ratio 1.017, 95% confidence interval 1.010-1.024, p<0.001), and a 15% decrease in bed days utilised for heart failure hospitalisations (1.1% relative annual decrease, rate ratio 0.989, 95% confidence interval 0.985-0.993, p<0.001) respectively.

2.4 Discussion

2.4.1 Major findings

Over a 15-year period of time from 1993 to 2007, we examined the trends in hospitalisations for atrial fibrillation across the entirety of Australia and contrasted these with those of myocardial infarction and heart failure.

We showed that the total number of hospitalisations for atrial fibrillation had increased significantly compared to myocardial infarction and heart failure. These differences were even more pronounced when the prevalence of these hospitalisations were examined. Furthermore, despite similar decreases in length of stay for all three conditions, there was a striking increase in the number of bed days utilised for atrial fibrillation. By the end of the study period, atrial fibrillation had surpassed heart failure with regards to number of hospitalisations and was approaching that for myocardial infarction.

2.4.2 Trends in hospitalisations for atrial fibrillation

Reports in recent years have highlighted the public health burden that atrial fibrillation increasingly represents. [4, 22] Importantly, it has been recognised that hospitalisations account for the majority of the cost associated with atrial fibrillation.[172, 176, 178, 179] A Scottish study on atrial fibrillation-related hospital activity found that, from 1986 through 1996, the number of hospitalisations for atrial fibrillation had increased three-fold from 1,869 to 5,757.[168] This was accompanied by

an 80% increase in bed days utilised each year, despite a decreasing median length of stay (6 to 3 days). An analysis of Danish data additionally revealed that hospitalisations had increased by 60% over a similar period, from 163 to 216 cases.[169] Another report utilised survey data to estimate hospitalisations in the entire United States.[170] From 1985 to 1999, these investigators estimated that hospitalisations for atrial fibrillation had increased from 154,086 to 376,487 in the United States.[170] Similarly, Canadian investigators have also described a rise in hospitalisations between 1997 and 2000.[171]

Despite the limitations of representative data and modest-sized cohorts, these studies highlighted a growing clinical and public health problem. We sought to not only confirm whether such trends were continuing in recent years and whether they were also occurring in populations outside North America and Europe, but additionally sought to contrast them with that of two common cardiovascular conditions. We observed that the increase in atrial fibrillation hospitalisations observed overseas is indeed occurring nationwide in Australia and has shown no sign of abating since prior studies, with a 203% increase from 1993 to 2007. Prior reports suggested that heart failure once accounted for twice as many hospitalisations as atrial fibrillation.[168] Whilst this may have been the case at the beginning of our study period, atrial fibrillation hospitalisations have since surpassed that for heart failure and are approaching that for myocardial infarction. The declining heart failure hospitalisation rate has also been observed elsewhere; from 1994 to 2004 in Canada, hospitalisations for heart failure fell by 27% compared to only 9% for myocardial infarction.[289] A Scottish study similarly concluded that the previous

'epidemic' of heart failure hospitalisations had peaked around 1993-1994.[290] More recently, the heart failure hospitalisation rate in the United States has been shown to have decreased by 29.5% from 1998 to 2007.[291] Though we were unable to link data on implantable cardioverter-defibrillator trends with heart failure hospitalisations in our study, the number of these procedures has been increasingly significantly in recent years.[292] The decrease in heart failure hospitalisations in contrast to this increase is thus more remarkable given many of these would have been associated with heart failure hospitalisations. With regards to myocardial infarction, our data showed that hospitalisations for myocardial infarction are continuing to increase though at a slower rate compared to atrial fibrillation. These findings are in contrast to other studies, however, which have noted a recent decrease in myocardial infarction incidence.[293-296] The reasons for this are not clear but may reflect differing burdens of predisposing conditions in the Australian population, such as obesity and diabetes, or the use of increasingly sensitive cardiac biomarkers; these trends require further study elsewhere.

2.4.3 Possible reasons for increase in hospitalisations for atrial fibrillation

A number of reasons are likely to be contributing to the rise in atrial fibrillation hospitalisations. The ageing population is certainly contributing. Improving medical care has also resulted in individuals having a more prolonged exposure to traditional and newer risk factors for atrial fibrillation, such as obesity and obstructive sleep apnoea.[3, 49, 256, 297] A previous report also noted that major "rate-versus-rhythm" trials in 2002 was followed by a decline in direct current cardioversions.[172] It is possible

that changing physician management practices with regard to not only direct current cardioversion but also other procedures, such as catheter ablation proedures, may be influencing trends.

It is also possible that an increasing emphasis on atrial fibrillation may have affected physicians' diagnoses and thus hospitalisation codes. This may have accounted in-part for some of the observed trends, particularly when both atrial fibrillation and heart failure were present concurrently. However, the total increase in the number of atrial fibrillation hospitalisations far exceeds the total decrease in heart failure hospitalisations and thus this could not completely account for the observed trends.

2.4.4 Clinical implications

The growing number of atrial fibrillation hospitalisations shows no sign of abating and in the context of ageing population structures represent a staggering economic burden. Hospitalisations have repeatedly been confirmed as the major cost driver associated with atrial fibrillation.[176, 178, 179, 287] Healthcare planning and practitioner-education is warranted to ensure that efficacious and cost-effective management strategies are employed to minimise the risk of hospitalisation in patients with atrial fibrillation. Greater attention on primary prevention strategies will also be required to contain this growing epidemic.

2.4.5 Limitations

As discussed above, an increased awareness of and/or emphasis on atrial fibrillation may have led to more frequent coding, particularly in place of heart failure. Our analysis on hospitalisations involving both conditions, however, suggests that this contribution is likely to have been small. It was also not possible to determine whether cases were de novo or repeat hospitalisations, though each still represents additional burden regardless. Finally, information on hospital demographics was not available; such data may have provided further insights into the factors driving hospitalisations.

2.5 Conclusion

This is the first report on nationwide trends in hospitalisations for atrial fibrillation outside North America and Europe. Hospitalisations for atrial fibrillation have increased dramatically in recent years in Australia. The public health burden of this condition is enormous and is increasing at a rate greater than that of other common cardiovascular conditions, such as myocardial infarction and heart failure. These findings have important implications for healthcare planning and the need for better primary prevention and treatment of atrial fibrillation.

Table 2.1: Atrial fibrillation hospitalisations and incidence (per 10 000 population)

Year	AF, No. (per 10 000)	MI, No. (per 10 000)	HF, No. (per 10 000)
1993	15 555 (8.8)	31 194 (17.7)	38 700 (21.9)
1994	17 995 (10.1)	31 624 (17.7)	39 617 (22.2)
1995	19 601 (10.9)	32 997 (18.3)	40 543 (22.4)
1996	22 055 (12.0)	32 807 (17.9)	40 851 (22.3)
1997	25 096 (13.6)	33 258 (18.0)	41 660 (22.5)
1998	27 245 (14.6)	33 548 (17.9)	41 825 (22.4)
1999	31 109 (16.4)	35 417 (18.7)	41 624 (22.0)
2000	32 248 (17.4)	37 670 (19.7)	41 049 (21.4)
2001	36 156 (18.6)	40 331 (20.8)	41 824 (21.5)
2002	36 654 (18.6)	43 764 (22.3)	41 007 (20.9)
2003	36 191 (18.2)	46 883 (23.6)	41 355 (20.8)
2004	38 296 (19.0)	47 629 (23.7)	41 263 (20.5)
2005	41 510 (20.4)	49 533 (24.3)	42 005 (20.6)
2006	45 618 (22.0)	51 664 (25.0)	43 631 (21.1)
2007	47 164 (22.4)	55 676 (26.5)	45 128 (21.5)
Relative increase 1993 to 2007*, %	**203.2 (155.0)**	**78.5 (50.0)**	**16.6 (-2.0)**

* 2007 value minus 1993 value divided by 1993 value, multiplied by 100.

AF = atrial fibrillation, MI= myocardial infarction, HF = heart failure.

Table 2.2: Length of stay and total bed days utilised

Year	Average length of stay (days)			Total bed days utilised (days)		
	AF	MI	HF	AF	MI	HF
1993	4.2	8.2	10.4	64 608	254 279	402 418
1994	4.0	7.5	9.6	71 367	237 122	381 102
1995	3.8	7.2	9.0	74 496	235 967	367 067
1996	3.6	7.0	8.6	80 263	230 268	353 498
1997	3.5	6.7	8.4	87 536	222 415	349 811
1998	3.3	6.5	8.2	90 520	219 319	343 417
1999	3.2	6.4	8.4	99 867	225 948	348 683
2000	3.1	6.2	8.1	104 152	234 325	334 792
2001	3.1	6.1	8.0	112 984	246 651	335 540
2002	3.3	5.9	7.9	119 285	258 544	324 459
2003	3.3	5.8	8.0	117 723	270 125	331 059
2004	3.2	5.7	7.9	122 193	270 756	324 892
2005	3.2	5.6	7.8	134 405	276 274	326 602
2006	3.2	5.5	7.7	144 476	284 696	335 832
2007	3.1	5.4	7.6	145 200	300 689	341 967
Relative increase 1993 to 2007*, %	**-26.2**	**-34.1**	**-26.9**	**124.7**	**18.3**	**-15.0**

* 2007 value minus 1993 value divided by 1993 value multiplied by 100.

AF = atrial fibrillation, MI= myocardial infarction, HF = heart failure.

Figure 2.1: Number of hospitalisations for atrial fibrillation, myocardial infarction and heart failure from 1993 through 2007 inclusive
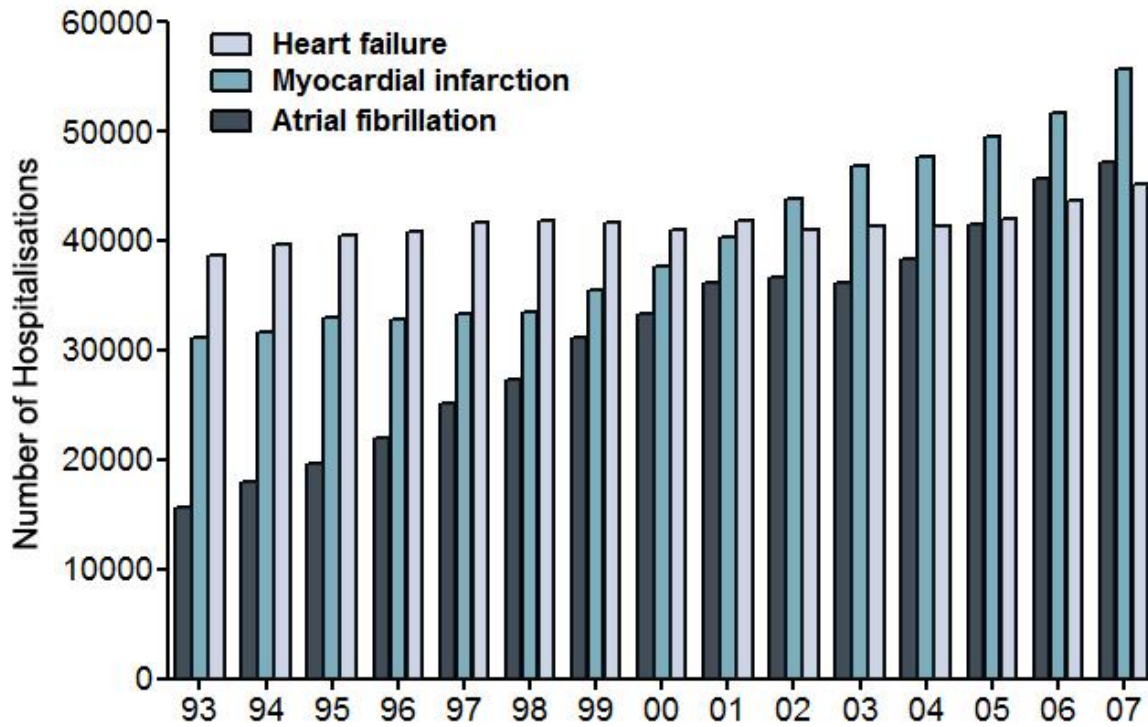
Figure 2.2: Hospitalisations for atrial fibrillation, myocardial infarction and heart failure as a percentage of total hospitalisations from 1993 through 2007 inclusive
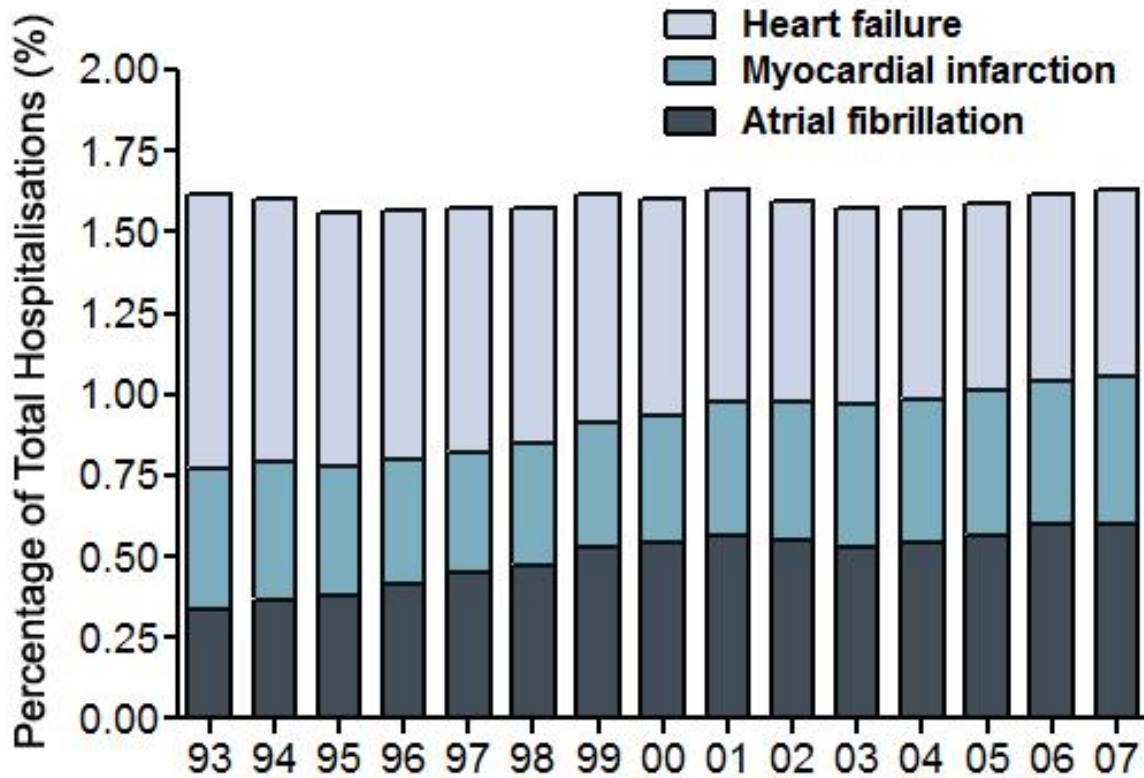
Figure 2.3: Trends in hospitalisation rates for atrial fibrillation, myocardial infarction and heart failure
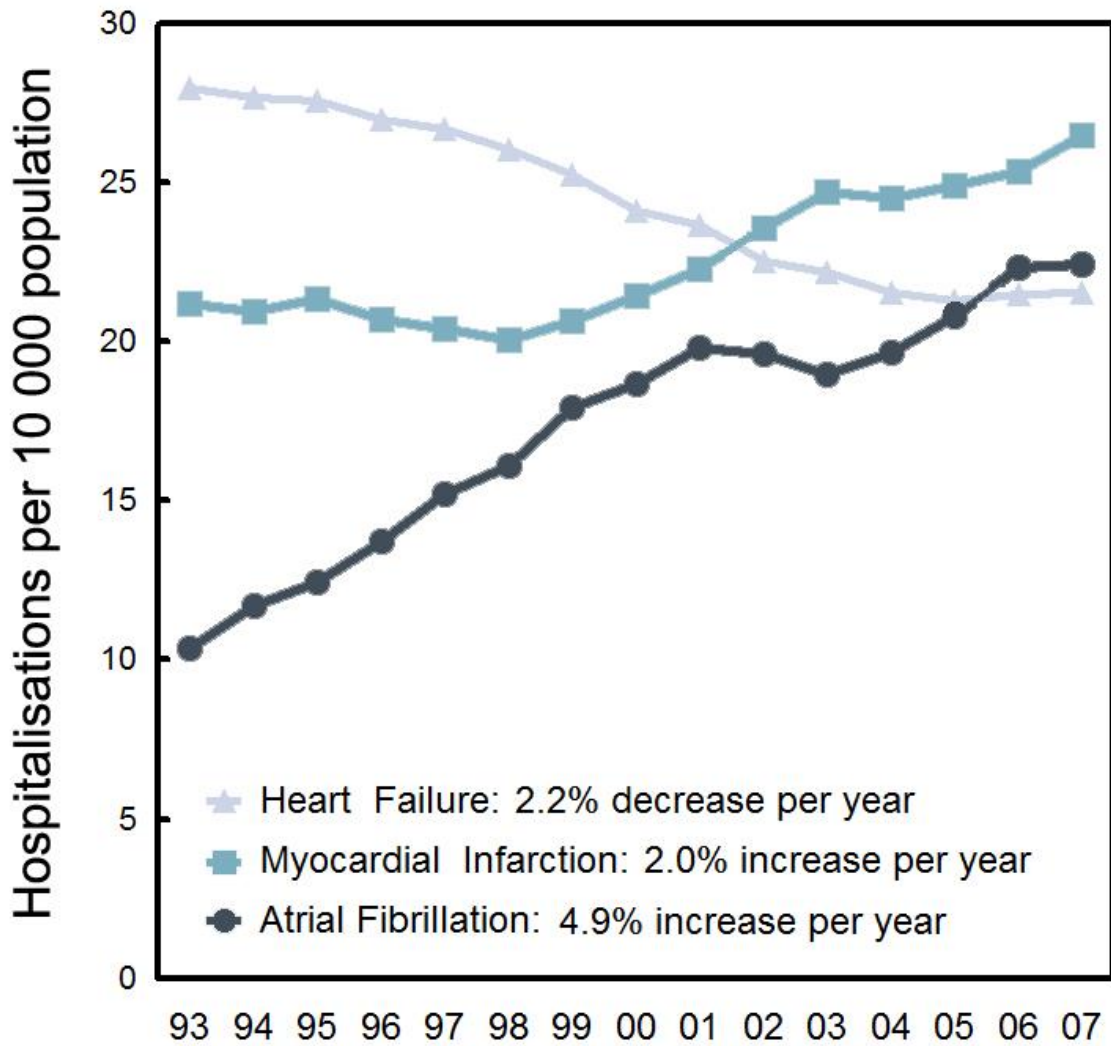
CHAPTER 3: DRIVERS OF ATRIAL FIBRILLATION HEALTHCARE BURDEN

3.1 Introduction

Numerous countries worldwide are facing the major challenge of rising healthcare expenditure, a concern driven particularly by advancing medical treatments and ageing population structures. Over the last 50 years in the United States, for example, increasing national healthcare expenditure has consistently outpaced growth in real gross domestic product per capita, exceeding every other country to peak at 18% of gross domestic product in 2012.[298] In Australia, healthcare is also responsible for significant and increasing proportion of national expenditure; in the 2012-2013 period, it accounted for 9.7% of gross domestic product, compared to 8.4% in the 2001-2002 period.[299]

Hospitals are, by far, the largest contributor to each dollar spent on healthcare; in Australia, public hospitals alone account for one-third of healthcare expenditure.[299] Given the deleterious hospitalisation trends for atrial fibrillation described in the previous chapter, the identification of factors that may be responsible for these trends is a logical first step in identifying possible opportunities to intervene and slow the rising demands on healthcare systems. In these analyses, we first sought to better characterise the atrial fibrillation hospitalisation trends in Australia. Subsequently, we review procedural trends to determine whether these may be in-part responsible. Finally, we further investigated myocardial infarction trends given not only their own importance, but also because a rising prevalence of myocardial

infarction might be contributing to overall atrial fibrillation burden as a risk factor for

atrial fibrillation.

3.2 Methods

3.2.1 Data source

Australia has a racially and culturally diverse population of 22.8 million. Since 1993, the Australian Institute of Health and Welfare has maintained the National Hospital Morbidity Dataset. This dataset includes information on hospitalisations nationwide throughout Australia in both the public and private sector.

We identified hospitalisations with a principal diagnosis of atrial fibrillation across a 15-year period from 1993 through to 2007 inclusive. The *International Classification of Diseases 9th Rev, Clinical Modification* (ICD-9-CM) and *ICD 10th Rev, Australian Modification* (ICD-10-AM), were used for coding hospitalisation diagnoses between 1993-1997 and 1998-2007 respectively. Codes were derived from physicians' diagnoses by trained clinical coders. Atrial fibrillation was defined for patients with ICD-9-CM codes 4273, and ICD-10-AM I48, codes that include both atrial fibrillation and atrial flutter.

We also identified hospitalisations with a primary discharge diagnosis of acute myocardial infarction based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) and *International Classification of Diseases, Tenth Revision, Australian Modification* (ICD-10-AM) from 1993-1997 and 1998-2010 respectively. ICD-9-CM codes 410.0 to 410.6 and 410.8, and ICD-10-AM codes I21.0 to I21.3, were classified as ST-elevation myocardial infarctions (STEMIs). ICD-9-CM codes 410.7 and 410.9, and ICD-10-AM codes I21.4 and I21.9,

were classified as non-STEMIs. To determine the accuracy and consistency of diagnostic coding over time, we performed a detailed chart review of 50 hospitalisations per year (25 presumed STEMIs and 25 presumed non-STEMIs) between 1993 and 2010. We applied standardised criteria from the joint European Society of Cardiology and American College of Cardiology Global Task Force.[300] The positive predictive value of the categorisation scheme was 98.6% for any myocardial infarction, 78.5% for STEMI and 91.5% for non-STEMI, with no significant differences for the latter two conditions across years.

We also calculated the total number of all hospitalisations for any diagnosis to characterise the relative burden of atrial fibrillation. Hospitalisation data are presented for the number of hospitalisations, age grouping, length of stay and total hospital bed utilisation. We have reported data in age groupings less than 50 years, 50-59 years, 60-69 years, 70-79 years and 80 years or greater. The prevalence of hospitalisations are expressed as the number per 10 000 population, and midyear population estimates were sourced from the Australian Bureau of Statistics.[288]

In order to ascertain the impact of procedures on hospitalisation trends for atrial fibrillation, we evaluated trends in direct-current electrical cardioversion, electrophysiological studies and radiofrequency to provide further insight into the factors driving atrial fibrillation hospitalisations. Data for electrical cardioversions, electrophysiological studies and radiofrequency ablation procedures were available from 2000. Given data for radiofrequency ablation procedures were only available separately from other electrophysiological studies from 2004, we therefore studied

trends in these procedures separately; electrophysiological studies were analysed from 2000 to 2003, and radiofrequency ablation procedures analysed from 2004 to 2007.

3.2.2 Statistical analysis

We calculated hospitalisation rates for atrial fibrillation, all myocardial infarctions, STEMIs and non-STEMIs (per 100,000 person-years) for each year. For the denominator, total person-months in each year were calculated in 10-year age intervals (<50 years, 50-59 years, 60-69 years, 70-79 years and ≥80 years). Direct methods for adjustment were used on the basis of the age and sex structure of the Australian population in 2010. Population estimates were sourced from the Australian Bureau of Statistics. Time trends in the yearly number of incident myocardial infarctions were assessed using negative binomial regression models, with year as a continuous predictor. Age, sex and their interaction were included in models to control for population changes over time. Finally, time trends in length of stay and bed days utilised were assessed using negative binomial regression models. All analyses were conducted using SAS Version 9.3 (SAS Institute Inc., Cary, NC, USA), and statistical significance set at $p<0.05$.

3.3 Results

3.3.1 Total atrial fibrillation hospitalisations

Over a 15-year period from 1993 to 2007, there were a total of 93,029,656 hospitalisations for any diagnosis in Australia (representing a follow-up period of almost 300 million person-years). There were a total of 473,501 hospitalisations for atrial fibrillation. The number of hospitalisations for atrial fibrillation increased from 15,555 in 1993 to 47,164 in 2007, a relative increase of 203% (7.9% annually, rate ratio 1.079, 95% confidence interval 1.069-1.088, p<0.001). This was in contrast to a relative increase in the number of all hospitalisations of only 71%, or an estimated 3.7% per year (rate ratio 1.037, 95% confidence interval 1.036-1.039, p<0.001). As a result, atrial fibrillation as a percentage of all hospitalisations increased by an estimated 4.0% per year (rate ratio 1.040, 95% confidence interval 1.031-1.050, P<0.001).

3.2.2 Age- and sex-specific atrial fibrillation hospitalisations

The proportion of atrial fibrillation hospitalisations for males and females was relatively steady over the study period, with men accounting for an average of 54.8% of hospitalisations and women for an average of 45.2% of hospitalisations. Figure 3.1 shows the age- and sex-specific incidence of hospitalisations for atrial fibrillation from 1993 to 2007. The incidence of hospitalisations was higher among older age groups for every year. The proportion of individuals hospitalised with atrial fibrillation

and aged 80 years or greater rose from 10 to 16% in men and from 25 to 34% in women.

3.2.3 Procedural trends

From 2000 to 2007, the percentage of atrial fibrillation hospitalisations for which electrical cardioversion was employed decreased from 27% to 14%. Trends in electrophysiological studies from 2000 to 2003 and radiofrequency ablation procedures from 2004 to 2007 were similarly analysed as a percentage of all atrial fibrillation hospitalisations respectively. From 2000 to 2003, electrophysiological studies as a percentage of atrial fibrillation hospitalisations increased from 15% to 17%. From 2004 to 2007, radiofrequency ablation procedures as a percentage of atrial fibrillation hospitalisations increased from 9% to 11%.

3.2.4 Myocardial infarction hospitalisations

We identified 714,262 hospitalisations for myocardial infarction between July 1993 and July 2010 (representing a period of 331,871,389 person-years; Table 3.1). Overall, 333,538 (46.7%) hospitalisations were for STEMIs and 380,724 (53.5%) were for non-STEMIs. The proportion of myocardial infarctions that were STEMIs decreased from 69.3% in 1993 to 27.7% in 2010.

The age- and sex-standardised incidence of myocardial infarction increased from 215 cases per 100,000 person-years in 1993 to 251 cases per 100,000 person-years in 2010, a relative increase of 76% (Figure 3.2). The age- and sex-adjusted

incidence of STEMIs decreased from 147 cases per 100,000 person-years to 70 cases per 100,000 person-years, a relative decrease of 30%. In contrast, the age- and sex-standardised incidence of non-STEMIs increased from 67 cases per 100,000 person-years to 182 cases per 100,000 person-years, a relative increase of 315%.

Negative binomial regression analysis revealed an increase of 1.98% per year in myocardial infarctions, a decrease of 4.81% per year in STEMIs and an increase of 9.20% per year in non-STEMIs ($p<0.0001$ for all; Table 3.2). There was a significant interaction between year and MI type, suggesting differing trends over time for incident STEMIs and non-STEMIs ($p<0.0001$).

When stratified by age groups, negative binomial regression analysis revealed a statistically significant interaction in myocardial infarction incidence between age groups over time, suggesting temporal trends differed between age groups ($p=0.017$, Figure 3.3). Both the <50 and ≥80 years of age groups demonstrated statistically significant increases in myocardial infarction incidence (3.88% and 2.88 per year respectively, Table 3.3).

3.4 Discussion

3.4.1 Major findings

We examined nationwide trends in hospitalisations for atrial fibrillation and myocardial infarction in Australia over a 15-year period to determine factors that might be contributing to the increasing burden of atrial fibrillation. Our findings highlight that the age-specific incidence of hospitalisations for atrial fibrillation is continuing to increase. Not only are ageing population structures resulting in a growing prevalence of atrial fibrillation, but elderly individuals in particular are being hospitalised for atrial fibrillation at an increasing rate. Our data additionally suggests that atrial fibrillation-related procedures, such as electrical cardioversions, electrophysiological studies and radiofrequency ablation procedures, were unlikely to have contributed significantly to the rising rates of atrial fibrillation hospitalisations. Myocardial infarction rates also appeared to increase slightly over a similar period of time in Australia. This is not only concerning in itself, but also, may indirectly suggest that coronary artery disease may be in-part responsible for the increasing burden of atrial fibrillation in Australia.

3.4.2 Trends in hospitalisations for atrial fibrillation

Reports in recent years have highlighted the public health burden that atrial fibrillation increasingly represents. [4, 22] Importantly, it has been recognised that hospitalisations account for the majority of the cost associated with atrial fibrillation.[172, 176, 178, 179] A Scottish study on atrial fibrillation-related hospital activity

found that, from 1986 through 1996, the number of hospitalisations for atrial

fibrillation had increased three-fold from 1,869 to 5,757.[168] This was accompanied

by an 80% increase in bed days utilised each year, despite a decreasing median

length of stay (6 to 3 days). An analysis of Danish data additionally revealed that

hospitalisations had increased by 60% over a similar period, from 163 to 216

cases.[169] Another report utilised survey data to estimate hospitalisations in the

entire United States.[170] From 1985 to 1999, these investigators estimated that

hospitalisations for atrial fibrillation had increased from 154,086 to 376,487 in the

United States.[170] Similarly, Canadian investigators have also described a rise in

hospitalisations between 1997 and 2000.[171] Despite the limitations of representative

data and modest-sized cohorts, these studies highlighted a growing clinical and

public health problem.

3.4.3 Possible reasons for the increase in atrial fibrillation hospitalisations

Given the increasing prevalence of atrial fibrillation with age, the ageing population

structures seen in developed countries around the world is clearly in part responsible

for the rising number of hospitalisations for atrial fibrillation. In addition to this,

however, our data highlight that the age-specific incidence of hospitalisations for

atrial fibrillation is also increasing. The reasons for this are multifactorial, but

improving medical care in recent years has resulted in individuals having a more

prolonged exposure to traditional and newer risk factors, such as obesity and

obstructive sleep apnoea; this exposure is likely to be contributing significantly to the

increasing incidence and resultant hospitalisations for atrial fibrillation.[3, 49, 256, 297] In

separate analyses, we also describe an apparent increase in myocardial infarction incidence, discussed in more detail below. Given myocardial infarction increases the risk of atrial fibrillation, both in the acute setting and in the longer-term, these trends might also in-part be contributing.

Other investigators have suggested that the emergence of interventional electrophysiological procedures may have accounted for part of the recent trends.[165, 172, 301] We were unable to link data on these procedures with atrial fibrillation hospitalisations in our study. However, when both electrophysiological studies and radiofrequency ablation procedures were considered as a percentage of atrial fibrillation hospitalisations nevertheless (a conservative approach given many of these would have been for other arrhythmias), they would have accounted for an increasing but very small proportion of atrial fibrillation hospitalisations. A previous report also noted that major "rate-versus-rhythm" trials in 2002 was followed by a slowing in atrial fibrillation hospitalisations in the United States, and this was paralleled by a decline in electrical cardioversions.[172] Our finding that electrical cardioversions were associated with a significantly smaller proportion of atrial fibrillation hospitalisations in Australia confirms that rhythm control with electrical cardioversion is no longer utilised as frequently. Thus, the observed increases in total atrial fibrillation hospitalisations occurring despite a decrease in atrial fibrillation hospitalisations for electrical cardioversion are even more striking.

3.4.4 Temporal trends in myocardial infarction incidence

Recent studies from North America and Europe have suggested that the incidence of myocardial infarction has changed from relatively stable rates in the 1980s and 1990s[295, 302-304] to declining rates after 2000.[293, 305-308] There has been a paucity of studies from other parts of the world, however, and in particular very few from Asia. A recent study described acute coronary syndromes in one Australian state from 1996 to 2007, where the direction of myocardial infarction trends appeared to be age-specific.[309] Whilst older age groups had stable or decreasing myocardial infarction rates, younger age groups had stable or increasing myocardial infarction rates in this report from Western Australia.[309] When we assessed the overall nationwide trends in myocardial infarction from 1993 to 2010 in the present study, we found that there was an overall increase in myocardial infarction rates. Given disease incidence rates reflect the ultimate success of clinical and public health efforts, the apparently slower rate of decline in the incidence of myocardial infarction in Australia compared to other parts of the world is of concern.

3.4.5 Possible reasons for the apparent increase in myocardial infarction incidence

The expanded use of highly sensitive cardiac biomarkers, particularly troponin, would be in-part contributing to the observed myocardial infarction rates.[310-312] Previous reports have shown that the introduction of troponin testing has attenuated the declining myocardial infarction trends described in other studies.[305, 313]

Consistent with this is the increase in the incidence of non-STEMIs seen after 1998 in the present study when troponin testing became widespread in Australia. However, the overall increase in myocardial infarction incidence is in contrast to stable or decreasing rates seen elsewhere in spite of troponin testing.[293, 314] Given troponin testing was used for the vast majority of suspected myocardial infarction cases by 2001 in Australia[309] and the similarities in uptake of these new cardiac biomarkers in both Australia and North America,[296, 309, 315] it would seem reasonable to be cautious and not conclude that the marked discrepancy in trends can be explained on the basis of troponin testing alone. Whilst there have been significant improvements in hypertension, cholesterol and smoking rates in Australia in recent years, there have been contrastingly unfavourable trends in obesity, diabetes, physical activity and dietary habits.[241] It has been suggested that such unfavourable risk factor trends can impact myocardial infarction incidence and this may in-part explain our findings.[316] A number of patients hospitalised with atherothrombotic disease in Australia have no prior history, suggesting that improvements may be required in primary preventative strategies.[309] Similarly, suboptimal application of evidenced-based practices in those with established cardiovascular disease may be in-part contributing to the observed trends.

3.4.6 Clinical implications

The growing number of atrial fibrillation hospitalisations shows no sign of abating and in the context of ageing population structures represent a staggering economic burden. Hospitalisations have repeatedly been confirmed as the major cost driver

associated with atrial fibrillation.[176, 178, 179, 287] Healthcare planning and practitioner-education is warranted to ensure that efficacious and cost-effective management strategies are employed to minimise the risk of hospitalisation in patients with atrial fibrillation, particularly in older age groups. Greater attention on primary prevention strategies will also be required to contain this growing epidemic.

3.4.7 Limitations

It was not possible to determine whether cases were de novo or repeat hospitalisations, though each still represents additional burden regardless. Not all procedures were able to be linked with an atrial fibrillation hospitalisation. However, our conservative approach assuming all of these were associated with atrial fibrillation suggested that they compromise a small percentage of total atrial fibrillation hospitalisations. Information on hospital demographics was not available; such data may have provided further insights into the factors driving hospitalisations. Data on atrial fibrillation in the setting of acute myocardial infarction was not available which, if available, could have explored the possibility that increasing myocardial infarction rates are contributing to an increase in atrial fibrillation in the acute setting.

3.5 Conclusion

In addition to the growing prevalence of atrial fibrillation secondary to the ageing population, there is an increasing age-specific incidence of hospitalisations for atrial fibrillation, particularly in older age groups. There is also an apparent increase in myocardial infarction incidence which may be one risk factor that is potentially contributing to the rising burden of atrial fibrillation. In contrast, changing procedural trends have contributed minimally to the increasing number of hospitalisations for atrial fibrillation. Greater attention on older individuals with atrial fibrillation is required to develop strategies to prevent hospitalisations and contain the growing burden on health care systems.

Table 3.1: Number and incidence of overall MI, STEMI and non-STEMI

Year	Number of all MIs	Number of STEMIs	Number of non-STEMIs	Incidence of all MIs (per 100,000 population)	Incidence of STEMIs (per 100,000 population)	Incidence of non-STEMIs (per 100,000 population)
1993	31,195	21,616	9,579	176.5	122.3	54.2
1994	31,623	21,952	9,671	177.1	122.9	54.2
1995	32,999	23,192	9,807	182.6	128.3	54.3
1996	32,808	22,975	9,833	179.1	125.5	53.7
1997	33,261	22,770	10,491	179.6	123.0	56.6
1998	33,550	21,279	12,271	179.3	113.7	65.6
1999	35,418	20,684	14,734	187.1	109.3	77.8
2000	37,672	20,847	16,825	196.6	108.8	87.8
2001	40,330	20,871	19,459	207.7	107.5	100.2
2002	43,766	19,153	24,613	222.6	97.5	125.2
2003	46,884	17,704	29,180	235.6	89.0	146.6
2004	47,631	16,291	31,340	236.6	80.9	155.7
2005	49,534	15,550	33,984	242.8	76.2	166.6
2006	51,666	15,917	35,749	249.5	76.9	172.7
2007	55,676	15,811	39,865	264.8	75.2	189.6
2008	55,223	16,095	39,138	258.3	75.3	183.1
2009	44,003	15,222	39,781	251.4	69.6	181.8
Relative increase 1993 to 2009*, %	76.3	-29.6	315.3	42.3	-43.1	235.3

* 2009 value minus 1993 value divided by 1993 value multiplied by 100. MI= myocardial infarction, STEMI = ST-segment elevation MI

Table 3.2: Temporal trends in overall MI, STEMI and non-STEMI

	Rate Ratio	Lower 95% Confidence Interval	Upper 95% Confidence Interval	P Value
Overall MI	1.020	1.017	1.023	<0.0001
STEMI	1.092	1.085	1.100	<0.0001
Non-STEMI	0.952	0.945	0.959	<0.0001

MI= myocardial infarction, STEMI = ST-segment elevation MI

Table 3.3: Temporal trends in overall myocardial infarction incidence according to age group

Age Group (years)	Rate Ratio	Lower 95% Confidence Interval	Upper 95% Confidence Interval	P Value
<50	1.039	1.023	1.055	<0.0001
50-59	1.015	0.999	1.030	0.07
60-69	1.006	0.991	1.022	0.45
70-79	1.009	0.993	1.024	0.29
≥80	1.029	1.013	1.045	0.0004

Figure 3.1: Age- and sex-specific hospitalisation rates from 1993 through 2007 inclusive
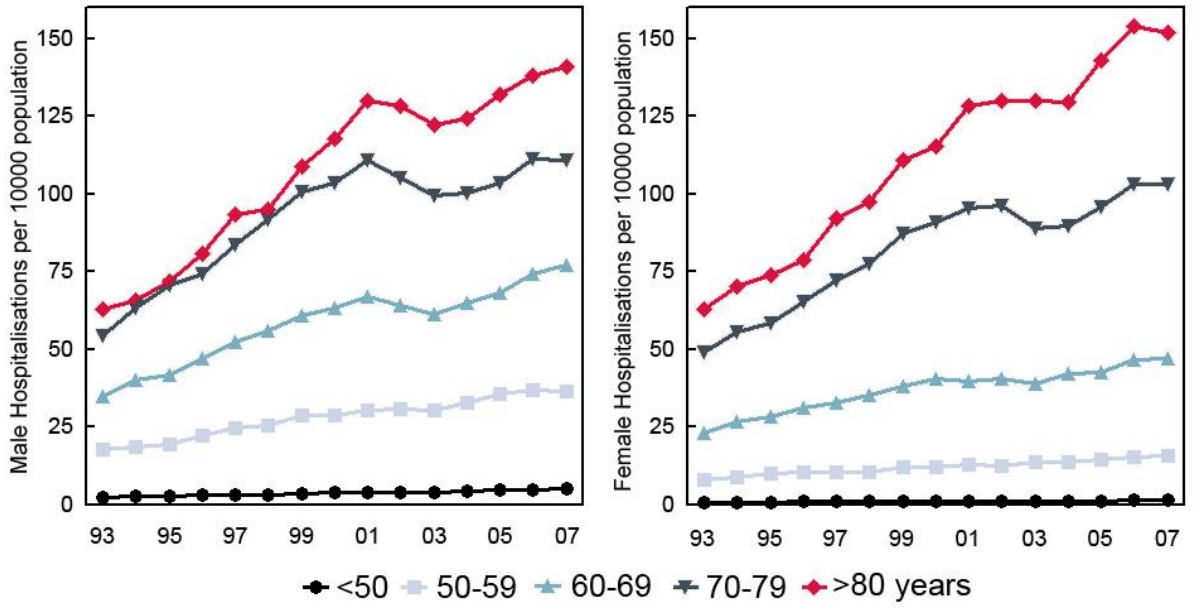
Figure 3.2: Age and sex-adjusted trends in myocardial infarction
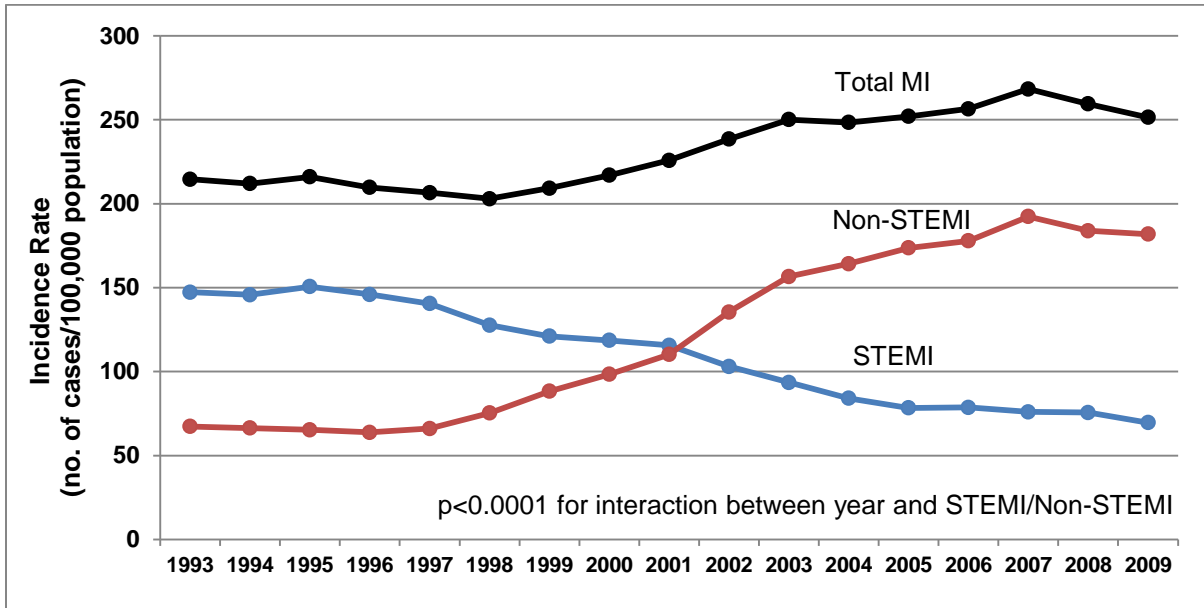
Figure 3.3: Age-specific trends in myocardial infarction
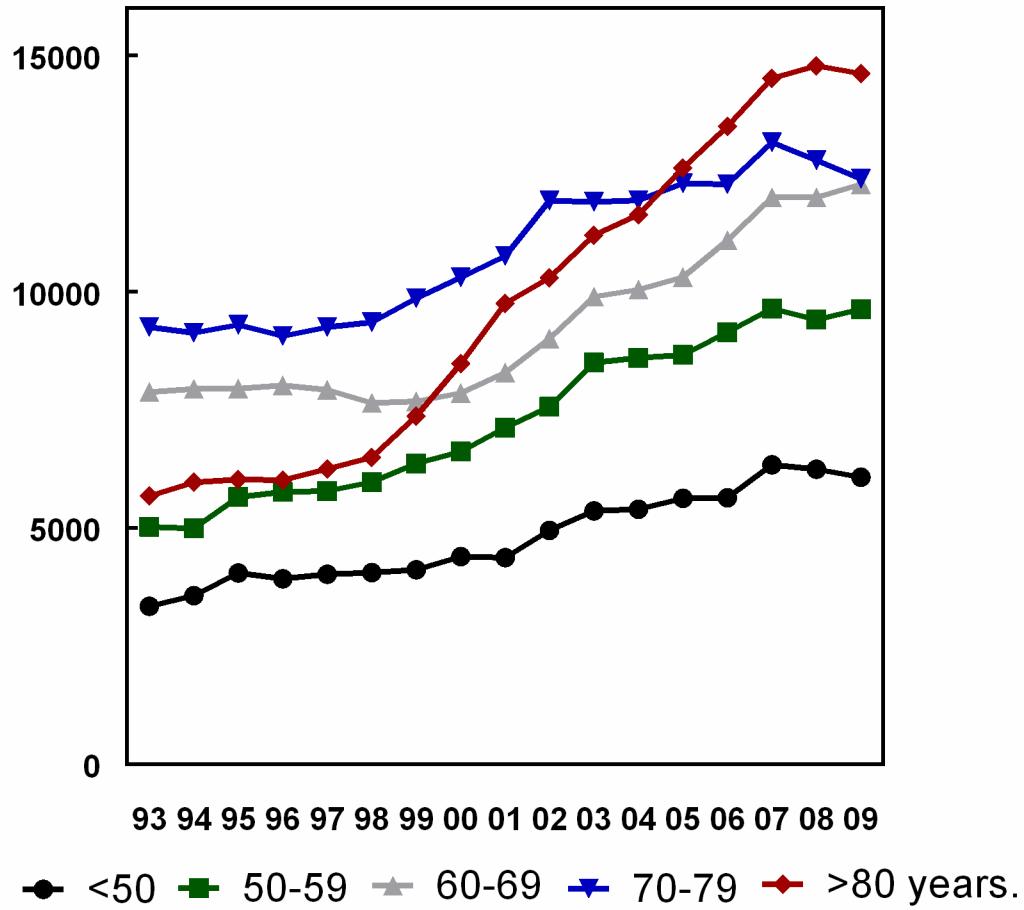
CHAPTER 4: OBESITY AND ATRIAL FIBRILLATION

4.1 Introduction

Atrial fibrillation is the most common, sustained arrhythmia diagnosed in clinical practice. Given it is associated with significant morbidity and mortality, it is concerning that there is a steadily rising prevalence of atrial fibrillation worldwide.[4, 317] As a result, a greater understanding of modifiable, predisposing risk factors is warranted in an attempt to slow the rising population and economic burden of atrial fibrillation.[318]

Obesity is one risk factor with increasingly broad implications for health in both developed and developing countries undergoing epidemiologic transition.[229, 319] Our evolving understanding regarding the relationship between atrial fibrillation and measures of obesity, body size and weight change are therefore particularly significant given the rising prevalence of both atrial fibrillation and obesity.[256] While previous analyses have studied the association between obesity and atrial fibrillation in the past, these have been limited by the heterogeneous measures of obesity reported in individual studies.[236, 320, 321] In addition, there has since been increasing recognition that obesity may influence the risk of atrial fibrillation in other clinical scenarios, such as that following cardiac surgery or catheter ablation procedures.[256, 322] Given that an accurate and reliable characterisation of atrial fibrillation risk associated with obesity would be immensely informative to clinical practice, we sought to describe the association between obesity and atrial fibrillation in different settings, with standardisation of obesity measures allowing for a more

comprehensive inclusion of eligible studies and detailed calculation of excess risk for

each incremental increase in obesity.

4.2 Methods

This systematic review was performed in accordance with both the Meta-Analysis of Observational Studies in Epidemiology and Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[323]

4.2.1 Search strategy and eligibility criteria

We performed a comprehensive, systematic search of observational studies in Medline and EMBASE databases available through to January 2012. This was supplemented by manual searching of the reference lists of individual studies and review articles. Search terms included obesity, overweight, body mass index, arrhythmia and atrial fibrillation. Studies were included if they were cross-sectional, case-control or cohort studies that allowed for assessment of associations between body mass index and incident atrial fibrillation, post-operative atrial fibrillation or post-ablation atrial fibrillation. Studies reporting risk estimates with body mass index as either a continuous and categorical variable were both included. Post-operative atrial fibrillation was defined as atrial fibrillation following cardiac surgery and post-ablation atrial fibrillation as recurrent atrial fibrillation following a catheter ablation procedure. Two investigators independently performed the searches and reviewed all identified studies for inclusion. The decision to include studies was hierarchical, initially based on the study title, followed by the abstract and then the full text of each remaining article. When duplicate reports from the same study or cohort were identified, only the most recent publication, or the one with the longest follow-up

period, was included. Disagreements were resolved by consensus with a third investigator.

4.2.2 Data extraction

Data from included studies were extracted independently by two investigators using a standard table. The following were tabulated where applicable: type of atrial fibrillation studied (incident, post-operative or post-ablation), study type, inclusion and exclusion criteria, cohort source, study dates, study country, number of patients enrolled, baseline patient characteristics, number of procedures, method of event determination, event numbers, duration of follow-up, risk estimates and other covariates adjusted for in any multivariate models.

4.2.3 Statistical analysis

Odds ratios per unit increase in body mass index were abstracted or calculated from observational studies reporting associations between body mass index and atrial fibrillation. Where risk estimates were reported as a series of dose-specific risk estimates compared to a reference body mass index category, these were transformed into risk estimates per unit of body mass index.[324] Authors were contacted for additional data allowing transformation (e.g. patient and event numbers within body mass index categories) where it was not reported in the publication. To assess the validity of this transformation, we plotted the natural logarithm of the atrial fibrillation risk estimates for studies that assessed at least three different body mass index groups against the assigned body mass index dose

for this category, after subtracting a factor β_1 x (X_{Aref} - 22.5), where X_{Aref} is the assigned dose in the reference category, as previously described.[324] There was some evidence of deviation but overall evidence of linearity consistent with that described in individual studies.[232, 235] If both dose-specific risk estimates compared to a reference body mass index category and risk estimates per unit of body mass index were reported, the latter were preferentially used. As an additional test, however, we also transformed categorical body mass index risk estimates using the above method in these studies, and transformed risk estimates per unit of body mass index were comparable to that reported by the investigators. Risk estimates for every five unit increase in body mass index were subsequently calculated and pooled using random effects meta-analysis.[325] Where risk estimates were reported separately by gender or other subgroups only, these were pooled separately. Risk estimates from multivariate models adjusting for potential confounders were used where available. Heterogeneity across studies was assessed using I^2 statistics and, where present, the potential role of study characteristics (age, gender, year, geographic region, study numbers, atrial fibrillation diagnostic method, follow-up duration, and atrial fibrillation type) explored via subgroup analyses and meta-regression techniques.[326] The presence of publication bias was assessed using funnel plots of effect size against standard error. A 2-tailed value of $p < 0.05$ was considered statistically significant, and all analyses were performed using SAS 9.3 (SAS Institute Inc.) and Stata 12.0 (Stata Corporation).

4.3 Results

4.3.1 Search results

The systematic search of electronic databases identified 2001 articles, from which

we identified 399 potentially relevant studies for more detailed full-text assessment

after screening of study titles and review of abstracts (Figure 4.1). An additional 7

were identified by manual searching of reference lists. After full-text assessment, a

total of 51 studies were included. Twenty-three studies reported on incident atrial

fibrillation, twelve on post-operative atrial fibrillation and sixteen on post-ablation

atrial fibrillation.

4.3.2 Obesity and atrial fibrillation

A total of nine cohort studies involving 157,518 individuals and 6,088 cases of atrial

fibrillation were identified (mean age 59, mean percent female 53% and mean

follow-up 10 months; Table 4.1). Three of the studies provided gender-specific

estimates and one study provided race-specific estimates on the association

between body mass index and atrial fibrillation; thus, 13 separate risk estimates

contributed to this analysis. The overall summary estimate from the 13 separate risk

estimates combined indicated that there was a 29% greater excess risk of

developing atrial fibrillation for every five unit increase in body mass index (odds

ratio 1.29, 95% CI 1.23-1.36; Figure 4.2). There was significant heterogeneity due to

between-study differences (I^2 statistic 54.7%), with some evidence of smaller

estimates in studies from North America (p=0.02) and studies diagnosing atrial

fibrillation using electrocardiograms (p=0.007). There was no evidence of significant publication bias.

Fourteen case-control studies involving 401,061 individuals and 65,546 cases of atrial fibrillation were identified (mean age 60, mean percent female 43%; Table 4.2). Pooled analysis from these studies similarly revealed a significantly greater 19% risk of atrial fibrillation for every five unit increase in body mass index (odds ratio 1.19, 95% CI 1.13-1.26; Figure 4.3). There was significant heterogeneity due between-study differences (I^2 statistic 80.0%), with again some evidence of smaller estimates in studies from North America (p<0.001). There was no evidence of significant publication bias.

4.3.3 Obesity and post-operative atrial fibrillation

A total of twelve studies involving 62,160 individuals and 16,768 cases of postoperative atrial fibrillation were identified (mean age 64, mean percent female 26%; Table 4.3). One study provided gender-specific estimates and thus 13 separate risk estimates contributed to this analysis. The overall summary estimate indicated that there was a 10% greater excess risk of post-operative atrial fibrillation for every five unit increase in body mass index (odds ratio 1.10, 95% CI 1.04-1.17; Figure 4.4). There was significant heterogeneity due to between-study differences (I^2 statistic 82.9%), with some evidence of larger estimates in studies from Asia (p=0.003) and in studies diagnosing atrial fibrillation with continuous monitoring or electrocardiograms (p=0.045). There was no evidence of significant publication bias.

4.3.4 Obesity and post-ablation atrial fibrillation

A total of sixteen studies involving 5,864 individuals were included (mean age 56, mean percent female 30%, mean follow-up 20 months; Table 4.4). The overall summary estimate indicated that there was a 13% greater excess risk of recurrent atrial fibrillation post-ablation for every five unit increase in body mass index (odds ratio 1.13, 95% CI 1.06-1.22; Figure 4.5). There was significant heterogeneity due to differences between studies (I^2 statistic 78.6%), though exploratory analyses could not identify any significant contributing factors. There was no evidence of significant publication bias.

4.4 Discussion

4.4.1 Major findings

The present meta-analysis pooled data from 51 studies and more than 600,000 individuals in a range of clinical settings. For every five unit increase in body mass index, there were 10-29% greater excess risks of incident, post-operative and post-ablation atrial fibrillation. These findings provide a comprehensive and reliable quantification of the relationship between incremental increases in obesity and the risk of atrial fibrillation in these different clinical settings.

4.4.2 Epidemic of atrial fibrillation

Atrial fibrillation is increasingly recognised as a major public health burden. The worldwide prevalence of atrial fibrillation is already estimated at 33 million, and this is possibly a significant underestimate of the true figure given the likelihood of study methodological limitations and under-diagnosis.[327, 328] The annual incremental cost of atrial fibrillation is estimated at US$26 billion in the United States alone and hospitalisations, the major driver of cost, appear to be increasing more rapidly than other cardiovascular conditions.[317, 327] Given the risk of atrial fibrillation increases rapidly with greater age, an already rising prevalence is expected to further accelerate given ageing population structures. Studies suggest, however, that the age-specific incidence of atrial fibrillation is increasing in addition to any effect from population ageing.[329] It is likely that the epidemiologic transition in both developed and developing countries towards increased longevity and unhealthy lifestyles is

resulting in an increasing prevalence and multiplicative effect of atrial fibrillation risk factors.[229] A greater focus on and effort to reduce these risk factors is thus required to prevent the initial development and the subsequent burden of atrial fibrillation.[330]

4.4.3 Obesity and atrial fibrillation

Obesity is an important contributor to the burden of atrial fibrillation, explaining one-fifth of all atrial fibrillation cases.[239] It has also been estimated that obesity may account for approximately 60% of the rising age- and sex-adjusted incidence of atrial fibrillation.[4] From a public health perspective, obesity is therefore a modifiable risk factor that could be profitably targeted. Moreover, dietary and lifestyle improvements addressing obesity would also favourably affect other atrial fibrillation risk factors, such as hypertension and diabetes, reducing the burden of atrial fibrillation greater than that attributable to obesity alone. We and other investigators have previously shown that obesity is associated with deleterious electrical, structural and hemodynamic abnormalities in the left atria, predisposing to atrial fibrillation.[242, 245] More recently, we described how a weight and risk factor management program can improve such cardiac remodelling and subsequent arrhythmia burden in people with atrial fibrillation.[331, 332]

While previous analyses have studied the obesity-related risk of atrial fibrillation in different clinical settings individually, the present report provides the most comprehensive summary estimates to date.[236, 320, 321] Key differences compared to prior studies include the greater power of our meta-analysis (51 studies, 626,603 individuals), the inclusion of studies reporting risk estimates with either body mass

index as a categorical or continuous variable, and the comparison of obesity-related risk across different clinical settings.[236, 320, 321] Our results suggest there is 10-29% excess risk of atrial fibrillation associated with every five increase in body mass index in the general population, after cardiac surgery, and after catheter ablation procedures. The consistency of obesity-related risk across these different settings lends further weight to reliability of obesity as an atrial fibrillation risk factor. Thus, even moderate reductions in population body mass indices are likely significant public health impact on the burden of atrial fibrillation.

4.4.4 Limitations

A number of limitations warrant discussion. The overall summary estimates obtained in these analyses may be overestimates due to coexistent confounding factors. While most studies adjusted for other comorbid atrial fibrillation risk factors, it is not possible to fully take into account the possible impact on the observed associations. On the other hand, overall summary estimates may be underestimates due to under-diagnosis of atrial fibrillation in some included studies, the magnitude of which has only recently become apparent with increasingly sensitive diagnostic modalities. Significant heterogeneity was also observed in the present analyses due to between-study differences. Subgroup analyses and meta-regression techniques suggested that this may be in-part due to differing study population characteristics (such as geographic region) and diagnostic methods of ascertaining atrial fibrillation. Despite this heterogeneity, however, our findings appeared consistent across a

broad range clinical settings, and thus provide the most comprehensive and reliable analysis so far in regard to the obesity-related risk of atrial fibrillation.

4.5 Conclusion

Incremental increases in body mass index are associated with a significant excess risk of atrial fibrillation in different clinical settings. For every five unit increase in body mass index, there were 10-29% greater excess risks of incident, post-operative and post-ablation atrial fibrillation. Given burgeoning rates of obesity are likely to have increasing impact on an already rising burden of atrial fibrillation, these data suggest that achieving even moderate reductions in body mass indices is likely to have significant clinical and public health impact.

Table 4.1: Obesity and atrial fibrillation - cohort studies

Study reference (year)	Cohort source	Dates of enrolment	Country	Subjects (% women)	Mean age (years)	Follow-up (years)	Cases of AF (%)	AF diagnosis	Other covariates in model
Wang et al[27] (2004)	Framingham Heart and Offspring Studies	1979-1983	United States	5,282 (55)	57	Mean 13.7	526 (10.0)	ECG	Age, systolic blood pressure, antihypertensive therapy, diabetes, left ventricular hypertrophy, myocardial infarction, congestive heart failure, smoking, cardiac murmur, left atrial size
Frost et al[230] (2005)	Danish Diet, Cancer and Health Study	1993-1997	Denmark	47,589 (53)	56	Mean 5.7	553 (1.2)	National healthcare registry	Age, systolic blood pressure, antihypertensive therapy, serum cholesterol, alcohol consumption, smoking, education, diabetes, ischaemic heart disease, heart failure, valve disease
Murphy et al[231] (2006)	Renfrew-Paisley Study	1972-1976	Scotland	15,402 (54)	54	Mean 20.0	175 (1.1)	National hospitalisation **and** death registries	Age, sex, systolic blood pressure, diabetes, cholesterol, forced expiratory volume, smoking, social class

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Gami et al[49] (2007)	Mayo Clinic	1987-2003	United States	3,542 (34)	49	Mean 4.7	133 (3.8)	ECG	Age, sex, smoking, hypertension, diabetes, ischaemic heart disease, heart failure
Rosengren et al[232] (2009)	Swedish Primary Prevention Study	1970-1973	Sweden	6,903 (0)	52	Maximum 34.3	1,253 (18.2)	National hospitalisation registry	Age, systolic blood pressure, antihypertensive therapy, diabetes, smoking, alcohol, social class
Tedrow et al[235] (2010)	Women's Health Study	1993-2004	United States	34,309 (100)	55	Mean 12.9	834 (2.4)	ECG or medical record	Age, ethnicity, hypertension, hypercholesterolemia, diabetes, alcohol consumption, smoking, physical activity, inflammatory markers
Smith et al[234] (2009)	Malmo Diet and Cancer Study	1991-1996	Sweden	30,447 (60)	58	Mean 11.2	1,430 (4.7)	National hospitalisation and death registries	Age, sex, myocardial infarction, heart failure, hypertension, diabetes, smoking
Schnabel et al[233] (2010)	Age, Gene/Environment Susceptibility-Reykjavik Study	2002-2006	Iceland	4,238 (63)	76	Mean 5.0	226 (5.3)	ECG or hospitalisation registries	Age, sex, antihypertensive therapy, PR interval, heart failure

| Schnabel et al[233] (2010) | Cardiovascular Health Study | 1989-1990 | United States | 9,806 (60) | 75 | Mean 5.0 | 958 (9.8) | ECG or hospitalisation registries | Age, sex, antihypertensive therapy, PR interval, heart failure |

ECG = electrocardiogram

Table 4.2: Obesity and atrial fibrillation - case control studies

Study reference	Cohort source	Dates of study	Country	Subjects (% women)	Mean age (years)	Cases of AF (%)	AF diagnosis	Other covariates in model
Krahn et al[6]	Manitoba Follow-Up Study	1948-1992	Canada	3,983 (0)	33	299 (7.5)	ECG	Age, hypertension, ischaemic heart disease, congestive heart failure, valvular disease, cardiomyopathy, palpitations, supraventricular rhythm disturbance, ventricular rhythm disturbance
Hanna et al[333]	ADVANCENT Registry	2003-2004	United States	25,268 (28)	66	7,027 (28)	Patient interview, ECG and medical records	Age, sex, hypertension, diabetes, left ventricular ejection fraction, NYHA class, etiology of heart failure, medication use
Dublin et al[238]	Group Health Cooperative	2001-2002	United States	1,132 (58)	71	425 (38)	Healthcare registry and medical records.	Age, sex, hypertension, hypertension duration, systolic blood

								pressure, diastolic blood pressure, diabetes, diabetes duration, hyperlipidemia, total and HDL cholesterol levels
De Bacquer et al[334]	Belgian Interuniversity Research on Nutrition and Health Survey	1980-1996	Belgium	160 (45)	64	40 (25)	ECG	Systolic blood pressure, ischaemic ECG changes, P wave duration, P wave morphology
Umetani et al[335]	University of Yamanashi Hospital	2001-2005	Japan	592 (41)	63	32 (5.4)	ECG	Hypertension, diabetes, HDL cholesterol, triglycerides
Yap et al[336]	Singapore Longitudinal Aging Study	2008	Singapore	1,839 (62)	≥55	26 (1.4)	ECG	Age, sex, hypertension, stroke, myocardial infarction, heart failure, diabetes, smoking
Zhang et al[337]	China Multicentre Collaborative Study of Cardiovascular Epidemiology	2004	China	18,615 (56)	61	194 (1.0)	Patient interview or ECG	Age, left ventricular hypertrophy, smoking, alcohol, myocardial infarction, diabetes

Haywood et al[113]	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial	1994-2002	United States	39,056 (46)	≥55	423 (1.1)	ECG	Age, sex, race, diabetes, coronary heart disease, left ventricular hypertrophy, hypertension, chronic kidney disease, HDL cholesterol, smoking, medication use, hypokalemia
Minami et al[338]	Kanazawa Social Insurance Hospital	1998-2006	Japan	207 (0)	57	69 (33.3)	ECG	Age, systolic blood pressure, cardiomegaly, alcohol, total cholesterol, gamma-glutamyl transpeptidase, uric acid, fasting plasma glucose, red blood cell count, hemoglobin, smoking
Bonhorst et al[339]	The FAMA Study	2010	Portugal	10,447 (55)	59	261 (2.5)	ECG	None
Suzuki et al[340]	Shinken Database	2004-2008	Japan	4,719 (45)	54	577 (12.2)	ECG and medical records	Age, sex, height, left atrial dimension
Soliman et al[341]	Chronic Renal Insufficiency Cohort	2001-2008	United States	3,267 (46)	59	602 (18)	ECG or patient interview	Age, sex, ethnicity, study center

Long et al[342]	Guangzhou Biobank Cohort Study	2003-2006	China	19,964 (72)	63	159 (0.8)	ECG	Age, sex, alcohol, smoking, hyperthyroidism, diabetes, hypertension, total cholesterol
Hodgkinson et al[343]	General Practice Research Database	1987-2007	United Kingdom	271,812 (50)	74	55,412 (20.4)	Healthcare registry	Age, sex, hypertension, heart failure, ischaemic heart disease, diabetes, stroke, chronic obstructive pulmonary disease, hyperthyroidism, medication use, smoking, alcohol

ECG = electrocardiogram, NYHA = New York Heart Association, HDL = high density lipoprotein

Table 4.3: Obesity and post-operative atrial fibrillation

Study reference	Dates of study	Country	Subjects (% women)	Mean age (years)	Postoperative cases of AF (%)	AF diagnosis	Other covariates in model
Moulton et al[344]	1991-1993	United States	2,299 (35)	62	833 (36.2)	N/A	Age, sex, ethnicity, procedure type, NYHA class, myocardial infarction, diabetes, chronic kidney disease, hypertension, chronic obstructive pulmonary disease, stroke, left ventricular ejection fraction, operation urgency, cardiac index, bypass time, cross-clamp time
Engelman et al[345]	1993-1997	United States	5,168 (32)	Median 67	1,518 (29)	N/A	Age, sex, ejection fraction, NYHA class, previous cardiac operation, diabetes, vascular disease, hypertension, chronic kidney disease, heart failure, myocardial infarction, chronic obstructive pulmonary disease, smoking, operation urgency, internal thoracic artery use, operation type
Brandt et al[346]	1998	Germany	500 (20)	64	187 (37.4)	N/A	None
Reeves et al[322]	1996-2001	United Kingdom	4,372 (21)	Mostly 45-65yo	675 (15.4)	Continuous monitoring	Age, sex, CCS class, NYHA class, unstable angina, myocardial infarction, diabetes, hypercholesterolemia, hypertension, smoking, chronic kidney disease, chronic obstructive pulmonary disease, stroke, angiography findings, peripheral vascular disease, Parsonnet score, ejection fraction, operation urgency, graft number, off-pump surgery
Zacharias et al[347]	1994-2004	United States	8,051 (33)	65	1,810 (22.5)	ECG, telemetry or physician finding	Age, sex, ethnicity, smoking, diabetes, chronic kidney disease, hypertension, chronic obstructive pulmonary disease, peripheral vascular disease, stroke, myocardial infarction, congestive heart failure, angina, angiography findings, ejection fraction, medications, operation variables
Yap et al[348]	2001-	Australia	4,053 (29)	65	1,425 (35.1)	N/A	Age, sex, diabetes, hypercholesterolemia, chronic kidney disease,

	2006						hypertension, stroke, peripheral vascular disease, chronic obstructive pulmonary disease, heart failure, pulmonary artery pressure, operation urgency and operation time
Girerd et al[349]	2000-2007	Canada	2,214 (0)	56	433 (19.6)	Continuous monitoring and ECG	Age, stroke, chronic obstructive pulmonary disease, diabetes, lipid studies, waist circumference, angiography findings, ejection fraction, medication use, operative variables
Alam et al[350]	1995-2010	United States	13,115 (25)	63	3,702 (28.2)	N/A	Age, gender, hypertension, diabetes, heart failure, NYHA class, myocardial infarction, chronic kidney disease, pulmonary disease, peripheral arterial disease, stroke, preoperative hypotension, medication use, angiography findings, graft number, use of internal mammary artery, operation variables
Bramer et al[351]	2003-2009	Netherlands	9,348 (27)	65	2,517 (26.9)	Continuous monitoring or ECG	Age, chronic obstructive pulmonary disease, peripheral vascular disease, stroke, myocardial infarction, ejection fraction, creatinine, operation type, operation variables, transfusion requirements, reoperation
Melduni et al[352]	2000-2005	United States	351 (33)	67	135 (38.4)	Continuous monitoring or ECG	Age, hypertension, mitral regurgitation, diastolic dysfunction, surgery type, perfusion time
Sun et al[353]	2000-2009	United States	12,367 (29)	~65	3,462 (28.0)	Continuous monitoring	Age, sex, ethnicity, obstructive sleep apnoea, hypertension, diabetes, family history, myocardial infarction, heart failure, ejection fraction, stroke, chronic kidney disease, operation urgency, smoking, hypercholesterolemia, medications, graft number
Tadic et al[354]	2006-2008	Serbia	322 (28)	60	72 (22.4)	Continuous monitoring or ECG	Age, sex, hypertension, diabetes, hypercholesterolemia, smoking, medications, left atrial diameter, left ventricular kinetic disturbances, triple vessel disease, leukocytosis

ECG = electrocardiogram, NYHA = New York Heart Association, CCS = Canadian Cardiovascular Society

Table 4.4: Obesity and post-ablation atrial fibrillation

Study reference	Dates of study	Country	Subjects (% women)	Mean age (years)	AF population (% paroxysmal)	Follow-up (months)	Follow-up frequency	Method of AF detection	Mean number of procedures	Freedom from AF (%)	Other covariates in model
Richter et al[355]	2002-2004	Austria	234 (28)	57	70.5	Median 13	3-monthly for one year, then 3-6 monthly	ECG and Holter monitor at follow-ups, additional if symptomatic	1.0	61.5 (at 6 months)	Age, sex, AF type, left ventricular ejection fraction, left atrial size, structural heart disease, antiarrhythmic use, ablation technique, inducibility
Jongnarangsin et al[356]	2005-2006	United States	324 (24)	57	72.2	Mean 7	3-6 monthly	ECG at follow-ups, additional if symptomatic, event recorder to those in sinus rhythm at 3-6 months	1.0	60.1	Age, sex, AF type, AF duration, left atrial size, left ventricular ejection fraction
Shah et al[357]	≤2008	United	264 (29)	57	87.0	Mean 34	1, 3, 6 and	Transtelephonic	1.1	91.3	None

		States					12 months, then annually	ECG monitoring for 3 months, Holter at 3 months then annually			
Letsas et al[358]	2004-2006	Germany	72 (19)	55	64.0	Mean 13	1, 3 and 6 months then at mean of 12.5 months	ECG and Holter monitor at follow-ups, additional if symptomatic and event monitor if no AF found	1.0	61.1	Age, sex, AF type, AF duration, hypertension, diabetes, dyslipidemia, structural heart disease, medication use, left ventricular dimensions, left ventricular function, white cell count, C-reactive protein, fibrinogen
Tang et al[359]	2005-2007	China	654 (29)	57	79.8	Mean 16	1, 3 and 6 months, then 6-monthly	ECG and Holter monitor at follow-ups, additional if symptomatic	1.0	63.0	AF type, AF duration, left atrial size, left ventricular end-diastolic diameter, hypertension,

										diabetes, lipid studies, ablation technique
Chang et al[360]	≤2008	Taiwan	282 (24)	52	76.6	N/A	1-3 monthly	Holter monitor or event recorder	1.0	70.6	Hypertension, diabetes, lipid studies
Wokhlu et al[361]	1999-2006	United States	774 (19)	54	55.2	Mean 36	3 months and annually	ECG and Holter monitor, additional and event monitor if clinically indicated	1.1	64.2	Age, AF type, hypertension, diabetes, family history, left atrial size, ablation technique
Patel et al[362]	2005-2008	United States	518 (100)	59	46.0	Mean 24	3, 6, 9 and 12 months, then 6-monthly	Event monitoring for 5 months, Holter monitor at follow-ups	1.0	68.5	Age, hypertension, diabetes, coronary artery disease, left ventricular function, left atrial size, AF type, non-pulmonary vein triggers
Hwang et al[363]	2005-2007	South Korea	81 (15)	52	71.6	Mean 9 months	1, 2, 3, 6 and 9	ECG and Holter monitor	1.0	63.0 (at 9 months)	None

							months				
Wong et al[256]	2008-2009	Australia	110 (23)	58	37.3	Mean 21	3,6,9,12,18 and 24 months, then annually	ECG and Holter monitor	1.4	88.2	Age, gender, hypertension, diabetes, ischaemic heart disease, left ventricular dysfunction, valvulopathy, obstructive sleep apnoea, left atrial volume
Winkle et al[364]	2003-2009	United States	423 (26)	62	0.0	N/A	3 and 12 months	Transtelephonic ECG monitor for 3 months, then ECG and Holter monitor	1.3	N/A	Age, left atrial size, AF duration, sex, antiarrhythmic use, coronary artery disease, hypertension, diabetes
Chao et al[365]	≤2011	Taiwan	232 (28)	53	100.0	Mean 25	1-3 monthly	Holter and/or event monitor	1.0	84.1	Age, hypertension, left atrial size, left ventricular ejection fraction, left atrial

											total activation time, left atrial voltage, renal function
Mohanty et al[366]	≤2011	United States	1,496 (26)	63	29.3	Mean 21	3,6,9 and 12 months	ECG and Holter monitor	1.0	66.0	Hypertension, diabetes, dyslipidemia, metabolic syndrome
Kang et al[367]	2006-2009	South Korea	94 (20)	59	0.0	Man 20	1,3,6 and 12 months	ECG and Holter monitor	1.0	66.0	Age, sex, AF type, AF duration, hypertension, diabetes, left atrial diameter, left ventricular ejection fraction
Letsas et al[368]	≤2011	Germany	226 (19)	56	59.3	Mean 14	3 and 6 months, then at mean of 14 months	Holter monitor	1.0	58.0	None
Ejima et al[369]	≤2011	Japan	80 (19)	58	81.3	Median 17	1,2,3,6,9 and 12 months,	ECG and Holter monitor	1.1	90.0	None

						then 6- monthly				

ECG = electrocardiogram, AF = atrial fibrillation,

Figure 4.1: Electronic database searches leading to study selection


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┌─────────────────────────────────────────────────────────────────────┐
│ 2001 potentially relevant studies assessed by title and abstract    │
└─────────────────────────────────────────────────────────────────────┘
        │
        │      ┌──────────────────────────────────────────────────────────────┐
        │─────▶│ 1602 studies were excluded because they did not investigate   │
        │      │ predictors of incident, post-operative or post-ablation atrial│
        │      │ fibrillation outcomes                                          │
        │      └──────────────────────────────────────────────────────────────┘
        ▼
┌─────────────────────────────────────────────────────────────────────┐
│ 399 studies retrieved for more detailed, full-text assessment       │
└─────────────────────────────────────────────────────────────────────┘
        │
        │   ┌────────────────────────────────────────────────────────────────────┐
        │   │ 348 studies excluded                                               │
        │   │     140 did not study obesity as a predictor                       │
        │──▶│     24 did not calculate body mass index as a measure of obesity  │
        │   │     85 did not assess atrial fibrillation as an endpoint          │
        │   │     24 were duplicate reports or from overlapping cohorts          │
        │   │     71 were review articles, editorials or letters                 │
        │   │     4 did not report or provide data allowing risk estimate        │
        │   │       calculation                                                  │
        │   └────────────────────────────────────────────────────────────────────┘
        ▼
┌─────────────────────────────────────────────────────────────────────┐
│ 51 studies included in the main analysis                            │
└─────────────────────────────────────────────────────────────────────┘
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Figure 4.2: Obesity and atrial fibrillation in cohort studies

Study	OR (95% CI)	Weight
Schnabel et al (AGES)	1.22 (1.05, 1.41)	6.10
Schnabel et al (CHS White)	1.14 (1.05, 1.23)	10.56
Schnabel et al (CHS African)	1.29 (1.10, 1.51)	5.58
Smith et al (Men)	1.47 (1.34, 1.61)	9.51
Smith et al (Women)	1.34 (1.22, 1.47)	9.38
Tedrow et al	1.28 (1.16, 1.34)	11.14
Rosengren et al	1.22 (1.10, 1.34)	9.25
Gami et al	1.40 (1.28, 1.61)	7.86
Murphy et al	1.28 (1.05, 1.47)	5.20
Frost et al (Men)	1.47 (1.28, 1.69)	6.53
Frost et al (Women)	1.34 (1.16, 1.54)	6.39
Wang et al (Men)	1.22 (1.05, 1.40)	6.25
Wang et al (Women)	1.22 (1.05, 1.40)	6.25
Overall	**1.29 (1.23, 1.36)**	**100.00**
(I-squared = 54.7%, p = 0.009)		

0.9   1   1.1   1.2   1.3   1.4   1.5   1.6   1.7

Obesity decreases AF   Obesity increases AF

Figure 4.3: Obesity and atrial fibrillation in case-control studies

Study	OR (95% CI)	Weight
Hodgkinson et al	1.10 (1.08, 1.11)	19.74
Long et al	1.34 (1.05, 1.69)	4.39
Soliman et al	1.22 (0.73, 1.93)	1.26
Suzuki et al	1.43 (1.25, 1.62)	9.73
Bonhorst et al	1.34 (1.10, 1.54)	7.25
Minami et al	1.69 (0.95, 3.18)	0.83
Haywood et al	1.25 (1.15, 1.36)	13.84
Zhang et al	5.38 (2.49, 14.20)	0.41
Yap et al	1.30 (0.59, 2.88)	0.48
Umetani et al	1.51 (0.82, 2.75)	0.82
De Bacquer et al	1.61 (0.90, 2.82)	0.93
Dublin et al	1.16 (1.05, 1.28)	12.47
Hanna et al	1.05 (1.05, 1.10)	19.20
Krahn et al	1.08 (0.94, 1.25)	8.65
Overall	**1.19 (1.13, 1.26)**	**100.00**
(I-squared = 80.0%, p < 0.001)		

Obesity decreases AF   Obesity increases AF

Figure 4.4: Obesity and post-operative atrial fibrillation

Study		OR (95% CI)	Weight
Melduni et al		1.14 (1.02, 1.29)	8.19
Sun et al		1.11 (1.08, 1.14)	11.79
Alam et al		1.05 (0.98, 1.13)	10.36
Bramer et al (Men)		1.13 (1.05, 1.22)	9.96
Bramer et al (Women)		1.18 (1.08, 1.29)	9.32
Tadic et al		1.41 (0.96, 2.08)	1.91
Girerd et al		1.26 (1.14, 1.39)	8.95
Yap et al		1.16 (1.06, 1.25)	9.79
Zacharias et al		1.22 (1.16, 1.28)	11.18
Reeves et al		0.91 (0.84, 0.98)	9.87
Brandt et al		0.72 (0.59, 0.87)	5.06
Engleman et al		1.07 (0.21, 5.42)	0.13
Moulton et al		1.14 (0.88, 1.49)	3.49
Overall		**1.10 (1.04, 1.17)**	**100.00**
(I-squared = 82.9%, p < 0.001)			

0.5 — Obesity decreases AF   1   2   3 — Obesity increases AF

Figure 4.5: Obesity and post-ablation atrial fibrillation

Study		OR (95% CI)	Weight
Ejima et al		1.15 (0.60, 2.08)	1.28
Chao et al		2.69 (0.79, 8.55)	0.35
Winkle et al		1.05 (0.82, 1.16)	15.96
Wong et al		0.21 (0.01, 6.86)	0.04
Letsas et al		1.21 (0.90, 1.57)	6.53
Hwang et al		0.73 (0.31, 1.61)	0.72
Patel et al		2.49 (1.84, 2.93)	9.16
Woklu et al		0.77 (0.59, 1.00)	7.12
Chang et al		1.33 (0.77, 2.10)	1.98
Tang et al		1.00 (0.77, 1.22)	9.65
Shah et al		0.95 (0.62, 1.28)	3.86
Letsas et al		1.40 (0.64, 2.97)	0.84
Jongnarangsin et al		1.00 (0.77, 1.22)	9.65
Richter et al		1.05 (0.77, 1.28)	7.89
Mohanty et al		1.08 (0.94, 1.25)	24.08
Kang et al		3.33 (1.57, 7.08)	0.87
Overall		**1.13 (1.06, 1.22)**	**100.00**

(I-squared = 78.6%, p < 0.001)

Obesity decreases AF   Obesity increases AF

CHAPTER 5: PERICARDIAL FAT AND ATRIAL FIBRILLATION

5.1 Introduction

Atrial fibrillation is the most common sustained arrhythmia, and its prevalence has been projected to continue to increase significantly in the coming decades.[4, 23, 28] Recent studies have highlighted obesity and body size as risk factors for atrial fibrillation.[230, 232, 235, 238] This is particularly significant given the obesity epidemic.[370]

While many studies have evaluated the relationship between systemic measures of adiposity and atrial fibrillation, pericardial adipose tissue depots have only recently been shown to be associated with atrial fibrillation.[254, 255] In addition, no study has quantified periatrial and periventricular fat volumes in relation to atrial fibrillation.

The current study thus aims to characterise the relationship between specific pericardial fat depots, as measured by cardiac magnetic resonance imaging, and atrial fibrillation. We sought to determine whether pericardial fat depots were associated with the presence and severity of atrial fibrillation, as assessed by atrial fibrillation chronicity and symptom burden. In addition, we also explored the association of these depots with left atrial volume and ablation outcome. Due to its contiguity to cardiac structures, we hypothesised that specific pericardial fat depots would be associated with the presence and severity of atrial fibrillation, larger left atrial volumes and poorer outcomes following atrial fibrillation ablation.

5.2 Methods

5.2.1 Study population

Consecutive patients (n=110) undergoing first-time ablation with no contraindication for cardiac magnetic resonance imaging were recruited into three groups based on atrial fibrillation chronicity, in accordance with the Heart Rhythm Society expert consensus statement.[371] Paroxysmal atrial fibrillation was defined as recurrent atrial fibrillation that terminates spontaneously within seven days. Persistent atrial fibrillation was defined as atrial fibrillation which is sustained beyond seven days, or lasting less than seven days but necessitating pharmacologic or electrical cardioversion. Permanent atrial fibrillation was defined as atrial fibrillation of >1 year duration in which cardioversion has either failed or not been attempted. atrial fibrillation symptom burden was evaluated in these patients using the University of Toronto Atrial Fibrillation Severity Scale.[372] A reference group of 20 volunteers without atrial fibrillation were also studied. The two groups were well-matched with regards to cardiovascular risk factors and systemic adiposity (Table 5.1).

All patients provided written informed consent for the study protocol which was approved by the Clinical Research and Ethics Committee of the Royal Adelaide Hospital.

5.2.2 Cardiac magnetic resonance imaging protocol and analysis

Patients underwent cardiac magnetic resonance imaging (1.5 Tesla, Siemens Avanto, Siemens Medical Solutions, Erlangen, Germany) in the week prior to ablation. Sequential steady state free precession short-axis cine sequences were acquired with 6mm slice-thickness and no interslice gaps through the atria, and 6mm slice-thickness with 4mm gap through the ventricles. Slices were taken from the most cranial aspect of the left atrium and sequentially to the cardiac apex at end expiration. The atria were additionally imaged in the horizontal long-axis plane with 6mm slice-thickness and no interslice gaps. Typical imaging parameters were: echo time 1.2ms, repetition time 63.7ms, flip angle 80°, matrix size 192×156, field of view 360-440mm. Of 110 subjects, 8 scans were non-interpretable due to motion artifact, leaving 102 in the study sample.

Pericardial fat volumes were measured offline by two blinded observers using proprietary software (Argus, Siemens Medical Solutions, Erlangen, Germany). Fat volumes were quantified using a previously validated technique found to be highly accurate and reproducible by our group in an ex-vivo ovine model.[373] Pericardial fat was defined as regions of high signal-intensity between the myoepicardium and parietal pericardium. Periatrial and periventricular fat was defined as any pericardial fat subtending the atria and ventricles respectively (Figure 5.1). Areas of fat were traced on consecutive end-diastolic short-axis images and multiplied by the slice-thickness to derive volume.[373] Intra- and inter-observer reproducibility with this technique was excellent (coefficient-of-variation 3.5% and 4.9% respectively). Left

atrial volumes were determined by manually tracing endocardial borders in the

horizontal long-axis views in ventricular end-systole and calculated using a modified

Simpson's rule.[374]

5.2.3 Risk factor definitions

Body mass index was calculated as weight in kilograms divided by height in metres

squared, and body surface area using the Mostellar formula.[375] The following risk

factors were ascertained as categorical variables: gender, hypertension, diabetes

mellitus, ischaemic heart disease, left ventricular dysfunction, valvulopathy, and

obstructive sleep apnoea. Left atrial volume was determined as above.

5.2.4 Electrophysiology study and ablation

The electrophysiological procedure was performed in the post-absorptive state with

conscious sedation using midazolam and fentanyl. The ablation technique has been

previously described.[215] In brief, a conventional transeptal puncture was utilised to

advance both a circular mapping catheter (Lasso) and a 3.5mm tip externally-

irrigated ablation catheter (Thermocool). Following trans-septal puncture,

unfractionated heparin was administered (100IU/kg) with repeated boluses to

maintain an ACT of 300-350s. Electroanatomic mapping (CARTO or NavX) was

utilised for non-fluoroscopic navigation. The ablation strategy included wide-

encircling ablation of the pulmonary veins with an endpoint of pulmonary vein

isolation and further substrate modification using linear ablation or electrogram-

based ablation in those with atrial fibrillation paroxysms>48hours, large atria (largest

diameter>57mm) or evidence of structural heart disease. Radiofrequency power of 30W was used with irrigation rates of 30-60mls/minute.

5.2.5 Follow-up

Patients were followed-up at 3, 6, 9, 12, 18 and 24 months, and then yearly, until atrial fibrillation recurrence. At each review, patients underwent ambulatory monitoring for a 7 day period. All patients had either flecainide or sotalol for 6 weeks after the procedure. Antiarrhythmic drugs were ceased at the discretion of the treating physician at the 6-week follow-up visit. Warfarin was continued in all patients for a period of at least 3 months. In patients with $CHADS_2$ score<2, warfarin was ceased in the absence of any arrhythmia, otherwise it was continued for a minimum of 12 months. Procedural success was determined as the absence of any atrial arrhythmia >30seconds without the use of anti-arrhythmic drugs after a blanking period of 3 months.

5.2.6 Statistical analysis

To study the relationship between pericardial fat and atrial fibrillation presence, we employed binary logistic regression models. Each adiposity measure was then studied separately, adjusting for the two strongest univariate risk factors (left atrial volume and obstructive sleep apnoea) to avoid overfitting, and then additionally for weight.

To determine the relationship between pericardial fat depots and atrial fibrillation chronicity, we compared pericardial fat depots according to atrial fibrillation chronicity using the Kruskal-Wallis test and post-hoc Wilcoxon rank sum tests as appropriate. We then dichotomised the study sample into two groups: paroxysmal and nonparoxysmal atrial fibrillation (persistent or permanent atrial fibrillation). Each adiposity measure was then studied separately, adjusting for the four strongest univariate risk factors (left atrial volume, left ventricular dysfunction, gender and valvulopathy) to avoid overfitting, and then additionally for weight. To determine the relationship between pericardial fat and atrial fibrillation symptom burden scores, multivariable linear regression models were utilised, adjusting for all the aforementioned risk factors and atrial fibrillation chronicity, and then additionally for weight.

To determine the relationship between pericardial fat and atrial fibrillation recurrence, patients were firstly divided into tertiles according to total pericardial fat and Kaplan-Meier methods employed. Secondly, a time-to-event Cox proportional hazards regression method was employed to study the individual relationship of specific adiposity measures as continuous variables to long-term atrial fibrillation recurrence. Multivariable Cox proportional hazards regression models were utilised adjusting for all the aforementioned risk factors and atrial fibrillation chronicity, and then additionally for weight. The proportional-hazards assumption was confirmed by the means of the Schoenfeld residuals test; no relevant violations of the assumption were found.

To determine the relationship between pericardial fat and left atrial volume, Pearson correlations between adiposity measures and left atrial volume were calculated. Multivariable linear regression models were then constructed to determine which specific adiposity measures were associated with LA volumes, adjusting for all the aforementioned risk factors and then additionally for weight.

Continuous variables are reported as mean±standard deviation or median and interquartile range as appropriate. Study sample characteristics according to group were compared using the unpaired Student t test, Wilcoxon rank sum test or Fisher's exact test as appropriate. All adiposity measures were standardised to a mean of 0 and a standard deviation of 1 to facilitate comparison between different fat depots. Statistical tests were performed using SPSS16 (SPSS Inc, Chicago, Illinois) and a 2-tailed value of $p<0.05$ was considered significant.

5.3 Results

5.3.1 Patient characteristics

Patient characteristics are summarised in Table 5.1. The two groups were well matched for age, sex and risk factors. However, atrial fibrillation patients had larger left atria (p=0.006).

5.3.2 Pericardial fat and atrial fibrillation presence

Atrial fibrillation patients had greater pericardial fat volumes than reference patients (Figure 5.2). By logistic regression modelling, pericardial fat depots were individually predictive of the presence of atrial fibrillation (Table 5.2), whereas systemic adiposity measures did not. Additional adjustment for risk factors and weight did not change these associations.

5.3.3 Pericardial fat and atrial fibrillation severity

Worsening baseline atrial fibrillation chronicity was associated with greater adiposity measures (Figure 5.2). All adiposity measures were individually predictive of nonparoxysmal atrial fibrillation (Table 5.3). However, only pericardial fat volumes were associated with nonparoxysmal atrial fibrillation in multivariable-adjusted models, and additional adjustment for weight did not change these associations.

Similarly, whilst all adiposity measures were individually associated with atrial fibrillation burden score, only pericardial fat volumes were still associated after

multivariable-adjustment (Table 5.4). Additional adjustment for weight also did not change these associations.

5.3.4 Pericardial fat and atrial fibrillation recurrence

There was no loss to follow-up after 16.7±11.1 months. Of 102 patients, 43 (42.6%) remained free of recurrence while off antiarrhythmic drugs after a single ablation procedure. Of those who suffered recurrence (n=59), 32 were re-commenced on antiarrhythmics drugs and 14 (43.8%) responded favourably to a previously ineffective antiarrhythmic drug after ablation and maintained normal sinus rhythm. Of the 59 patients who suffered recurrence, 37 went onto have a second procedure and 5 went onto have a third procedure. After 1.4±0.6 procedures and 21.0±12.0 months after the last procedure, 90 (88.2%) patients were free of recurrence while off antiarrhythmic drugs.

By Kaplan-Meier analysis, patients with more extensive total pericardial fat suffered recurrence at earlier time points after the index ablation procedure (p=0.035 by log rank test; Figure 5.3).

Pericardial fat volumes were predictive of atrial fibrillation recurrence by Cox regression modelling, whereas body mass index and body surface area were not (Table 5.5). After multivariable adjustment, periventricular fat (p=0.024) remained predictive of atrial fibrillation recurrence. This association remained significant after additional adjustment for weight (p=0.025).

5.3.5 Pericardial fat and left atrial volume

Periatrial (r=0.43), periventricular (r=0.48) and total pericardial fat volumes (r=0.49) correlated with left atrial volume (all p<0.001). In contrast, neither body mass index nor body surface area were significantly correlated with left atrial volume (p=0.22 and p=0.38 respectively).

In multivariable-adjusted models, all pericardial fat depots were associated with left atrial volume. Per one standard deviation increase in periatrial fat, periventricular fat and total pericardial fat, left atrial volume was 12.10mL (p=0.004), 12.34mL (p=0.003) and 14.04mL (p=0.001) larger respectively. These associations persisted after additional adjustment for weight (p=0.041 for periatrial, p=0.024 for periventricular and p=0.022 for total pericardial fat).

5.4 Discussion

5.4.1 Major findings

In consecutive patients with atrial fibrillation presenting for first-time radiofrequency ablation and a group of reference patients, we undertook detailed cardiac magnetic resonance imaging examination to present new information regarding the interrelationships between localised pericardial fat depots and atrial fibrillation.

First, we showed there to be an association between pericardial fat and the presence of atrial fibrillation. Second, we demonstrate there to be a strong dose-response association between pericardial fat and atrial fibrillation severity, as assessed by atrial fibrillation chronicity and symptom burden. Third, our data demonstrates that pericardial fat was independently predictive of atrial fibrillation recurrence following ablation. Finally, we found independent associations between pericardial fat depots and left atrial volume.

These associations were not seen with more systemic measures of adiposity. Our findings are consistent with the hypothesis of a local pathogenic effect of pericardial fat promoting an arrhythmogenic substrate.

5.4.2 Pericardial fat and atrial fibrillation

Significant associations between body mass index and the development of atrial fibrillation have been reported.[27, 230, 232, 235, 238] Prior studies have shown that the association with body mass index is stronger for sustained atrial fibrillation than it is

for less severe forms, and that obesity causes progression to more severe atrial fibrillation.[237, 238] Short-term increases in body mass index have also been associated with an increased atrial fibrillation risk.[235] A recent report has suggested that computed-tomography measured total pericardial fat volumeis associated with prevalent atrial fibrillation.[376] Another recent study reported an association between computed tomography-measured epicardial thickness over the left atrium and atrial fibrillation chronicity.[255] The present investigation extends the results of these studies to a cohort of patients who have had specific pericardial fat volumes measured with a previously validated cardiac magnetic resonance imaging technique.[373] After multivariable-adjustment, only pericardial fat and not systemic adiposity measures remained independently predictive of both the presence and severity of atrial fibrillation. Whilst studies with larger study samples have previously reported associations between systemic adiposity and atrial fibrillation, the finding that pericardial fat but not systemic adiposity were significantly associated with atrial fibrillation in our study suggests that pericardial fat depots may be more influential than body mass index or body surface area. Furthermore, we found that pericardial fat was predictive of ablation outcomes, providing evidence of the deleterious role that pericardial fat may also have on substrate remodelling following ablation.

5.4.3 Pericardial fat and cardiac structure

Pericardial fat has been previously shown to be associated with left atrial dimensions.[266, 377-379] However, periatrial and periventricular fat has not been previously studied in relation to left atrial volume, a superior predictor of outcome

than left atrial dimension.[380] We found that specific pericardial fat depots were associated with cardiac magnetic resonance imaging-assessed left atrial volumes. In contrast, we observed no such association between systemic adiposity and left atrial volume. This may reflect our small sample size compared to previous epidemiological studies, our use of left atrial volume, or the atrial fibrillation population studied. Nevertheless, our data suggest that pericardial fat may have a pathogenic effect on the anatomically contiguous atria, above and beyond systemic effects of generalised adiposity.

5.4.4 Potential mechanisms

The association between pericardial fat and atrial fibrillation were not weakened by risk factor adjustment, suggesting they play a lesser role in mediating the relationship. Previous studies have reported that the association between body mass index and atrial fibrillation was attenuated when left atrial dimension was accounted for, suggesting that left atrial enlargement accounts for this association.[27] We found that pericardial fat, but not systemic adiposity, was associated with left atrial volume. Furthermore, adjustment for left atrial volume did not attenuate the association between pericardial fat, the presence and severity of atrial fibrillation, and ablation outcomes. Thus, whilst previous reports have explained the association between obesity and atrial fibrillation as due to left atrial enlargement, our findings suggest that the association between pericardial fat measures and atrial fibrillation are independent of left atrial size.

Circulating markers of inflammation, microvasculopathy and hemodynamic strain have been linked to atrial fibrillation and obesity.[53, 381] At a local level, pericardial fat has been associated with increased expression of numerous inflammatory markers.[262] Intra-cardiac inflammatory markers have also been observed to be greater than peripheral inflammatory markers and greatest in the left atrium which plays a critical role in atrial fibrillation genesis.[382] Cytokines have also been shown to activate fibroblasts, with the extracellular matrix deposition and fibrosis causing electroanatomical remodelling.[383] Therefore, the present finding that only pericardial fat measures are associated with atrial fibrillation supports the notion that pericardial fat, the local fat depot, may exert deleterious effects on the anatomically contiguous atria and promote arrhythmogenesis.

5.4.5 Implications

We demonstrate that pericardial fat volumes are associated with the presence and severity of atrial fibrillation, independent of other risk factors and systemic adiposity. With the increasing use of cardiac magnetic resonance imaging, pericardial fat measurement may yield additional information on the risk of developing atrial fibrillation, the risk atrial fibrillation progressing and the risk of recurrence following ablation and thereby constitute a novel risk marker. With the emerging significance of obesity in cardiovascular disease, further investigation is required into the underlying pathophysiologic mechanisms.

5.4.6 Limitations

The cross-sectional study design limits inferences of causality. The predominantly White-Australian patients also limits generalisability of our findings to non-White individuals. We also did not measure waist circumference or waist-hip ratio; these measures may have added incremental information on the effects of local versus systemic adiposity. Finally, due to small subgroup sizes the number of variables adjusted for in the binary logistic regression models was limited to avoid over-fitting models.

5.5 Conclusion

Pericardial fat is associated with the presence and severity of atrial fibrillation, left atrial volumes and poorer outcomes following atrial fibrillation ablation. These associations are both independent of and stronger than more systemic measures of adiposity. Our findings are consistent with the hypothesis of a local pathogenic effect of pericardial fat on the arrhythmogenic substrate supporting atrial fibrillation.

Table 5.1: Study sample characteristics

	AF (n=102)	Reference (n=20)	P
Age, y(SD)	58(9)	54(6)	0.15
Men, %(n)	76(72)	11(55)	0.20
BMI, kg/m^2(SD)	28.0(3.5)	27.2(3.4)	0.46
BSA, m^2(SD)	2.04(0.22)	1.93(0.20)	0.08
Periatrial fat, cm^3(IQR)	118.5(70.8-173.8)	69.7(47.7-88.0)	<0.001
Periventricular fat, cm^3(IQR)	154.7(114.4-233.8)	101.2(84.9-111.2)	<0.001
Total pericardial fat, cm^3(IQR)	299.9(192.2-407.2)	168.8(130.4-189.0)	<0.001
Paroxysmal AF, %(n)	37(38)	-	-
Persistent AF, %(n)	33(34)	-	-
Permanent AF, %(n)	29(30)	-	-
AF Episode Frequency Score(SD)	8.5(1.9)	-	-
AF Episode Duration Score(SD)	8.5(2.1)	-	-
LA volume, mL(SD)	123(36)	90(26)	0.006
Valvulopathy, %(n)	6.9(7)	0.0(0)	0.60
Hypertension, %(n)	56.9(58)	55.0(11)	0.99
Diabetes, %(n)	5.9(6)	10.0(2)	0.61
Ischaemic heart disease, %(n)	17.6(18)	10.0(2)	0.52
Left ventricular dysfunction, %(n)	14.7(15)	5.0(1)	0.47
Obstructive sleep apnoea, %(n)	17.6(18)	10.0(2)	0.52

BMI = body mass index, BSA = body surface area, AF = atrial fibrillation, LA = left atrial, SD = standard deviation, IQR = interquartile range

Table 5.2: Multivariable-adjusted odds ratios of adiposity measures and the presence of atrial fibrillation

	Univariate	P	Multivariable-Adjusted	P	With Additional-Adjustment for Body Weight	P
BMI	1.26 (0.74-2.15)	0.391	1.16 (0.61-2.22)	0.645	…	…
BSA	1.61 (0.94-2.73)	0.081	1.25 (0.65-2.41)	0.509	…	…
Periatrial fat	4.61 (1.72-12.39)	0.002	5.35 (1.30-2.19)	0.020	5.33 (1.25-22.66)	0.023
Periventricular fat	13.63 (3.04-61.15)	0.001	10.94 (1.69-70.73)	0.012	11.97 (1.69-84.88)	0.013
Total pericardial fat	10.47 (2.87-38.21)	<0.001	11.25 (2.07-61.24)	0.005	13.26 (2.23-79.98)	0.005

BMI = body mass index, BSA = body surface area.

Table 5.3: Multivariable-adjusted odds ratios of adiposity measures and atrial fibrillation chronicity

	Univariate	P	Multivariable-Adjusted	P	With Additional-Adjustment for Body Weight	P
BMI	1.76 (1.08-2.87)	0.024	1.72 (0.89-3.32)	0.108	…	..
BSA	2.05 (1.27-3.30)	0.003	1.57 (0.74-3.33)	0.243	…	...
Periatrial fat	4.64 (2.20-9.76)	<0.001	4.87 (1.87-12.69)	0.001	4.84 (1.75-13.4)	0.002
Periventricular fat	2.67 (1.46-4.89)	0.001	2.10 (1.08-4.09)	0.030	1.96 (1.01-3.82)	0.047
Total pericardial fat	4.33 (2.08-9.02)	0.005	3.56 (1.41-9.00)	0.007	3.28 (1.25-8.59)	0.015

BMI = body mass index, BSA = body surface area

Table 5.4: Multivariable-adjusted regressions between adiposity measures and atrial fibrillation burden

	Univariate	P	Multivariable-Adjusted	P	With Additional-Adjustment for Body Weight	P
BMI	1.10 (0.33-1.88)	0.005	0.87 (-0.49-2.24)	0.205	…	…
BSA	1.18 (0.42-1.94)	0.003	1.00 (-0.32-2.33)	0.133	…	…
Periatrial fat	1.57 (0.88-2.27)	<0.001	1.71 (0.79-2.64)	<0.001	1.59 (0.59-2.60)	0.003
Periventricular fat	1.46 (0.74-2.19)	<0.001	1.21 (0.23-2.19)	0.017	1.11 (0.11-2.11)	0.031
Total pericardial fat	1.69 (0.99-2.39)	<0.001	1.71 (0.73-2.68)	0.001	1.57 (0.54-2.60)	0.003

BMI = body mass index, BSA = body surface area

Table 5.5: Multivariable-adjusted hazard ratios of adiposity measures and atrial fibrillation recurrence

	Univariate	P	Multivariable-Adjusted	P	With Additional-Adjustment for Body Weight	P
BMI	1.03 (0.79-1.34)	0.842	0.72 (0.35-1.47)	0.364	…	…
BSA	1.27 (0.96-1.67)	0.096	1.07 (0.47-2.42)	0.874	…	…
Periatrial fat	1.34 (1.05-1.71)	0.020	0.69 (0.30-1.55)	0.366	0.60 (0.25-1.46)	0.259
Periventricular fat	1.55 (1.23-1.96)	<0.001	3.83 (1.19-12.29)	0.024	3.95 (1.19-3.34)	0.025
Total pericardial fat	1.51 (1.19-1.90)	0.001	1.42 (0.56-3.59)	0.465	1.39 (0.52-3.67)	0.509

BMI = body mass index, BSA = body surface area

Figure 5.1: Cardiac magnetic resonance imaging assessment of periatrial and periventricular fat volumes

A. Periatrial Fat
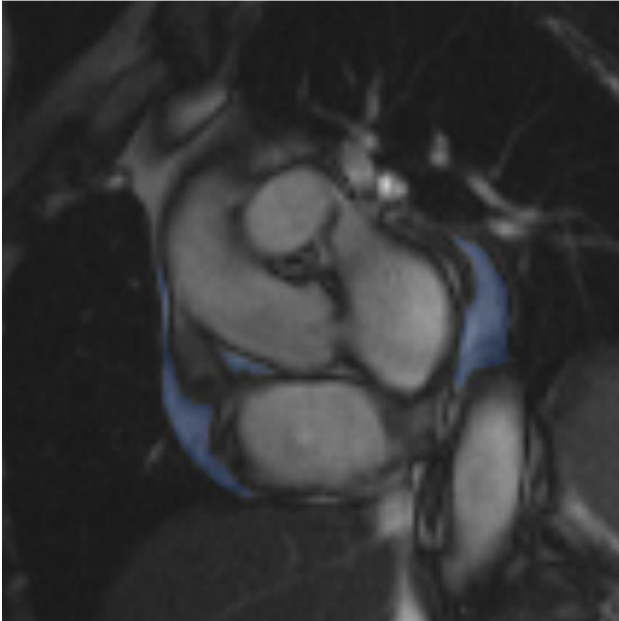
B. Periventricular Fat
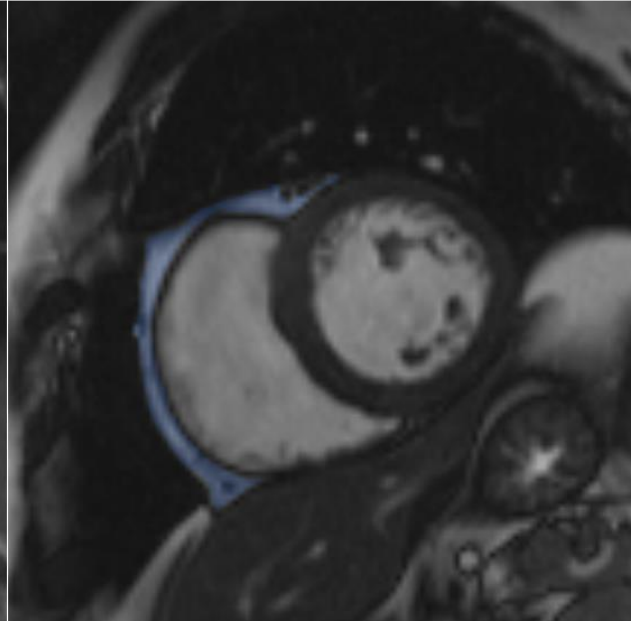
Figure 5.2: Pericardial fat volumes according to presence and chronicity of atrial fibrillation
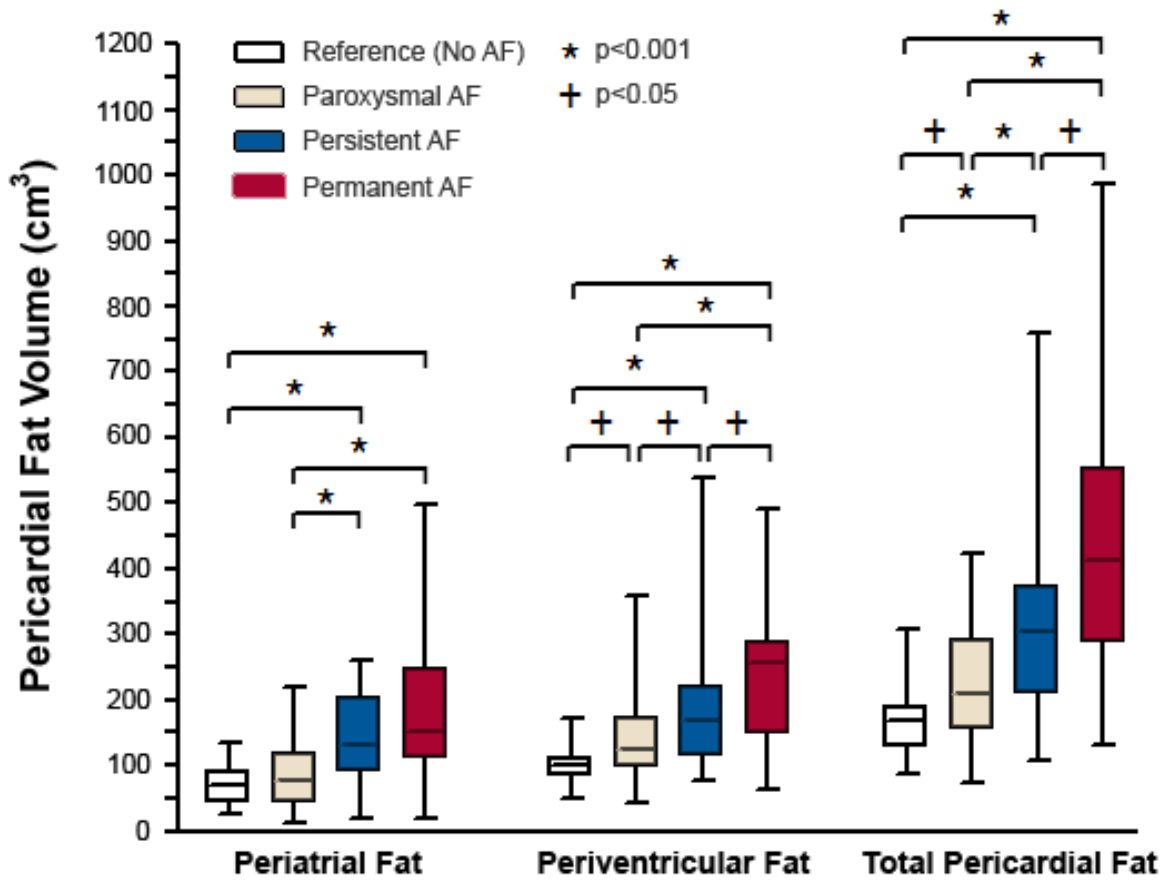
Figure 5.3: Pericardial fat volumes are ablation outcome
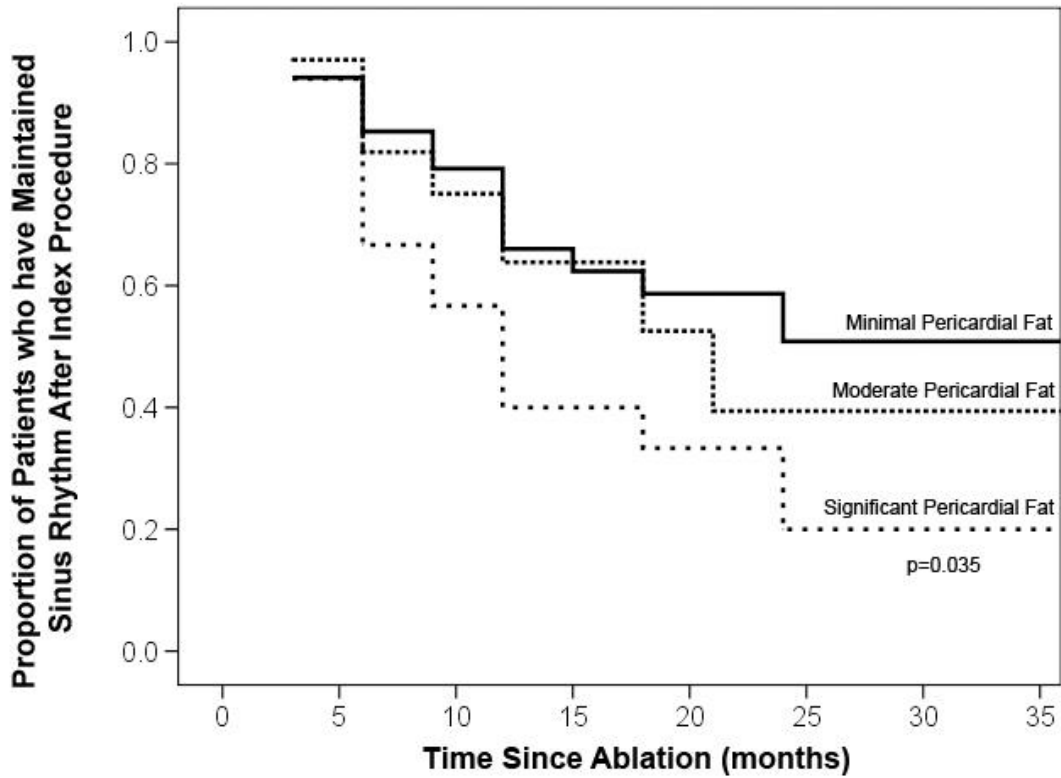
Minimal Pericardial Fat	34	32	27	23	22	20	20	20
Moderate Pericardial Fat	34	33	28	23	20	17	17	17
Significant Pericardial Fat	34	32	20	15	13	9	9	9
Total	102	97	75	61	55	46	46	46

CHAPTER 6: ATRIAL FIBRILLATION IN INDIGENOUS AND NON-INDIGENOUS AUSTRALIANS

6.1 Introduction

Atrial fibrillation is the most common arrhythmia encountered in clinical practice. Whilst previous studies have suggested it to affect 2% of the unselected population, recent reports have revealed that the prevalence and subsequent burden of atrial fibrillation on the health system is continuing to increase.[4, 22, 170, 179, 317, 329] Put together, these data point towards atrial fibrillation as a growing public health concern.[175, 179]

A recognised limitation of prior epidemiologic reports on atrial fibrillation has been a lack of racial diversity.[3, 4, 28] With the advent of studies with broader representation has emerged evidence that the prevalence of atrial fibrillation may vary according to race.[5, 22, 59, 62, 285, 384] Given the important mechanistic and clinical implications of such findings, we sought to study the prevalence of atrial fibrillation in Indigenous Australians, a racial subgroup in which atrial fibrillation has not been previously characterised. We also examined for differences in cardiac structure and function between Indigenous and non-indigenous Australians using echocardiography.

6.2 Methods

6.2.1 Data source

The Royal Adelaide Hospital is a 700 bed tertiary referral centre and teaching hospital of the Universities of Adelaide and South Australia. We identified all hospitalisations over a 10 year period from 2000 through 2009 inclusive from the coding database. The study protocol was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital, Adelaide, Australia.

6.2.2 Data collection

The *International Classification of Diseases, 10th Rev, Australian Modification* (ICD-10-AM) was used for coding hospital diagnoses. Atrial fibrillation was defined for patients with ICD-10-AM diagnosis code I48 that include both atrial fibrillation and atrial flutter. Hypertension was defined for patients with ICD-10-AM diagnosis codes I10-I15. Ischaemic heart disease was defined for patients with ICD-10-AM diagnosis codes I20-I25. Heart failure was defined for patients with ICD-10-AM diagnosis code I50. Conditions were deemed to be present if they were coded as being a principal or secondary diagnosis during any hospitalisation. In addition, it was noted whether these conditions were pre-existing at first clinical contact, or whether they were new diagnoses made during study period at subsequent hospitalisations. Hospitalisations were categorised as being for Indigenous or non-Indigenous individuals. Additional variables identified from the coding database included age and gender.

6.2.3 Echocardiographic study

Patients without atrial fibrillation who underwent echocardiography were identified. Resting transthoracic two-dimensional guided M-mode Doppler echocardiography by standard techniques in the left lateral decubitus position was performed. Standard M-mode left atrial linear dimensions were obtained from the parasternal long-axis view in end-systole.[385] Measurements of left ventricular end-diastolic diameter, left ventricular end-systolic diameter and left ventricular ejection fraction were additionally determined in accordance with the American Society of Echocardiography guidelines.[385] Left ventricular ejection fraction was calculated using Biplane Simpson's rule.

6.2.4 Statistical analysis

Continuous variables are reported as mean±standard deviation as appropriate. Study sample characteristics according to group were compared using an independent samples t-test or chi-square test as appropriate. To identify predictors of the risk of atrial fibrillation, a logistic regression model was employed. To identify predictors of the number of admissions, a negative binomial regression model was employed. To identify predictors of length of stay, a negative binomial estimating equation was employed. To determine the influence of race on echocardiographic measurements, linear regression models were utilised. Statistical tests were performed using SAS Version 9.2 (SAS Institute Inc., Cary, NC, USA) and $p<0.05$ was considered significant.

6.3 Results

6.3.1 Patient characteristics

A total of 629,024 hospitalisations for 204,668 individuals were identified (Table 6.1). Of these, 22,821 (3.6%) and 606,203 (96.4%) hospitalisations were for Indigenous and non-Indigenous Australians respectively. Compared to non-Indigenous Australians, Indigenous Australians were more likely to be younger and female. Whilst pre-existing hypertension, new hypertension, new ischaemic heart disease and new congestive heart failure were more prevalent in non-Indigenous Australians, pre-existing ischaemic heart disease was more prevalent in Indigenous Australians. There were no significant racial differences in the prevalence of pre-existing congestive heart failure.

6.3.2 Race and atrial fibrillation

There were a total of 14,373 individuals with a diagnosis of atrial fibrillation. Overall, the prevalence of atrial fibrillation was 3.8% for Indigenous Australians and 7.1% for non-Indigenous Australians ($p<0.0001$). In those under 60 years of age, however, the prevalence of atrial fibrillation was more common in Indigenous Australians compared to non-Indigenous Australians (2.57 vs. 1.73%, $p<0.0001$; see Figure 6.1). In contrast, the prevalence of atrial fibrillation was less common in Indigenous Australians compared to non-Indigenous Australians in those over 60 years of age (4.61 vs. 9.26%, $p<0.0001$).

Indigenous Australian atrial fibrillation patients were younger than non-Indigenous Australian atrial fibrillation patients (55±13 vs. 75±13 years, p<0.0001). Despite their younger age, Indigenous Australian atrial fibrillation patients had a similar or greater prevalence of cardiovascular comorbidities (Table 6.1). Whilst hypertension was the most common secondary diagnosis for both Indigenous and non-Indigenous Australians hospitalised with a primary diagnosis of atrial fibrillation, ischaemic heart disease and congestive heart failure were the most common primary diagnoses for Indigenous and non-Indigenous Australians hospitalised with a secondary diagnosis of atrial fibrillation respectively (Table 6.1).

6.3.3 Predictors of atrial fibrillation

To identify predictors for the presence of atrial fibrillation, a binary logistic regression model was utilised (Table 6.2). After adjusting for potential confounders, male gender, age and common cardiovascular comorbidities were predictive of the presence of atrial fibrillation.

6.3.4 Echocardiographic measurements

Of the 190,315 individuals without atrial fibrillation that were studied, a total of 4,477 (2.4%) had echocardiograms available for review. The mean left atrial diameter was 38±7mm and mean left ventricular ejection fraction 53±12%. After adjusting for age, gender and comorbidities, in those under 60 years of age, Indigenous Australian status was an independent predictor of larger left atrial diameter (p<0.001, Table 6.3). In those over 60 years of age, however, Indigenous Australian status was no

longer an independent predictor of left atrial diameter after multivariable adjustment (p=0.197). Similarly, Indigenous Australian status was an independent predictor of lower left ventricular ejection fraction in those under 60 years of age (p<0.001), but not in those over 60 years of age after multivariable adjustment (p=0.07; Table 6.4).

6.3.5 Hospital utilisation

We also studied predictors of length of stay and the number of hospitalisations, two measures of hospital service utilisation. Negative binomial generalised estimating equations were employed, and the results of these analyses shown in Tables 6.5 and 6.6. Whilst age, atrial fibrillation and other common comorbidities were predictive of an increased length of stay, Indigenous Australian status was not. Similarly, whilst age, male gender, atrial fibrillation and other common comorbidities were predictive of the number of hospitalisations, Indigenous Australian status was not.

6.4 Discussion

6.4.1 Major findings

To the best of our knowledge, this report provides the first comparative assessment of atrial fibrillation in Indigenous and non-Indigenous Australians. We found that atrial fibrillation was more prevalent Indigenous Australians in those under 60 years of age, and more prevalent in non-Indigenous Australians in those over 60 years of age. Indigenous Australians under 60 years of age, but not those over 60 years of age, had significantly greater left atrial diameters and rates of left ventricular systolic dysfunction than non-Indigenous counterparts after multivariable adjustment. These differences in cardiac structure and function may in-part explain the excess prevalence of atrial fibrillation seen in young Indigenous Australians that would contribute to the disparity in life-expectancies between Indigenous and non-Indigenous Australians.

6.4.2 Evidence for racial variation in atrial fibrillation

A number of previous studies have reported that Caucasian race is associated with a greater prevalence of atrial fibrillation and that African American race is associated with a lower prevalence of atrial fibrillation. [5, 22, 59, 62, 285, 384] Since then, further differences in the prevalence of atrial fibrillation have been variably noted in Chinese, Japanese, Korean, African and Latino populations. [20, 62, 336, 386-390] Despite the above studies, however, there continues to be a paucity of epidemiological data on atrial fibrillation from many parts of the world, including Australasia.

In the present study, we thus sought to characterise atrial fibrillation in Indigenous Australians. Compared to their non-Indigenous counterparts, we found a greater prevalence of atrial fibrillation in young Indigenous Australians, and in contrast, a lesser prevalence of atrial fibrillation in older Indigenous Australians.

6.4.3 Possible reasons underlying racial differences in atrial fibrillation

Despite the expanding literature describing racial differences in atrial fibrillation prevalence, the mechanisms underlying these observations remain unclear. There is a growing body of evidence suggesting that there exists a genetic predisposition to atrial fibrillation, with racial-specific differences in atrial fibrillation prevalence being one readily-recognised manifestation of this.[391] Since familial atrial fibrillation was first reported in 1942, recent studies have shown an increased risk of atrial fibrillation associated with family history, various mutations and genetic loci.[392] One study described how European ancestry was a risk factor for developing atrial fibrillation.[61] It has been hypothesised that genes governing atrial dimensions may be responsible. Left atrial diameter is a well-established risk factor for atrial fibrillation.[5] Two previous studies have noted smaller left atria in African Americans compared to Caucasians, which they hypothesised might contribute to their lesser burden of atrial fibrillation.[62, 393] Our finding that Indigenous Australians have larger left atria lends further weight to this theory and may in-part explain the excess burden of atrial fibrillation seen in younger Indigenous Australians observed in the present study. Similarly, left ventricular systolic dysfunction is a powerful risk factor for atrial

fibrillation and our data confirms the previously described excess burden of ventricular dysfunction in Indigenous Australians.[66]

Varying risk factor profiles have also been speculated to be in-part responsible for these racial differences. Indigenous Australians have an excess burden of cardiovascular disease and 11-year lower life expectancy compared to other Australians.[69, 70] In recent data from the Heart of the Heart Study, comprehensive heart failure and risk factors data in Indigenous Australians was reported.[66] In six Indigenous Australian communities in Central Australia, the burden of heart failure and risk factors was extremely high. Consistent with these findings, in our comparatively urban population of Indigenous Australians with atrial fibrillation we also noted similar or greater rates of cardiovascular comorbidities compared to non-Indigenous Australians, despite their younger age. However, varying risk factor profiles are not always consistent with racial differences in atrial fibrillation prevalence; in African American populations, for example, there is a paradoxically lower prevalence of atrial fibrillation in spite of their greater risk factor burden.[240, 394]

It has also been hypothesised that under ascertainment of atrial fibrillation could explain some divergences, with a reported lower burden of atrial fibrillation in African Americans potentially a result of poorer access to medical care. However, under ascertainment would be less likely in prior reports from integrated healthcare facilities and prospective studies where the ability to diagnose atrial fibrillation has been consistent across races.[22, 62] Additionally, this would not readily explain the

greater, and not lesser, burden of atrial fibrillation noted in younger Indigenous Australians observed in the present study.

Differences in mortality might in-part explain the greater atrial fibrillation prevalence seen in older non-Indigenous Australians. The disproportionately early morbidity and mortality faced by Indigenous Australians could in turn lead to a lower prevalence of atrial fibrillation in older age groups if only healthier individuals survived; simultaneously, access to better medical care in non-Indigenous Australians would improve survival despite concurrent comorbidities such as atrial fibrillation. Such a possible mortality difference may have resulted in the similar overall prevalence of atrial fibrillation observed after multivariable adjustment, despite the greater prevalence of atrial fibrillation in younger Indigenous Australians.

6.4.4 Implications

From a mechanistic perspective, our findings further support the notion that differences in cardiac structure and function may underlie the racial variation in atrial fibrillation prevalence. On a clinical level, the excess burden of atrial fibrillation and other comorbidities observed in young Indigenous Australians is of concern. These data suggest that risk factor modification may mitigate the excess burden of morbidity and mortality due to atrial fibrillation in younger Indigenous Australians.

6.4.5 Limitations

Our study has a number of limitations. Firstly, asymptomatic atrial fibrillation may not have been detected. Secondly, there may be incomplete identification of Indigenous Australians in hospital records given race was self-reported and the racial make-up of any given individual can be complex. Thirdly, a significant number of Indigenous Australians reside in rural regions, compared to the presently studied urban setting. Fourthly, our cohort comprised hospitalised patients who, in contrast to the general population, have a greater prevalence of comorbidities and thus atrial fibrillation. As a result, our findings may not necessarily reflect that of the general population. Finally, there may be other potential confounders that were not measured, including other predictors of atrial fibrillation such as diabetes, obesity and obstructive sleep apnoea.[256]

6.5 Conclusion

To the best of our knowledge, the present study provides the first assessment of atrial fibrillation in Indigenous Australians. Young Indigenous Australians have a significantly greater prevalence of atrial fibrillation and have similar, or more, comorbidities than their non-Indigenous counterparts. These findings that may be in-part due to the comparatively larger left atrial dimensions and rates of left ventricular systolic dysfunction observed in young Indigenous Australians.

Table 6.1: Patient characteristics

	All Indigenous Australians (n=5,892)	All Non-Indigenous Australians (n=198,776)	P	Indigenous Australians with AF (n=221)	Non-Indigenous Australians with AF (n=14,152)	P
Age, year (SD)	42.2 (16.2)	54.0 (20.9)	<0.001	55.4 (13.2)	74.5 (13.1)	<0.001
Male, % (n)	51.7 (3,049)	53.8 (106,992)	0.002	52.5 (116)	54.1 (7662)	0.63
Pre-existing hypertension, % (n)	15.0 (886)	47.9 (24,478)	<0.001	32.6 (72)	32.1 (4539)	0.87
New hypertension, % (n)	4.28 (252)	19.8 (10,103)	<0.001	16.3 (36)	16.5 (2329)	0.95
Pre-existing ischaemic heart disease, % (n)	13.3 (783)	9.6 (19,071)	<0.001	36.2 (80)	26.3 (3715)	<0.001
New ischaemic heart disease, % (n)	2.6 (153)	3.1 (6,096)	0.04	13.1 (29)	12.6 (1777)	0.80
Pre-existing congestive heart failure, % (n)	3.3 (193)	3.3 (6,504)	0.99	17.2 (38)	17.7 (2504)	0.85
New congestive heart failure, % (n)	1.7 (101)	2.5 (4,936)	<0.001	16.7 (37)	15.2 (2149)	0.52

AF = atrial fibrillation, SD = standard deviation

Table 6.2: Multivariable-adjusted associations with prevalent atrial fibrillation

	Univariate OR (CI)	P	Multivariate OR (CI)	P
Indigenous Australian	1.471 (1.233-1.755)	<0.001	1.183 (0.977-1.432)	0.085
Age	1.086 (1.082-1.091)	<0.001	1.069 (1.064-1.074)	<0.001
Male	1.992 (1.817-2.185)	<0.001	1.798 (1.633-1.979)	<0.001
Hypertension	6.138 (5.603-6.723)	<0.001	2.109 (1.892-2.352)	<0.001
Ischaemic heart disease	6.341 (5.761-6.979)	<0.001	1.556 (1.383-1.750)	<0.001
Congestive heart failure	21.562 (19.146-24.283)	<0.001	8.812 (7.72-10.059)	<0.001

OR = odds ratio, CI = confidence interval

Table 6.3: Multivariable-adjusted associations with left atrial diameter

	Univariate regressions (CI)	P	Multivariate regressions (CI)	P
Indigenous Australian	0.255 (0.143 to 0.367)	<0.001	0.261 (0.096 to 0.426)	0.002
Age	0.016 (0.013 to 0.018)	<0.001	0.012 (0.008 to 0.016)	<0.001
Male	0.299 (0.234 to 0.365)	<0.001	0.344 (0.249 to 0.439)	<0.001
Hypertension	0.249 (0.169 to 0.329)	<0.001	0.135 (0.011 to 0.259)	<0.001
Ischaemic heart disease	0.301 (0.224 to 0.379)	<0.001	0.043 (-0.071 to 0.156)	0.46
Congestive heart failure	0.653 (0.530 to 0.775)	<0.001	0.417 (0.232 to 0.602)	<0.001
LV ejection fraction	-0.022 (-0.026 to -0.018)	<0.001	-0.012 (-0.017 to -0.008)	<0.001

LV = left ventricular, CI = confidence interval

Table 6.4: Multivariable-adjusted associations with left ventricular ejection fraction

	Univariate regressions (CI)	P	Multivariate regressions (CI)	P
Indigenous Australian	-5.915 (-8.908 to -2.923)	<0.001	-5.050 (-7.621 to -2.479)	<0.001
Age	-0.101 (-0.164 to -0.038)	0.002	-0.049 (-0.105 to 0.008)	0.09
Male	-2.166 (-3.940 to -0.039)	0.017	-2.525 (-4.015 to -1.035)	0.001
Hypertension	-3.266 (-5.436 to -1.096)	0.003	-0.675 (-2.626 to 1.276)	0.497
Ischaemic heart disease	-5.575 (-7.500 to -3.651)	<0.001	-3.324 (-5.098 to -1.550)	<0.001
Congestive heart failure	-21.225 (-23.735 to -18.715)	<0.001	-20.632 (-23.120 to -18.144)	<0.001

CI = confidence interval

Table 6.5: Multivariable-adjusted associations with length of stay

|	Ratio of means	Lower 95% CI	Upper 95% CI	P
Age	1.0088	1.0077	1.0099	<.0001
Male gender	1.0334	0.9918	1.0767	0.1173
Atrial fibrillation	1.4049	1.2733	1.5502	<.0001
Hypertension	1.0317	0.9635	1.1048	0.3709
Ischaemic heart disease	0.9891	0.9198	1.0637	0.7682
Congestive heart failure	1.3035	1.1726	1.4491	<.0001
Indigenous Australian	1.0889	0.9321	1.2720	0.2832

CI = confidence interval

Table 6.6: Multivariable-adjusted associations with number of hospitalisations

	Ratio of means	Lower 95% CI	Upper 95% CI	P
Age	1.0002	0.9999	1.0005	0.1210
Male gender	1.0503	1.0405	1.0603	< 0.0001
Atrial fibrillation				< 0.0001
New case vs. none	1.8566	1.8055	1.9092	< 0.0001
Pre-existing vs. none	0.8276	0.8077	0.8479	< 0.0001
Hypertension				< 0.0001
New case vs. none	3.2332	3.1700	3.2977	< 0.0001
Pre-existing vs. none	1.3815	1.3606	1.4028	< 0.0001
Ischaemic heart disease				< 0.0001
New case vs. none	1.8299	1.7835	1.8775	< 0.0001
Pre-existing vs. none	0.7628	0.7494	0.7764	< 0.0001
Congestive heart failure				< 0.0001
New case vs. none	2.4691	2.4009	2.5393	< 0.0001
Already present vs. none	0.9940	0.9663	1.0224	0.6751
Indigenous Australian	1.0196	0.9915	1.0484	0.1734

CI = confidence interval

Figure 6.1: Prevalence of atrial fibrillation in Indigenous and non-Indigenous Australians according to age group.
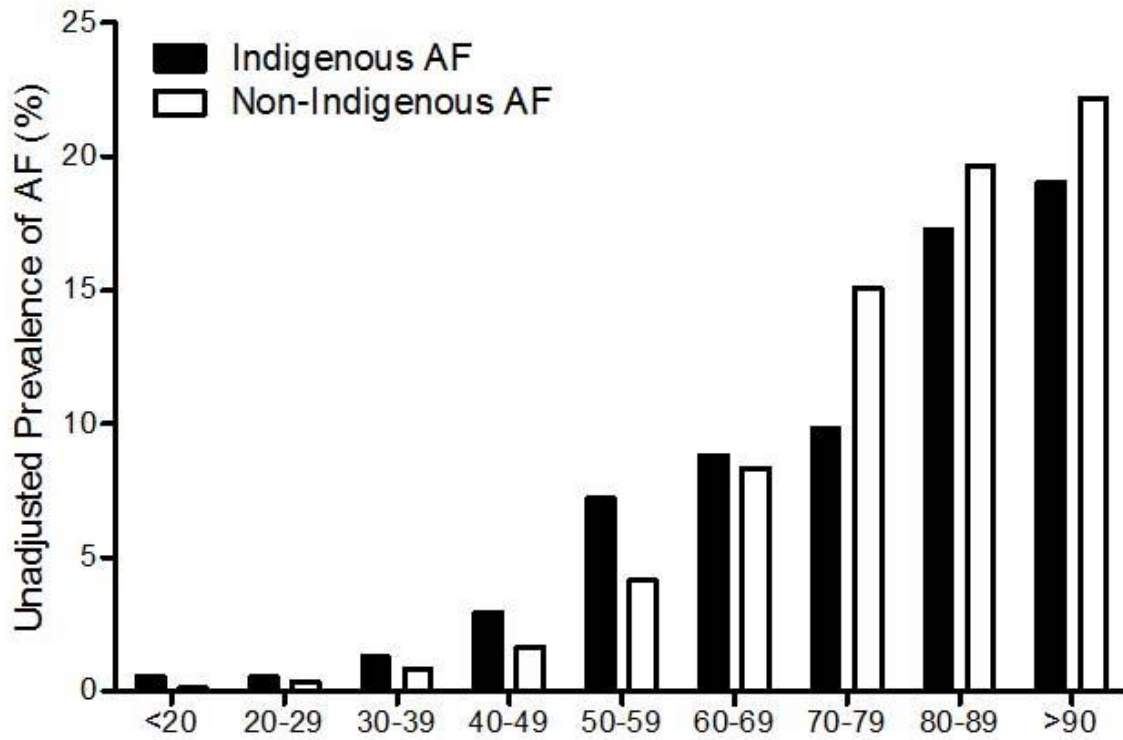
AF = atrial fibrillation

CHAPTER 7: ANTICOAGULATION FOR ATRIAL FIBRILLATION

7.1 Introduction

Indigenous Australians face a disproportionate burden of stroke.[67] Data show that the age-adjusted incidence rate of stroke in Indigenous people is approximately three-times that of other Australians.[67] National hospitalisation rates for stroke are subsequently two-times greater and associated with a reduced quality of inpatient care and outcomes.[67, 68] As a result, death attributable to stroke in Indigenous Australians is two-times greater, and up to five-times greater in younger age groups, than in non-Indigenous Australians.[68]

Atrial fibrillation causes up to one-quarter of ischaemic strokes and its prevalence is increasing as society ages.[82, 317, 318, 329] In addition to symptomatic strokes from atrial fibrillation resulting in greater disability than other causes of stroke, silent cerebral infarction is a common occurrence.[83, 110] As anticoagulation is appropriate for many individuals with atrial fibrillation, and reduces the risk of ischaemic stroke by almost 70 percent, it is critical to ensure that eligible individuals are considered for and receive anticoagulant therapy.[119] In addition, our ability to identify the small proportion of individuals with atrial fibrillation who are at very low risk of thromboembolism has also become increasingly refined.[395] In such people, the bleeding hazards from anticoagulation, particularly from intracranial haemorrhage, may outweigh any small absolute reductions in thromboembolic events. Thus, it is just as important to ensure a definite net benefit from anticoagulant therapy exists in people with atrial fibrillation and low thromboembolic risk.

We have recently described that the burden of atrial fibrillation may be greater in Indigenous Australians, raising the possibility that atrial fibrillation and associated under- and over-anticoagulation may be in-part contributing to disparate stroke-related morbidity and mortality.[396] While other comorbid risk factors associated with stroke in Indigenous Australians have been characterised, atrial fibrillation has not been previously studied.[68, 397] Given atrial fibrillation is a leading cause of preventable stroke, we sought to assess the current use of anticoagulant therapy in hospitalised Indigenous Australians with atrial fibrillation and compared this to current evidence-based guideline recommendations.

7.2 Methods

7.2.1 Study population

Indigenous and non-Indigenous Australians were identified from administrative databases at the Royal Adelaide Hospital, a tertiary referral centre and teaching hospital of the Universities of Adelaide and South Australia. Administrative, clinical and prescription data were linked and aggregated over a 14-year period from 1999 to 2012. Cases of non-valvular atrial fibrillation without other clinical indications mandating anticoagulation were identified with the *International Classification of Diseases, 10th Rev, Australian Modification (ICD-10-AM)* diagnosis code I48. The study protocol was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital, Adelaide, Australia.

7.2.2 Stroke risk assessment and antithrombotic use

Assessment of stroke risk was calculated for all patients with both the $CHADS_2$ and CHA_2DS_2VASc scores. The $CHADS_2$ score ascribes one point for heart failure, hypertension, age≥75 years and diabetes, and two points for prior stroke or transient ischaemic attack The more recent CHA_2DS_2VASc score refines the $CHADS_2$ score by ascribing one additional point for vascular disease, female gender and age between 65 and 70 years, and two points instead of one point for age≥75 years.[398] Clinical data allowing for the calculation of the aforementioned stroke risk scores were abstracted for each included individual. Antiplatelet and anticoagulant prescriptions were also identified and, where not prescribed in Indigenous

Australians, individual medical records reviewed for any possible contraindications to antithrombotic therapy.

7.2.3 Statistical analysis

Continuous variables are reported as mean ± standard deviation as appropriate. Study sample characteristics were compared using the unpaired Student t-tests or chi-square tests as appropriate. Logistic generalised estimating equation models were employed to study the appropriateness of antithrombotic therapy according to risk scores as recommended by evidence-based guidelines.[122, 126] These models were adjusted for age, gender and other comorbidities (hypertension, dyslipidaemia, diabetes, ischaemic heart disease, heart failure, valvular heart disease, cerebrovascular disease, peripheral vascular disease, obesity, chronic obstructive pulmonary disease and chronic kidney disease). Statistical analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC, USA) and a two-tailed p-value of $p < 0.05$ was considered statistically significant.

7.3 Results

7.3.1 Baseline characteristics and stroke risk

A total of 19,613 individuals with atrial fibrillation were identified; 1.6% of these were Indigenous (n=308) and 98.4% were non-Indigenous (n=19,305; Table 7.1). Indigenous Australians were significantly younger (p<0.001) and had a greater prevalence of diabetes (p<0.001) and vascular disease (p=0.028) compared to their non-Indigenous counterparts. In contrast, fewer Indigenous Australians had a history of stroke or transient ischaemic attack compared to non-Indigenous Australians (p=0.004). Mean $CHADS_2$ (1.19±0.32 vs 1.99±0.47, p<0.001) and CHA_2DS_2VASc scores (1.47±0.03 vs 2.82±0.08, p<0.001) were lower in Indigenous compared to non-Indigenous Australians. Similarly, the percentage of patients with $CHADS_2$ (39.6% vs 44.1% p<0.0001) and CHA_2DS_2VASc scores (62.9% vs 78.8%, p<0.0001) greater than or equal to 2 was lower in Indigenous compared to non-Indigenous Australians (Figures 7.1 and 7.2 respectively).

7.3.2 Antithrombotic use

Overall, 72.1% of Indigenous Australians versus 68.9% of non-Indigenous Australians with $CHADS_2$ scores ≥2 were not receiving anticoagulant therapy (Figures 7.1 and 7.2). Similar underutilisation of anticoagulation therapy was observed when stroke risk was assessed using CHA_2DS_2VASc scores; 76.3% of Indigenous Australians and 71.3% of non-Indigenous Australians with scores ≥2 were not receiving anticoagulant therapy. Despite underutilisation of anticoagulant

therapy, possible contraindications to anticoagulation were documented in a minority of Indigenous Australians, including recent procedure (6%), alcohol use (4%), prior bleeding (2%), falls (1%) and other reasons (<1%). In contrast, 27.4% of Indigenous Australians and 24.1% of non-Indigenous Australians at low risk of thromboembolism ($CHADS_2$ scores of 0) received anticoagulant therapy. Similarly, 16.7% of Indigenous Australians and 24.0% of non-Indigenous Australians with a CHA_2DS_2VASc score of 0 received anticoagulant therapy. There was significant use of antiplatelet therapy across all levels of stroke risk (Figures 7.3 and 7.4). While antithrombotic use increased with stroke risk in non-Indigenous Australians (p<0.001), there was no significant trend seen in Indigenous Australians (p=0.63). In multivariate analyses, Indigenous status was a significant predictor of either under- or over-anticoagulation in multivariate analyses according to $CHADS_2$ score (odds ratio 1.27, 95% confidence interval 1.01-1.60) and CHA_2DS_2VASc scores (odds ratio 1.60, 95% confidence interval 1.25-2.05).

7.4 Discussion

7.4.1 Major findings

The present report describes the use of anticoagulant therapy to prevent thromboembolism in Indigenous and non-Indigenous Australians with atrial fibrillation. We found that anticoagulant prescribing is frequently discordant to guideline recommendations. This reflects both underuse of anticoagulant therapy in those at high thromboembolic risk, and overuse of anticoagulant therapy in those at low thromboembolic risk. Importantly, Indigenous Australians with atrial fibrillation were more likely to receive non-guideline recommended anticoagulant therapy than their non-Indigenous counterparts, reflecting both under- and over-anticoagulation. Furthermore, there was no clear relationship between increasing thromboembolic risk and greater anticoagulant therapy use in Indigenous Australians. Given the disproportionate burden of stroke faced by Indigenous Australians, reconciling anticoagulant use with evidenced-based guidelines may thus be a useful strategy to reduce both ischaemic and haemorrhagic strokes in these individuals.

7.4.2 Atrial fibrillation and thromboembolic risk

Ischaemic stroke is the most common and serious thromboembolic complication from atrial fibrillation. Individuals with CHADS2 scores ≥2 have an annual risk of stroke ranging from 4.0% to 18.2%, and those with CHA_2DS_2VASc scores ≥2 with annual risk of stroke ranging from 2.2% to 15.25%.[122] At these moderate to high levels of thromboembolic risk, anticoagulation has definite and significant net clinical

benefit. Our data demonstrate, however, that almost three-quarters of Indigenous and non-Indigenous Australians with atrial fibrillation at such high levels of risk were not receiving anticoagulant therapy. Conversely, stroke risk scores can identify subjects who are likely to be at low risk of stroke, and in whom bleeding hazards from anticoagulation may outweigh any reductions in thromboembolism. Approximately one-quarter of non-Indigenous and Indigenous Australians with $CHADS_2$ and CHA_2DS_2VASc scores of 0 and low risk of stroke, however, were receiving anticoagulation in the present study.

Comparable discordance between real-world use of anticoagulation and guideline recommendations have been observed in other populations. In an observational study of 10,614 individuals with atrial fibrillation in 19 countries from the GARFIELD registry, 38.0% of patients with $CHADS_2$ scores ≥2 did not receive anticoagulation and 42.5% of those with scores of 0 received anticoagulation.[399] Analyses from a nationwide database from the United States also described anticoagulant use in 42.1% of atrial fibrillation patients at high risk and 40.1% in those at low risk.[400] Similarly, the Euro Heart Survey of patients from 35 countries reported that 67% of eligible patients with atrial fibrillation received anticoagulation, as did 49% of ineligible patients.[401] To the best of our knowledge, however, the use of anticoagulation for atrial fibrillation in comparison to stroke risk has not been previously described in Australia, and the present data suggest adherence to current guideline recommendations is possibly lower than that reported in other developed countries. This is an important observation as non-guideline recommended

treatment in patients with atrial fibrillation has been associated with higher

thromboembolic rates, total strokes and all-cause mortality in multiple studies.[402, 403]

7.4.3 Stroke in Indigenous Australians

Stroke is well recognised as a major contributor to Indigenous disease burden. The

determinants of disease in Indigenous Australians originate from entrenched social,

economic and educational disadvantage, necessitating comprehensive and

multifactorial approaches. From a clinical perspective, however, attempts to modify

highly prevalent behavioural risk factors (such as smoking and sedentary lifestyles)

and medical comorbidities (such as hypertension and diabetes) are worthwhile and

previously identified priorities to reduce both stroke and other vascular outcomes.[404]

The present study now highlights that atrial fibrillation and the appropriate

modification of associated stroke risk is also important, and discordance between

guideline directed therapy and practice may be contributing to entrenched

cardiovascular inequalities for Indigenous Australians. We observed that

anticoagulation therapy use did not correlate with the risk of stroke in Indigenous

Australians with atrial fibrillation, and in multivariate analyses Indigenous Australians

were less likely to receive guideline-recommended therapy. This was in contrast to

non-Indigenous Australians in whom anticoagulation use, while also suboptimal, was

progressively used more commonly with increasing atrial fibrillation stroke risk. Our

data suggests that improving atrial fibrillation anticoagulation management may

reduce the disproportionate incidence and burden of stroke in Indigenous

Australians. As atrial fibrillation-related strokes cause greater disability than other

strokes, a focus on better management for established stroke is also warranted (such as with early antithrombotic use, thrombolysis where eligible, physical rehabilitation and coordinated stroke unit) given previously described disparities in stroke-care.[397] Addressing atrial fibrillation in Australia may also be particularly timely given recent developments in and improvements in our understanding of atrial fibrillation management. Stroke risk prediction has become increasingly refined with the advent of the CHA_2DS_2VASc score, which has better discriminative ability for those at intermediate risk of stroke and subsequent recommendations for anticoagulation therapy.[398] There is also increasing recognition that antiplatelet therapy is inferior to anticoagulation.[126] Use of the CHA_2DS_2VASc score has now reclassified many individuals for whom aspirin was an option based on $CHADS_2$ scores between 0-1 into categories where anticoagulation should be considered. For truly low risk individuals, recommendations for aspirin have also become more circumspect; European guidelines suggesting it only if patients refuse anticoagulation and American guidelines suggesting it as an alternative to either no antithrombotic or anticoagulation in those with CHA_2DS_2VASc score of 1. Finally, there are now also novel anticoagulants which have significant advantages over Vitamin K antagonists, particularly with regard to consistently observed reductions in intracranial haemorrhage, which may present more favourable risk-benefit balance for those especially at lower risk.[129]

7.4.4 Possible reasons for non-guideline recommended anticoagulation

There are multiple possible reasons for the discrepancies between anticoagulation prescribing and guideline recommendations observed. The individuals studied were managed over a period of time in which there has been considerable evolution of stroke risk prediction, subsequent antithrombotic recommendations and availability of new anticoagulants, the latter of which became available after the study period of this paper. Comparable rates of underuse and overuse of anticoagulation were still observed in the second half of the study period, however, and other reports have also observed similar discrepancies in contemporary time periods.[399] Another reason may be a lack of knowledge by clinicians about guidelines, though this may improve over time as new recommendations become more widely known.[405] Clinicians may be also placing greater emphasis on avoiding bleeding risks, potentially overestimating these hazards in contrast to the benefits of stroke risk reduction.[405] This overestimation and other biases against anticoagulation may also originate from patients themselves, leading to prescription reluctance or discontinuation even if anticoagulation is started. The role of these and other factors reported elsewhere should be explored in Australian cohorts in the future to clarify why non-guideline recommended therapy is common, particularly in Indigenous Australians, and how anticoagulation practices can be targeted for improvement.

7.4.5 Limitations

A number of study limitations warrant consideration. The changing landscape of stroke risk scores and guideline recommendations is discussed above. Anticoagulant use can nevertheless be compared with past recommendations, however, and is still suboptimal by these and revised recommendations. The single centre nature of this study limits the generalisability of our findings to the broader Australian population. Previous data suggest that referral centre management is a predictor of guideline adherence, however, and thus underuse and overuse of anticoagulation for atrial fibrillation may be comparable (or worse) in other settings. Finally, stroke risk scores have not been studied specifically in Indigenous Australian populations who have different age and risk-factor profiles compared to non-Indigenous Australians. However, it is likely that scores would underestimate, rather than overestimate, true stroke risk in Indigenous Australians and allowance for this would, if anything, increase the magnitude of under-anticoagulation.

7.5 Conclusion

Anticoagulation is frequently not prescribed in accordance with guideline recommendations. Underuse of anticoagulation in those at high risk of stroke, and overuse in those at low risk, is common and more likely in Indigenous Australians. These results highlight an opportunity to prevent a significant number of ischaemic and haemorrhagic strokes in both Indigenous and non-Indigenous Australians.

Table 7.1: Baseline characteristics in Indigenous and non-Indigenous Australians

	Non-Indigenous Australians (n=19,305)	Indigenous Australians (n=308)	P
Age group, n (%)			
< 65 years	3,924 (20.3)	242 (78.6)	
65-74 years	4,761 (24.7)	53 (17.2)	<0.001
≥ 75 years	10,620 (55.0)	13 (4.2)	
Gender, % (n)			
Male	10,497 (54.5)	170 (55.2)	
Female	8,808 (45.6)	138 (44.8)	0.77
Comorbidities, n (%)			
Hypertension	7,086 (36.7)	127 (41.2)	0.10
Diabetes	3,353 (17.4)	130 (42.2)	<0.001
Heart Failure	4,593 (23.8)	80 (26.0)	0.37
Vascular Disease	2,013 (10.4)	44 (14.3)	0.028
Stroke/TIA	1,304 (6.8)	8 (2.6)	0.004
Risk scores, mean ± SD			
$CHADS_2$	1.99±0.47	1.19±0.32	<0.001
CHA_2DS_2VASc	2.82±0.08	1.47±0.03	<0.001

SD = standard deviation, TIA = transient ischaemic attack.

Figure 7.1: Distribution of CHADS$_2$ scores in Indigenous and non-Indigenous Australians
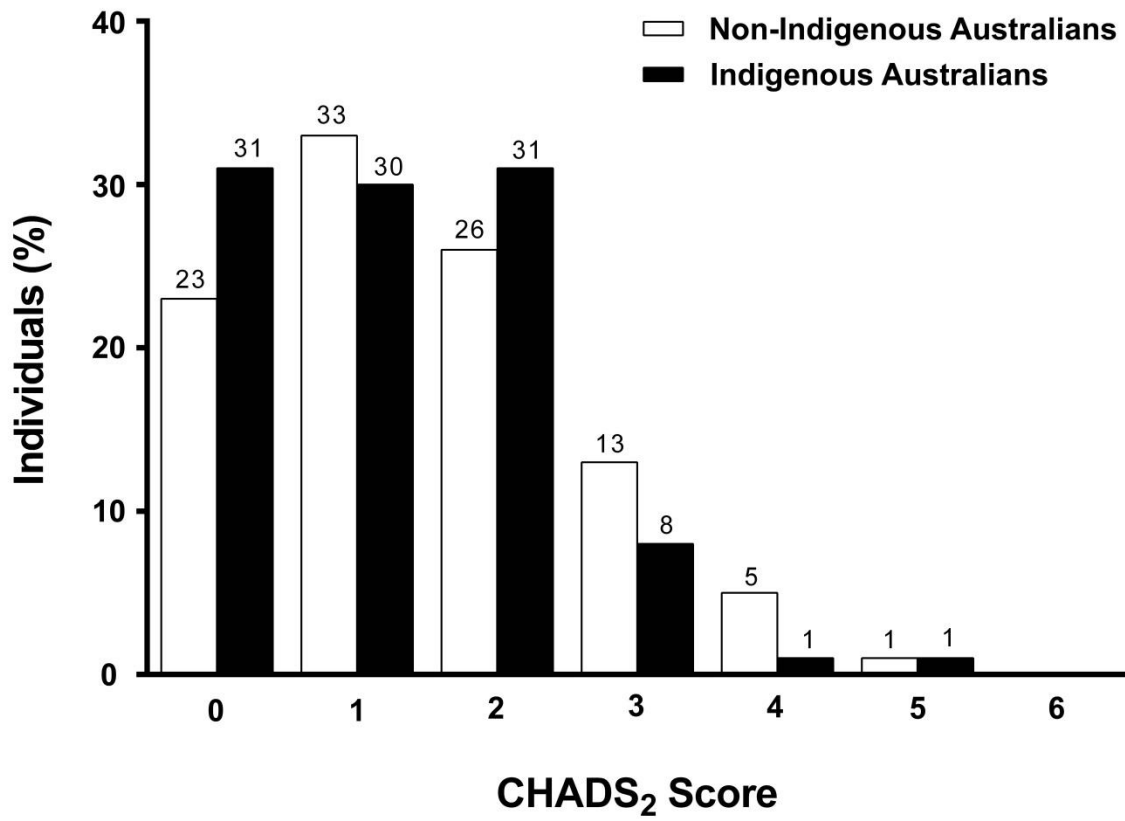
Figure 7.2: Distribution of CHA$_2$DS$_2$VASc scores in Indigenous and non-Indigenous Australians
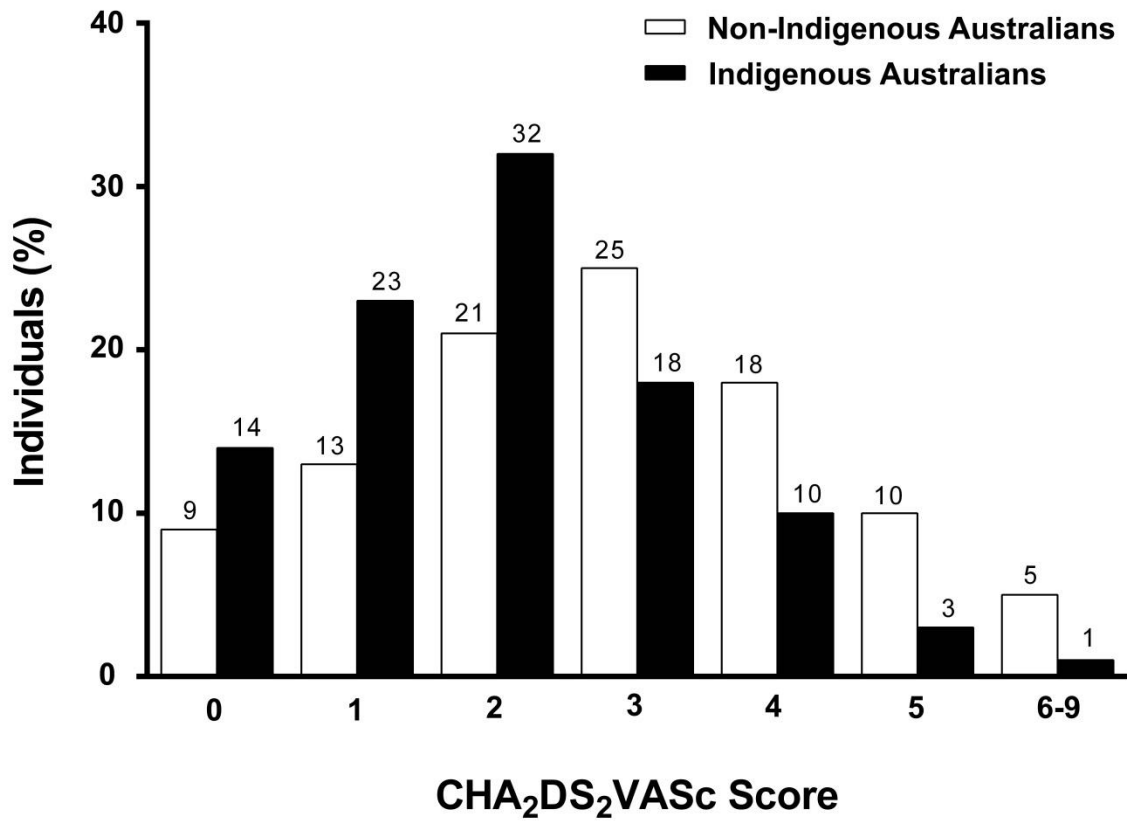
Figure 7.3: Antithrombotic use in non-Indigenous and Indigenous Australians according to CHADS$_2$ scores
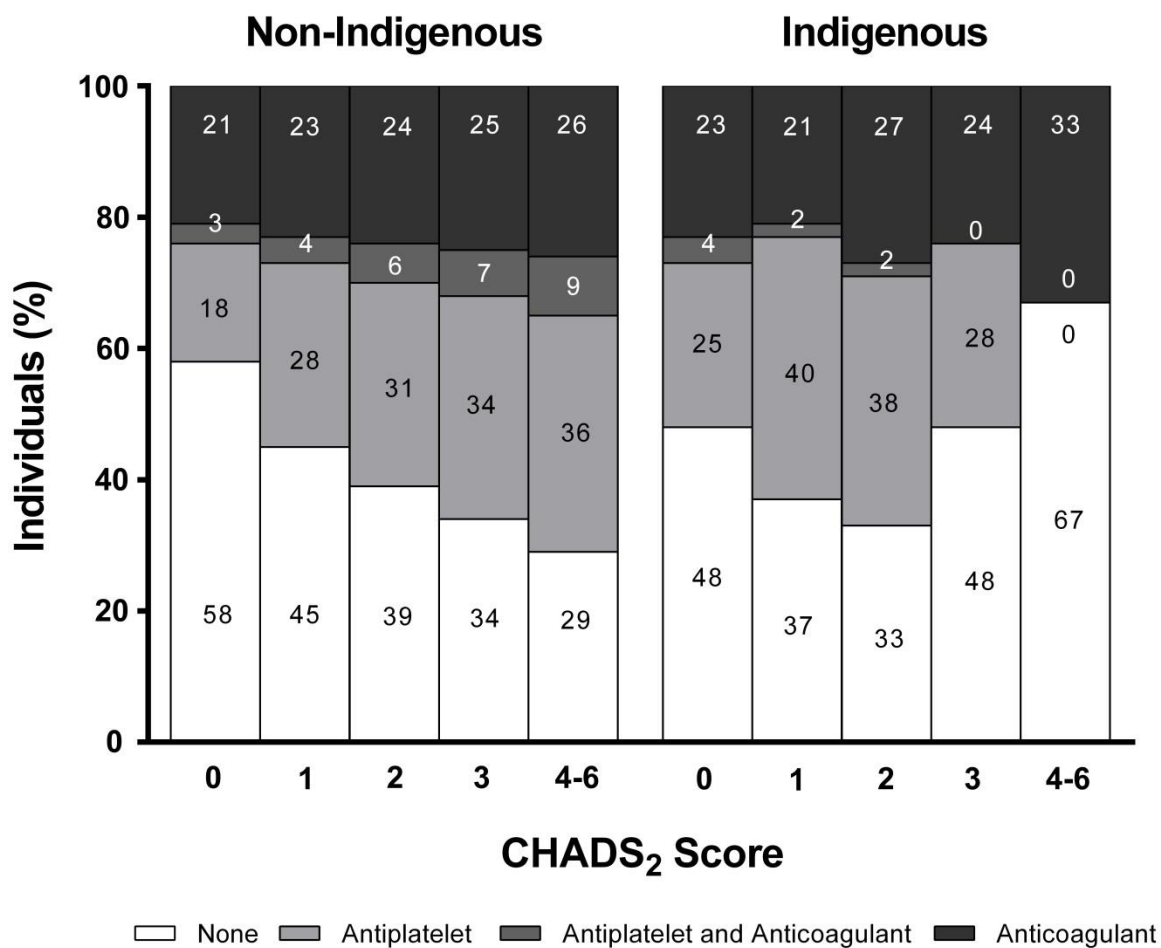
Figure 7.4: Antithrombotic use in non-Indigenous and Indigenous Australians according to CHA$_2$DS$_2$VASc scores
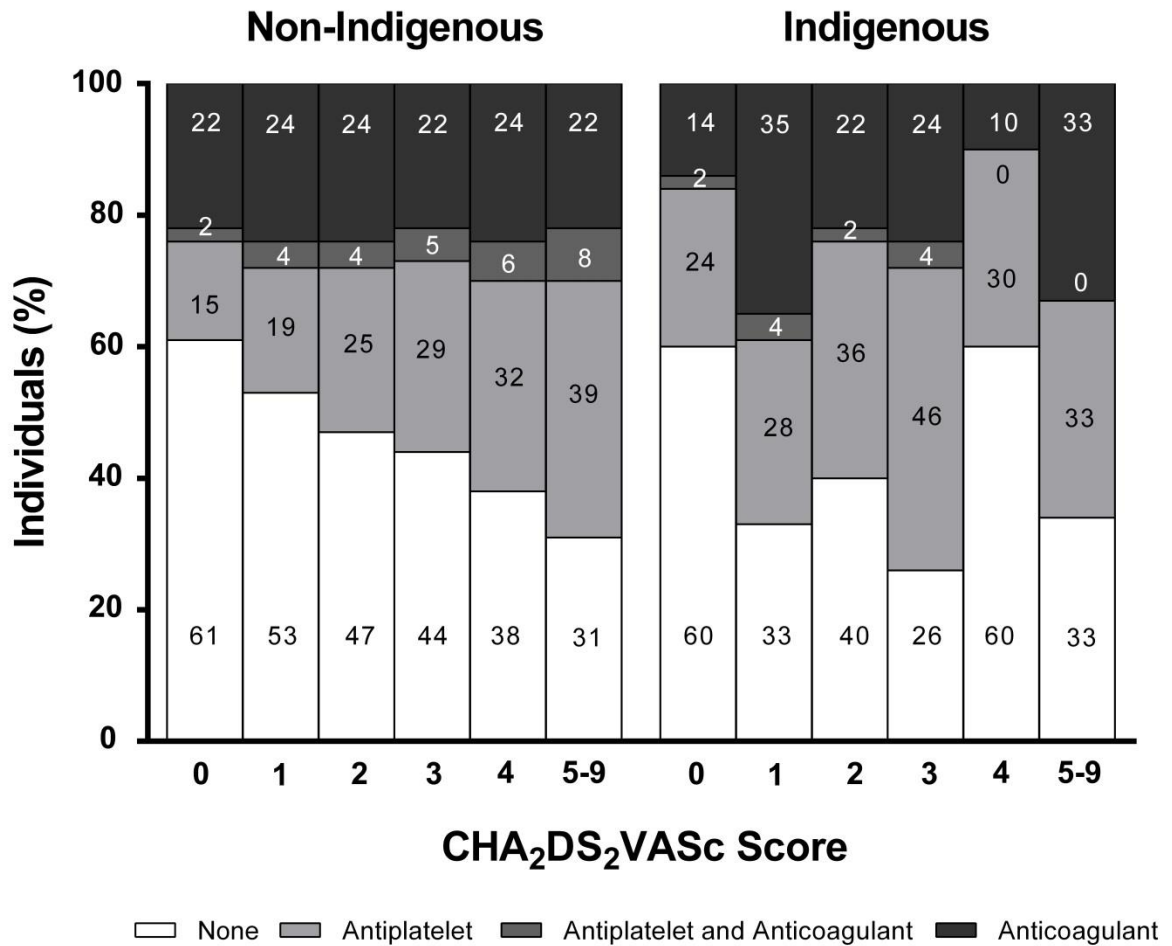
CHAPTER 8: FINAL DISCUSSION

This thesis has examined aspects related to the epidemiology, pathogenesis and management of atrial fibrillation, the most common arrhythmia encountered in clinical practice. It has provided new information on the increasing population burden of atrial fibrillation, factors contributing to these rising trends, pathogenic mechanisms underlying these factors, and areas where the management of atrial fibrillation can be improved. These observations provide further insight into how atrial fibrillation is afflicting affected patients and the wider society, and how we may potentially reduce its impact.

The incidence and prevalence of atrial fibrillation has been described to be increasing in recent years. As a result, the economic and societal burden of atrial fibrillation is growing considerably, and this is driven primarily by hospitalisations. A detailed understanding of trends in atrial fibrillation hospitalisations is therefore crucial to facilitate healthcare planning and to devise strategies to reduce demands on healthcare systems.

In Chapter 2, we characterise trends in hospitalisations for atrial fibrillation across the entirety of Australia. Observations from thus study include the fact that rising hospitalisation trends seen overseas are indeed also occurring in Australia and that in recent years they are continuing to grow. Chapter 3 analyses factors potentially contributing to these rising trends. The ageing populations in Australia and other countries are undoubtedly contributing, but the present data suggest that the age-specific rate is also increasing, and this was most prominent in the elderly age

groups. Other investigators have suggested that changing physician practices and procedures, such as direct current cardioversion and catheter ablation, may be contributing to hospitalisation trends. In contrast, we found little evidence that these procedures are contributing significantly to increasing hospitalisation rates. To put these trends into context, we also compared hospitalisations for atrial fibrillation to two other cardiovascular conditions, myocardial infarction and heart failure, in Chapters 2 and 3. We found that hospitalisations for atrial fibrillation have surpassed those for heart failure and are approaching that for myocardial infarction, further evidencing the public health burden of this condition. Given the paucity of data on myocardial infarction trends outside North America and Europe, we also characterised these hospitalisations in greater detail. While STEMIs decreased over the study period, the incidence of non-STEMIs increased. Overall myocardial infarction incidence increased over the study period in contrast to that observed in other parts of the world. This increase was seen most in those less than 50 years of age and over 80 years of age.

A rising incidence of atrial fibrillation and myocardial infarction are likely to be in-part due to the increasing prevalence of cardiovascular risk factors. The exact contribution of specific risk factors, however, is important to characterise so that the potential effect of interventions can be estimated. Chapter 4 provides analyses overviewing the totality of evidence on the relationship between obesity and the risk of incident, post-operative and post-ablation atrial fibrillation. Data presented suggest that even incremental increases in body mass index are associated with excess risk of atrial fibrillation in these circumstances, suggesting that even

moderate reductions in obesity may have significant effects. The mechanisms by which obesity facilitates the development of atrial fibrillation, however, remains uncertain. Pericardial fat is emerging as a potentially pathogenic factor in atrial arrhythmogenesis. Chapter 5 examines the relationship measures of pericardial fat have to left atrial structure, function and atrial fibrillation, providing further insight into the pathogenic role of pericardial fat.

Finally, in Chapters 6 and 7, the prevalence and management of atrial fibrillation is studied in Indigenous Australians. Despite the disproportionate morbidity and mortality experienced by Indigenous Australians, atrial fibrillation has not been previously explored in this population. Analyses suggested that atrial fibrillation was more prevalent in Indigenous Australians, and that this difference might be attributable to differences in age, comorbidities and cardiac structure and function. Furthermore, both non-Indigenous and Indigenous Australians frequently were not managed in accordance with guideline recommendations for anticoagulation. This was more likely to occur in Indigenous Australians, however, and thus may be contributing to their greater stroke burden.

CHAPTER 9: FUTURE DIRECTIONS

Improving our understanding of the epidemiology, pathogenesis and management of atrial fibrillation is crucial in our effort to reduce the burden of this common arrhythmia. The knowledge that hospitalisations for atrial fibrillation are increasing in Australia, for example, provide a strong impetus to develop specific strategies to reduce this healthcare utilisation. This is particularly needed given the rising cost of healthcare in Australia, an ageing population, and the fact that hospitalisations are the major contributor to the economic cost of atrial fibrillation.

In similar vein, more attention must be directed at the prevention of atrial fibrillation. The increasing prevalence of risk factors for atrial fibrillation thus also requires intervention. Obesity is a major and increasingly influential risk factor for atrial fibrillation. Even moderate reductions in population body mass indices would have beneficial effects on atrial fibrillation and overall health. Further studies into how obesity predisposes to arrhythmogenesis may also provide greater mechanistic insight and the potential for future therapies.

Finally, Indigenous Australians continue to experience a significantly worse disease burden and life expectancy compared to non-Indigenous Australians. Given the suggestion that this population may have more prevalent atrial fibrillation and disparities in related quality of care, further studies are required to confirm whether these observations extend to other Indigenous healthcare settings in Australia before action is taken to address these healthcare inequalities.

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"Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning."

Winston S. Churchill