Sleep-Disordered Breathing and Atrial Fibrillation: Prevalence, Detection and Mechanistic Insights

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

Doctor of Philosophy

May 2022

To my parents Imad and Fariqa,
my wife Shams,
and my children Zeena and Faris

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Abstract

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, and its incidence, prevalence, and health- and economic-costs are expected to proliferate in the coming decades. Sleep-disordered breathing (SDB) is increasingly recognised as an important modifiable risk factor that increases AF risk and negatively affects treatment outcomes. However, our understanding of the epidemiology of SDB within AF, which AF patients are at increased SDB risk, or how SDB mediates that risk remains incomplete. This thesis focused on addressing these knowledge gaps.

Chapter 2 examined the utility of self-reported symptoms of daytime sleepiness for identification of AF patients with concomitant SDB. The principal finding was that most AF patients do not experience excessive daytime sleepiness, regardless of the presence or severity of SDB. This questions the current clinical practice of assessment of SDB symptoms prior to consideration of a sleep study.

Chapter 3 is a systematic review and meta-analysis of the literature aiming to quantify the prevalence of SDB in the AF population, which was found to be high. The study also reviewed the various methods with which SDB is assessed in the literature and demonstrated the need for a standardised approach in testing and reporting of SDB in AF research.

Chapter 4 aims to assess the feasibility of simplifying SDB testing in the AF population. The study found that an oxygen-desaturation index, a metric derived from simple overnight oximetry, had a good diagnostic yield comparable to that of a full overnight sleep study in identifying patients with clinically-relevant SDB. The simplified test would allow for wider availability of SDB testing and therefore

potentially improve access to diagnosis and management of SDB in the AF population.

Chapter 5 studied ways to improve the patient-selection process for SDB testing by deriving and validating a clinical risk score for AF patients most likely to benefit from treatment of SDB with positive airway pressure. This study utilised two separate observational cohorts and identified multiple characteristics that can readily be ascertained in a clinical setting to help prioritise testing for SDB. Subsequently, a simplified score comprising Male gender, Overweight or Obesity, and history of Diabetes or Stroke (MOODS) was found to have a good discrimination ability to identify AF patients most likely to benefit from SDB testing.

The main metric for SDB assessment, the apnoea-hypopnea index (AHI), does not consider a number of important physiological processes that accompany the respiratory events associated with SDB, such as overnight oxygenation, hypoxaemic burden, or the amplitude, nadir, and duration of respiratory events. **Chapter 6** examined these metrics in a cohort of AF patients and assessed their correlation atrial remodelling and the prevalence of persistent AF as an indicator of disease progression. The main finding was that the duration of respiratory events independently predicted atrial dilatation, and that patients with longer events had a higher prevalence of persistent AF.

Finally, the thesis touches on future avenues of exploration to establish the role of SDB treatment in AF-related outcomes and to address outstanding challenges in the field of concomitant SDB and AF.

Declaration

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

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Kadhim Imad Kadhim

March 2022

Acknowledgements

I am eternally grateful to Professor Prash Sanders for the opportunity to undertake this PhD under his supervision, and for the mentorship, support, and friendship throughout the years. I have been continuously humbled by his kindness, enthusiasm, and dedication to science and to improving patient care. I would also like to thank my co-supervisors Prof Dominik Linz and A/Prof Dennis H Lau for their guidance and continuous support. Working alongside Prof Dominik Linz, brainstorming ideas and debating hypotheses and research findings were amongst the most enjoyable highlights of my doctoral training. I am very privileged to have joined such a world-leading research group and I aspire to always maintain the scientific curiosity instilled in me by my supervisors. I am indebted to the University of Adelaide and to The Hospital Research Foundation for the scholarships received during my candidature, without which this research would not have been possible.

I am grateful to all the members of the Centre for Heart Rhythm Disorders research group, particularly Dr Adrian Elliott, Dr Melissa Middeldorp, Dr Celine Gallagher and Professor Jeroen Hendriks for their help and encouragement throughout my research training. Multiple parts of this thesis would not have been possible without fruitful collaboration with esteemed and generous researchers whom I must acknowledge. I am grateful to Professor Doug McEvoy from the Adelaide Institute for Sleep Health, whose vast experience as a sleep physician has been invaluable. I am also grateful to Professor Jonathan Kalman from the University of Melbourne, a giant of the field of cardiac electrophysiology and a true role model, for his assistance with providing the validation cohort for Chapter 5 and his guidance throughout my candidature. I am also grateful to A/Prof Mathias Baumert from the School of

Electrical and Electronic Engineering at the University of Adelaide, whose specialist support with MATLAB® signal processing was integral to three of this thesis chapters.

My clinical cardiac electrophysiology fellowship at the Royal Adelaide Hospital was formative and educational, and I would like to thank A/Prof Glenn Young and A/Prof Kurt Roberts-Thomson for their training and mentorship. I am fortunate to have worked within such a hard-working and collaborative group of fellows-in-training comprising Drs Kashif Khokhar, Andien Munawar, Anand Thiyagarajah, Mehrdad Emami, Ricardo Mishima, Varun Malik, Catherine O'Shea, Chris Wong, Jonathan Ariyaratnman and John Fitzgerald; I thank them all for their support during my candidature and for contributing to a driven and productive research environment.

In the UK, I would like to thank Dr Darragh Twomey for his help and encouragement to undertake this fellowship. I would also like to thank Dr Chris Plummer who supported me to undertake my fellowship, and whose guidance and help allowed me to finalise this thesis.

On a personal note, I would like to thank my parents Imad and Fariqa, for their faith in me and their unwavering love and support. I would also like to thank my siblings Besma, Ula, Sana and Ahmed for all their love and encouragement. Finally, this thesis would simply not have been possible without the boundless patience and love from my wife, Shams, who also gave birth to our own little Adelaideans during the fellowship, Zeena and Faris. I cannot thank her enough for the personal and professional sacrifices she has made to allow me to undertake this fellowship. I am truly blessed to have my family by my side, they are my rock and my motivation. This is for them.

Publications and Communications to Learned Societies

Chapter 2:

- **Manuscript:** Kadhim K, Middeldorp ME, Elliott AD, Jones D, Hendriks JML, Gallagher C, Arzt M, McEvoy RD, Antic NA, Mahajan R, Lau DH, Nalliah C, Kalman JM, Sanders P, Linz D. Self-Reported Daytime Sleepiness and Sleep-Disordered Breathing in Patients With Atrial Fibrillation: SNOozE-AF. Can J Cardiol. 2019 Nov;35(11):1457-1464. doi: 10.1016/j.cjca.2019.07.627. Epub 2019 Aug 1. PMID: 31604670.
- **Presentation:** Poster presentation at the Annual Heart Rhythm Scientific Sessions, May 2018, Boston, USA. Published in abstract form (Heart Rhythm, Volume 15, Issue 5, May 2018, S388 - S487).
- **Presentation:** Nimmo Prize, Finalist. Royal Adelaide Hospital Research, Adelaide Australia, 2018**.**
- **Presentation:** Poster presentation at the Annual Congress of the European Heart Rhythm Association (EHRA), March 2019, Lisboa, Portugal. Published in abstract form (EP Europace, Volume 21, Issue Supplement 2, March 2019, Pages ii251–ii531).
- **Presentation:** Poster presentation at the 12th Asia Pacific Heart Rhythm Society Scientific Session (APHRS 2019), Bangkok, Thailand. Published in abstract form ((2019), Atrial Fibrillation. J Arrhythmia, 35: 76-327. https://doi.org/10.1002/joa3.12267).

Chapter 3:

- **Manuscript:** Kadhim K, Middeldorp ME, Elliott AD, Agbaedeng T, Gallagher C, Malik V, Wong CX, McEvoy RD, Kalman JM, Lau DH, Linz D, Sanders P. Prevalence and Assessment of Sleep-Disordered Breathing in Patients With Atrial Fibrillation: A Systematic Review and Meta-analysis. Can J Cardiol. 2021 Nov;37(11):1846-1856. doi: 10.1016/j.cjca.2021.09.026. Epub 2021 Oct 1. PMID: 34606918.

Chapter 4:

- **Manuscript:** Linz D*, Kadhim K*, Brooks AG, Elliott AD, Hendriks JML, Lau DH, Mahajan R, Gupta AK, Middeldorp ME, Hohl M, Nalliah CJ, Kalman JM, McEvoy RD, Baumert M, Sanders P. Diagnostic accuracy of overnight oximetry for the diagnosis of sleep-disordered breathing in atrial fibrillation patients. Int J Cardiol. 2018 Dec 1;272:155-161. doi: 10.1016/j.ijcard.2018.07.124. Epub 2018 Jul 25. PMID: 30057161 (* shared first authorship).
- **Presentation:** Poster presentation at the Annual Congress of the European Heart Rhythm Association, March 2019, Lisboa, Portugal. Published in abstract form (EP Europace, Volume 21, Issue Supplement 2, March 2019, Pages ii251–ii531).

Chapter 5:

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- **Presentation:** Poster presentation at the Annual Congress of the European Heart Rhythm Association, March 2019, Lisboa, Portugal. Published in abstract form (EP Europace, Volume 21, Issue Supplement 2, March 2019, Pages ii251–ii531).
- **Presentation:** Poster presentation at the European Society of Cardiology Congress 2019, Paris, France. Published in abstract form (European Heart Journal, Volume 40, Issue Supplement_1, October 2019).
- **Presentation:** Young Investigator Award, Finalist. 12th Asia Pacific Heart Rhythm Society Scientific Session (APHRS 2019), Bangkok, Thailand. Published in abstract form ((2019), Atrial Fibrillation. J Arrhythmia, 35: 76-327. https://doi.org/10.1002/joa3.12267).

Chapter 6:

- **Manuscript:** Kadhim K, Baumert M, Nalliah CJ, Elliott AD, Middeldorp ME, McEvoy RD, Antic NA, Ariyarathnam J, Lau DH, Kalman JM, Linz D, Sanders P. Nocturnal Respiratory Events in Atrial Fibrillation Patients: Role of Event Duration in Atrial Remodelling and Disease Progression. **In review**.
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Other Awards During Candidature

- The Leo J Mahar Electrophysiology Scholarship
- The Hospital Research Foundation Scholarship

Other Publications During Candidature

1. **Kadhim K**, Lau DH, Linz D, Sanders P. Improved survival and reduced stroke risk in patients with atrial fibrillation: Is catheter ablation winning the rhythm-control race? Int J Cardiol. 2018 Sep 1;266:153-154. doi:10.1016/j.ijcard.2018.04.105. PMID: 29887435.

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Abbreviations

AF	Atrial fibrillation
AFSS	Atrial fibrillation severity scale
AHI	Apnoea-hypopnea index
BMI	Body mass index
(C)PAP	(Continuous) positive airway pressure
CSA	Central sleep apnoea
ECG	Electrocardiogram
EDS	Excessive daytime sleepiness
ESS	Epworth sleepiness scale
LA	Left atrium
LV	Left ventricle
ODI	Oxygen desaturation index
OSA	Obstructive sleep apnoea
PSG	Polysomnography
SDB	Sleep-disordered breathing

Chapter 1: Literature Review

1.1 Atrial Fibrillation - Introduction and Epidemiology

Atrial fibrillation (AF) is the most common cardiac arrhythmia in adults. The most recent report from the Global Burden of Disease Study in 2017 estimates that over 37.5 million people affected with AF globally[1, 2]. AF is characterised by uncoordinated atrial activity resulting in irregular, and often rapid ventricular contractions[3]. This can lead to multiple symptoms including palpitations, chest pain, lethargy and breathlessness along with significant impairment in quality of life[4, 5]. Importantly, AF is associated with increased morbidity and mortality, with some studies suggesting up to a 4-fold increase in mortality risk conferred by the development of AF[2, 6-8].

Stroke is one of the main feared consequences of AF, and AF-related strokes tend to be more severe, recurrent and associated with worse prognosis[9-13]. Additionally, AF is associated with increased risk of heart failure[14, 15], myocardial infarction[16] and cognitive decline or dementia[17] independent of stroke[18]. The burden of AF hospitalisations has been steadily increasing, and now exceeds both heart failure- and myocardial infarction-related hospitalisations in Australia[19]. Globally, AF poses a public health challenge, and is ever more recognised as an emerging epidemic that requires significant healthcare resource allocation[2, 20, 21].

It is estimated that 1-4%[22-24] of the general population are affected with AF, with the prevalence increasing with age from <1% in the younger than 55 years to 9% in those 80 years of age or older[24, 25]. Longitudinal data from population-based observational studies show a trend of increasing AF risk over time. The Rotterdam

Study in 2006 estimated the lifetime risk of AF development at 23.8% and 22.2% for men and women respectively[26]. Findings from the Framingham Heart Study in 2004 indicated a lifetime risk of 1 in 4 for developing AF for men and women aged ≥ 40 years[27]. However, more recent reports from the same study described a lifetime risk of 37%[28]. Further, in 2018. the Atherosclerosis Risk in Communities (ARIC) cohort reported an estimated risk of AF of 1 in 3 among whites (and 1 in 5 among African Americans)[29]. Subsequently, AF prevalence in the United States is projected to increase from 5.2 million in 2010 to 12.1-15.9 million cases in 2030[30, 31]. In Europe, the estimated number of adults aged ≥ 55 years with AF is expected to double from 8.8 million in 2010 to 17.9 million in 2060[32].

The increasing AF prevalence may be attributable in part to ageing populations[30, 31] and enhanced detection[33]. However, the trends of AF increase mirror those of its risk factors, such as hypertension and obesity[34, 35]. Since the recognition that 'pulsus irregularis perpetuus' was due to 'auricular fibrillation' over 100 years ago[36], there have been major strides made in our understanding of AF, its pathophysiology and treatment options resulting in improving outcomes[33, 37]. However, there remains much to be elucidated particularly in terms of the role the 'novel' modifiable risk factors such as sleep-disordered breathing, which is the focus of this thesis[38, 39].

1.2 Pathophysiology of Atrial Fibrillation

Numerous, highly complex processes underpin the pathophysiological mechanisms behind AF initiation and maintenance[40]. Conceptually, AF is believed to be the result of a trigger that initiates the arrhythmia, and a substrate that allows the arrhythmia to perpetuate and sustain[41]. Prior to exploring the theories behind AF initiation and maintenance, several key electrophysiological concepts are reviewed.

1.2.1 Electrophysiological Concepts of Arrhythmia

1.2.1.1 Abnormal Impulse Formation

Abnormal impulse formation (i.e. focal activity) can be due to either automaticity or triggered activity[42].

1.2.1.1.i Automaticity

Refers to the property of the cardiomyocytes to spontaneously generate their own electrical impulse[43, 44]. The sinoatrial (SA) node is a prime example for automaticity and was first described in 1907 by Keith and his medical student Flack[45]. During diastole, whereas in the atrial muscle there is a stable resting potential, in the sinus node there is a slow, progressive reduction in the resting membrane potential after a cell has reached its maximal diastolic potential. Once the threshold potential is reached, a new action potential is generated[43, 46]. This unique property is also found in the accessory atrial pacemaker cells, atrioventricular node, and His-Purkinje system. The further away cells are located from the sinus node, the slower their intrinsic rate is, and are kept ‘dormant’ by the wavefront initiated by the dominant pacemaker[43, 47].

1.2.1.1.ii Triggered activity

Refers to impulse formation within the cardiomyocytes that is dependent on afterdepolarisation[48]. Afterdepolarisations are abnormal oscillations in cardiomyocyte membrane potential that follow the action potential. When these oscillations reach the threshold for generating another action potential, a new, 'triggered' action potential is initiated. Afterdepolarisations can occur either late after the complete repolarisation of cell membrane, hence 'delayed' afterdepolarisations (DADs), or interrupt the repolarisation in its 'early' stages, thus dubbed early afterdepolarisations (EADs)[48, 49]. Afterdepolarisations, particularly the delayed type, are believed to give rise to ectopic atrial foci which can play an important role in AF initiation and maintenance[50, 51].

1.2.1.2 Abnormal Impulse Conduction

Conduction abnormalities are integral to the AF substrate[52], and allow the initiation and maintenance of AF by promoting reentry[53]. Reentry is defined as a self-sustaining activation wavefront, propagating around an anatomic or functional obstacle or core, traveling in a closed loop, and returning to its site of origin to reactivate that site[54].

1.2.1.2.i Circus movement reentry

First described by Mayer in 1906 on jellyfish tissue[55], it was in 1913 that reentry was first conceived as a mechanism for cardiac arrhythmias by Mines[56]. He described reentry around an obstacle as a mechanism of arrhythmia in rings of dog cardiac tissue. This type of reentry requires a fixed anatomic obstacle, and is referred to as *anatomic reentry* or *circus movement reentry*, a concept with far-reaching theoretical

and clinical implications[57]. A prerequisite for circus movement reentry is recovery of excitability after the previous activation before the next activation reaches the tissue again. As a consequence of this, a short refractory period and a slow conduction velocity make circus movement reentry more likely[40]. The gap between the tail of refractoriness of the last tachycardia impulse and the time of arrival of the next tachycardia impulse allows that particular part of tissue to propagate an electrical impulse, and is known as the “excitable gap”[58].

1.2.1.2.ii Leading circle concept

Allessie and colleagues published a series of seminal papers in the 1970s that demonstrated the concept of *functional reentry* using isolated preparations of rabbit left atria by applying properly timed premature extra-stimuli. They illustrated that reentry does not necessarily require an anatomical obstacle, but can utilise a functionally-determined region of unexcitable tissue or a refractory core among neighbouring fibres with different electrophysiologic properties[40, 59-61]. That core of tissue inside the leading circle is deemed to receive a centripetal excitation wavefront, which renders it refractory[62]. This form of functional reentry is known as the *leading circle concept*, where the ‘head of the circulating wavefront is continuously biting its tail of refractoriness’, allowing for no excitable gap[61].

1.2.1.2.iii Rotational reentry

Is a form of functional reentry in which concentric circular waves result in reverberators or rotating vortices of electrical activity (rotors) around a central core[63, 64]. A major difference between rotors and leading circles is that in rotors, the curved wavefront meets its tail in a single point, called *phase singularity*, which is not excited, but is excitable[65]. The resultant 2-dimensional wavefront from a rotor

activation is called a “spiral wave”, while the 3-dimensional representation of a spiral wave is termed a “scroll wave”, and its centre of rotation is a hollow filament formed by the revolving trajectory of the spiral tip.

1.2.2 Electrophysiological Mechanisms of Atrial Fibrillation

Multiple theories have been proposed to try and explain the electrical activity in AF which utilise the electrophysiological concepts reviewed above of abnormal impulse formation, abnormal impulse conduction, or a combination of the two[41, 42, 66].

1.2.2.1 Multiple wavelets theory

In the late 1950s, Gordon Moe, dissatisfied with the prevailing theories of AF at the time which comprised circus movement and ectopic foci, postulated that it is ‘unrealistic to propose that only one of these mechanisms can exist in patients’. Using canine hearts, he demonstrated that AF can sustain itself beyond an initial trigger, and that a ‘rapidly circulating circus movement’ can cause irregular atrial activation[67]. Further computer models of AF by Moe and colleagues demonstrated that reentry wavelets meander through an excitable medium in a seemingly chaotic pattern[68]. The fibrillatory wavefront was seen to continuously undergo complex interaction resulting in generation of new wavefronts. Conversely, some interaction resulted in collision, block and fusion with reduction in total wavelet numbers. As long as the number of wavefronts remained above a critical level, the arrhythmia self-sustained[69]. Slowed conduction, heterogenous refractoriness, shortening of refractory periods, and increased tissue mass are factors that favour stability of fibrillation[40, 67, 69].

Experimental support to the above was provided by Allessie and colleagues, who, using in-vitro canine atrial model, revealed that 4–6 simultaneously circulating, random, wandering wavelets were necessary to sustain AF[70]. Subsequently, the surgical maze procedure was the primary non-pharmacological treatment of AF in that era. The goal was to establish anatomical and electrical barriers in the atria using incisions, creating a controlled path or 'maze' for the atrial signal to conduct to the ventricles. By reducing the atrial mass available for depolarisation, the number of wavelets that can be sustained is minimized, thus preventing the perpetuation of AF[71, 72].

1.2.2.2 Focal ectopic activity – pulmonary veins

The understanding of AF pathophysiology and its non-pharmacological treatment were transformed by the pivotal work by Haïssaguerre and colleagues in 1998, in which AF was demonstrated to frequently arise from foci of ectopic beats located in the pulmonary veins (PVs), with radio-frequency ablation of these foci effectively terminating up to 90% of cases of paroxysmal AF[73]. To this day, pulmonary vein isolation remains the cornerstone of catheter-based AF treatment[74].

Cheung demonstrated in the early 1980s that isolated pulmonary veins from guinea pigs were capable of independent firing[75], and Masani used electronic microscopy to demonstrate the presence of nodal-like cells in the myocardial sleeves of the PVs of adult rats[76]. In humans, electronic microscopy studies demonstrated that the muscular sleeves within the PVs in adults contain nodal-like cells, transitional cells, and large Purkinje-like myocytes in patients with a history of AF, and absence of such cells in patients without a history of AF[77].

Early work by Nathan and Eliakim described the PV myocardial sleeves in human hearts, showing better development in the upper rather than the lower veins[78]. The myocardial architecture of those muscular sleeves were seen to be highly complex and variable by Ho et al[79] with frequent patchy areas of fibrosis, thus lending itself to anisotropic conduction and reentry. This was indeed demonstrated using a combination of optical mapping and micro-electrode recordings in canine PVs by Po and colleagues[80].

1.2.2.3 Focal ectopic activity – non pulmonary foci

In addition to the PVs, a number of structures possess similar properties of initiating ectopic electrical activity and are implicated in the pathogenesis of AF. A recent clinical study suggested that up to 73% of patients with persistent AF had non-PV triggers[81].

The left atrial posterior wall (LAPW) is considered an embryological sibling of the PVs[82], sharing many of the properties conducive to anisotropic conduction, abnormal impulse generation and reentry. This has been demonstrated in preclinical as well as clinical studies where the LAPW was shown to harbor regular, fast, and highly organized electrical activity with higher voltage and electrogram fractionation compared to the rest of the atrium[83, 84].

The proximal superior vena cava (SVC) contains cardiomyocytes that have been seen to possess potentially arrhythmogenic pacemaker-like properties, with enhanced automaticity and afterdepolarisation[85]. Clinically, isolation of SVC in addition to the PVs has been shown to improve clinical outcomes[86, 87].

The muscular portion of the coronary sinus extends to 3-5 cm, and can trigger AF and allow for reentry; electrically disconnecting the coronary sinus from the left atrium with ablation following isolated the pulmonary veins, can terminate AF in up to 30% of patients[88-90].

Other non-PV triggers that have been demonstrated to play a role in triggering AF are the left atrial appendage[91], interatrial septum[92], oblique vein/ligament of Marshall[93], crista terminalis[94] and mitral annulus[95].

1.2.3 Atrial Remodelling

Any persistent changes in the atrial structure or function constitute remodelling, which promotes both AF initiation and its maintenance[96]. A number of conditions, including AF, can lead to anatomical, structural, molecular and subsequently electrical remodelling in the atria giving rise to the 'AF substrate'[97]. In 1995 Morillo and colleagues were the first to show alteration in the ultrastructure of atrial myocytes as a consequence of rapid atrial pacing in a canine model[98]. Shortly after, Wijffels et al. published their landmark study in which they demonstrated that artificial maintenance of AF resulted in a progressive increase in the inducibility and duration of AF, which became sustained after a mean of 7 days of rapid atrial pacing. The mantra 'AF begets AF' was henceforth born[99].

Left atrial dilatation is known to increase the risk of AF[100, 101]. For example, the Cardiovascular Health Study showed a four-fold increase in the risk of new AF with an LA diameter >5 cm[102]. In itself, AF can result in dilatation of the left atrium[98, 103], likely due to the haemodynamic consequences of atrioventricular dyssynchrony and loss of uniform contractility[104, 105]. The association between AF and atrial dilatation is further corroborated by the presence of atrial dilatation in a number of conditions that

are linked to AF, such as mitral valve disease[106, 107], hypertension[108], heart failure[109] and obesity[110, 111], with atrial stretch being an important mediator of the AF substrate formation in these conditions[112, 113]. Further, increased atrial size contributes to the AF substrate by increasing the amount of atrial tissue 'i.e. critical mass' that can support reentry circuits[114]. A recent meta-analysis showed that increased left atrial volume is associated with increased AF recurrence post catheter ablation for AF[115].

Atrial fibrosis refers to the formation of excessive extracellular matrix consisting of mainly fibroblasts and elastic and collagen fibres[113]. It is a key structural change in the AF substrate, being almost ubiquitous in histopathological assessments of atrial tissue in experimental AF models[113, 116], and a reproducible finding in a number of human studies[117-119]. The process of proliferation of fibroblasts which differentiate into profibrotic collagen-secreting myofibroblasts is a highly complex one[116]. It involves a number of signalling pathways that are not fully understood, but are known to involve the renin-angiotensin-aldosterone axis[120, 121], platelet-derived growth factors[122-124], connective-tissue growth factor[124], and transforming growth-factor β[116]. In humans, atrial fibrosis is a common feature in AF-patients and the extent of fibrosis is a predictor of AF-recurrence after catheter ablation[125].

Another important remodelling process relevant to AF is gap junction remodelling. Cell-to-cell electrical conduction requires direct cytoplasmic continuity to fill the gap in cardiomyocytes. In the human atria, the gap junctions are filled with proteins known as connexins (40, 43 and 45). Genetic defects in the gene encoding connexin 40 (GJA5) have been demonstrated to predispose patients to AF[126-128]. In goat, CX40 distribution was seen to be highly heterogenous in AF, with increased heterogeneity correlating to increased stability of AF[129]. Immunohistochemical

assessments of atrial tissue obtained from patients undergoing cardiac surgery revealed significant disorganisation of gap junctions in AF patients compared to those in sinus rhythm[130]. Bikou and colleagues successfully halted the progression to persistent AF using gene therapy for connexin 43 in a porcine model[131].

On a molecular level, ionic channels, particularly calcium channels, play a vital role in the pathophysiology of AF[132]. Cardiac excitability and muscle contraction are critically regulated by calcium influxes which enter the cells primarily through L-type Ca^{2+} channels ($I_{Ca,L}$)[133]. The increased atrial rate in tachycardia substantially increases Ca^{2+} loading, and as a protective mechanism, cardiomyocytes downregulate $I_{Ca,L}$ to prevent potentially cytotoxic intracellular calcium overload[134]. This then results in abbreviation of the action potential duration and shortening of the atrial refractoriness, which in turn increases tissue excitability and promotes multiple wavelets[135]. Additionally, calcium dysregulation can lead to contractile dysfunction[136] and atrial dilatation, which further promotes AF[137].

Downstream, these remodelling processes lead to increased tissue excitability, slowing of atrial conduction velocity, heterogenous atrial refractoriness, and anisotropic wavefront propagation[138]. Collectively, these electrical remodelling changes provide fertile grounds for AF to generate and self-sustain using the aforementioned key electrophysiological concepts of abnormal impulse generation and conduction.

1.3 Risk Factors for AF

There is a growing body of evidence that the risk of AF is modulated by a number of factors, some of which are non-modifiable, such as age and sex, while some are,

such as hypertension, obesity and physical (in)activity. Cardiac disease including heart failure and valvular heart disease is an established cause for AF[139]. Sleep-disordered breathing, despite being an important modifiable AF risk factor, is discussed in a separate section given its relevance to this thesis.

1.3.1 Age

Reports from large prospective cohort studies have established age as an important determinant of AF development[26, 140, 141]. Observations from the Framingham study over 50 years revealed age to be the most important independent risk factor for AF, and that the incidence of AF almost doubles for every 10-year increment of age above 60 years[33]. The Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study, a cross-sectional study of 1.9 million individuals in the United States, showed that nearly half of incident AF was in those 75 years or older, with a prevalence of 0.1% in persons aged 50 years or younger, compared to nearly 10% in those aged ≥80 years[24]. Moreover, age is an independent predictor of progression of AF[142], and permanent AF is significantly more prevalent in the elderly compared to paroxysmal forms[143]. Accordingly, increment in age has been incorporated in AF prediction scoring systems[144, 145].

Numerous preclinical studies demonstrated structural changes related to age, or 'aging cardiomyopathy'[146]. Anyukhovsky and colleagues recorded endocardial action potentials in young (<5 years) and older (>8 years) dogs, and showed significant differences in the action potential contours between the two groups, and a two-fold increase in the amount of fibrous tissue on histopathological assessment[147]. More recently, Jansen et al reproduced those histopathological findings in mice, and showed reduction in conduction velocity and action potential duration, with

associated increase in the sustained AF duration in older mice[148]. In humans, Spachs and Dolber used right appendageal specimens removed from patients undergoing surgery to demonstrate age-related increased interstitial fibrosis, impaired transverse conduction, and change from uniform to nonuniform anisotropic conduction[149]. Three-dimensional electroanatomical mapping of patients without structural heart disease by Roberts-Thomson and colleagues showed a reduction in conduction velocity with age, and an increase in the proportion of complex fractionated electrograms in the right atrium, from 2.7%±2.1% in patients younger than 30 years old, to 14.6%±7.7% (P=0.001) in patients older than 60[150], findings that echoed an earlier study that also showed change in atrial refractoriness and conduction slowing across the right atrium[151].

In addition to age-related atrial remodelling, many important AF risk factors become more prevalent with age[146]. For example, hypertension, which independently confers a 1.5-fold increased risk of new-onset AF[27], increases in prevalence with advancing age[152]. Approximately 90% of community-dwelling non-hypertensive individuals at 55-65 years of age were seen to develop hypertension by the age of 80–85[153] in one analysis from the Framingham study[153]. Heart failure, another condition closely related to AF[154], steadily increases in prevalence with advancing age[155]. Other AF risk factors with known age association include diabetes[156], metabolic syndrome[157], valvular[158] and coronary heart disease[159].

1.3.2 Sex differences

The epidemiology of AF is recognised to differ between men and women[160]. The age-adjusted AF incidence is estimated to be higher by 1.5-2 times in men compared to women[160]. A large retrospective study reporting on >400,000 Medicare

beneficiaries who are older than 65 years in the United States, reported the prevalence of AF to be 7.4% in women and 10.3% in men[161]. The Framingham study reported the prevalence of AF during the 1998–2007 period to be 49.4 in women compared with 96.2 in men (per 1000 person-years)[33]. Using intermittent ECG recordings, the prospective STROKESTOP Study actively screened for AF in 2 Swedish regions in patients aged 75-76 years, and demonstrated a higher prevalence of AF in men (15%) compared to women (9.2%)[162]. However, owing to the increased life expectancy for women, the lifetime risk of AF is comparable for men and women(~23%)[26], and the absolute number of women with AF is estimated to be higher than in men[161]. These epidemiological differences are less consistent in East Asian epidemiological studies, where the AF prevalence varied from being equal, to even lower, in men compared to women[160].

The increased AF risk in men is potentially mediated by other factors, such as stature and the increased prevalence of comorbid diseases[163]. This is supported by reports from the CHARGE-AF consortium who, after adjusting for AF-related risk factors, found male sex to no longer be an independent risk factor for AF[144]. While the underlying mechanisms to explain the sex disparity in AF risk are yet to be elucidated, some evidence exists that female sex is associated with some structural and electrophysiological changes conducive to AF. In ex-vivo rabbit tissue treated with adenosine, acetylcholine, and isoproterenol, Tsai et al reported significantly increased spontaneous rate, burst firing and more delayed after-deporalisation in male versus female tissue[164]. A recent study of human pulmonary vein sleeves excised during mitral valve surgery, demonstrated a higher degree of fibrosis in women with long-standing AF compared to men. Additionally, Li and colleagues provided possible mechanistic insights by demonstrating differential expression and

upregulation of fibrosis-related genes and proteins (TGFβ/Smad3) in women[165]. The Utah group showed that the proportion of atrial late-gadolinium enhancement on MRI, an indication of fibrosis, was higher in women compared with men (17.5±10.1% vs. 15.3±8.9%; P<0.001)[166].

It is important to recognise that AF is associated with worse symptoms and quality of life in women[167], and that women have higher risk of AF-related adverse events including stroke and death[168]. Accordingly, female sex is considered an important predictor of stroke in the presence of other risk factors, and is incorporated in the CHA_2DS_2VASc score which is integral to daily practice[3].

1.3.3 Racial and Genetic Factors

In contrast to early epidemiological AF studies, the past couple of decades have witnessed more representative inclusion of different races in cardiovascular research. The accumulating evidence indicate that the Caucasian ethnicity is a risk factor for AF[169]. A meta-analysis of 10 studies involving 1,031,351 subjects showed African Americans to have nearly half the risk of developing AF compared to Caucasian race (odds ratio 0.51, 95% CI 0.44 to 0.59, P < 0.001), despite the higher prevalence of comorbid AF risk factors[170]. The Atherosclerosis Risk in Communities (ARIC) study showed that the AF risk was ~1 in 3 among whites, and ~1 in 5 among African Americans[29]. These findings are not unique to African ancestry. Dewland and colleagues reported on incident AF in 13,967,949 patients receiving hospital-based care in California between 2005 and 2009. Using Cox multivariable regression analysis adjusting for patient demographics and established AF risk factors, blacks, Hispanics, and Asians each exhibited lower AF risk compared to whites (hazard ratio of 0.84, 0.78 and 0.78 respectively)[171]. A report from Multi-Ethnic Study of

Atherosclerosis (MESA) mirrored the above findings, and demonstrated that the incidence of hospitalized AF was significantly lower in Hispanics, non-Hispanic blacks, and Chinese compared to non-Hispanic whites[172].

1.3.4 Familial AF is a recognised phenomenon[173], with clustering of AF in families was reported as early as 1941[174]. More recently, researchers from the Framingham study reported that parental AF increases the future risk for offspring[175]. An interesting report from Iceland in 2006 showed strong evidence of heritability. For example, when examining those developing AF before the age of 60, first-degree relatives of AF patients were nearly five times more likely to have AF than the general population[176]. Genetic studies have shown that single-nucleotide polymorphism (SNP) is responsible in part for the increased risk of AF[177]. Genome-wide association studies have revolutionised genetic studies for common AF. Thus far, approximately 260 SNPs in 166 new genetic loci have been identified as associated with AF in multiple ethnic populations[169, 178, 179]. However, whole exome sequencing data from 1,734 individuals with and 9,423 without atrial fibrillation, did not show any significant associations between coding variation and AF, demonstrating that large effect coding variation is unlikely to be a predominant mechanism of common forms of atrial fibrillation encountered in the community[180]. When genetic testing is expanded to include cardiomyopathy and arrhythmia genes in a

study of ~1300 participants, disease-associated rare variants in cardiomyopathy and arrhythmia genes were identified in 10.1% of participants younger than 66 years and 16.8% of those younger than 30 years. These findings suggest that genetic testing in early-onset AF may have a role in identifying underlying inherited cardiomyopathy and/or arrhythmia syndromes[181].Hypertension

Hypertension, probably owing to its high prevalence in the general population[182], co-exists in up to 90% of AF patients[183, 184]. Hypertension contributed the highest to the AF risk in the ARIC study, which showed the population-attributable fraction for AF risk to be 21.6% for elevated BP, 12.7% for body mass index (BMI), 7.45% for smoking, 8.77% for diabetes, and 5.35% for history of cardiac disease. In a large cohort of healthy women, a stepwise increase in the risk of AF was seen as both systolic and diastolic blood pressure increased, with a stronger association with systolic blood pressure[185]. That incremental relationship was also seen in the CHARGE-AF consortium and was utilised in the AF prediction model[144]. Fifty-year trends in AF prevalence and its risk factors studied as part of the Framingham study, demonstrate a substantial increase in the population-attributable AF risk for hypertension treatment[33].

Different experimental models have demonstrated the abnormal left atrial substrate necessary for AF in hypertension models[38, 186-188]. Kistler et all used prenatal corticosteroids to cause sustained elevation in blood pressure in an ovine model. They demonstrated that elevated blood pressure was associated with significant atrial structural and electrical remodelling[189]. Lau used a ‘one kidney, one clip’

technique to induce sustained hypertension in sheep, and demonstrated that hypertensive sheep had larger left atria, reduced left atrial contractility, slower electrical conduction, higher conduction heterogeneity and greater propensity for AF[108]. These electrical abnormalities and AF inducibility correlated significantly with both atrial inflammation and fibrosis[190]. Similar findings were later reproduced by Lau in a spontaneously hypertensive rat model[191].

Much of the structural remodelling induced by hypertension in believed to be due to the activation of the renin-angiotensin-aldosterone system (RAAS)[192]. Exogenous aldosterone administration in rats showed increase atrial fibroblasts and interstitial collagen, and hypertrophy of atrial myocytes with associated conduction disturbance and increased AF inducibility[193]. Comparable findings have been noted in mice treated with angiotensin II[194].

Additionally, sustained hypertension increases afterload in the left ventricle and causes muscular thickening and subsequent left ventricular hypertrophy, which in turn increases ventricular stiffness, reduces diastolic function and increases left atrial pressure[40]. This then can cause left atrial dilatation which has been seen in clinical studies to be associated with the degree of hypertension[195]. Dilated atria are associated with slower and more heterogeneous atrial conduction and increased pulmonary vein firing. In addition, increased left atrial mass supports multiple reentry circuits as previously discussed[163].

1.3.5 Obesity

Numerous population-based studies have shown an association between elevated body mass index (BMI) and increased AF risk[35, 196]. A recent meta-analysis which included nearly 600,000 participants showed that obesity, defined as BMI ≥ 30 Kg/m^2

was associated with over 50% increased risk of new-onset AF (relative risk (RR) = 1.51, 95% confidence interval (CI) 1.35 to 1.68) regardless of gender[197]. A dose–response relationship between increased BMI and AF has been observed, with each unit increase of BMI associated with a 3% to 4.7% increase in AF risk[35, 198]. The dose-response relationship was also noted in post-operative and post-ablation AF risk by Wong et al, who demonstrated in a meta-analysis of 51 studies including 626,603 individuals, that for every 5-U increase in BMI, there were 10% to 29% greater excess risks of incident, post-operative, and post-ablation AF[34].

Obesity also predisposes to other, established risk factors for AF, including hypertension[199], diabetes mellitus[200], ischaemic heart disease[201], left ventricular hypertrophy[202], left atrial enlargement[203], heart failure[154], and sleep-disordered breathing[141]. Importantly, obesity increases the risk of progression from paroxysmal to persistent AF[204], and is a predictor of incident AF even when adjusting for other risk factors[141, 144]. A causal relationship between BMI and AF is supported by a mendelian randomization analysis of >50 000 individuals which demonstrated that a genetic risk score comprised of 39 polymorphisms associated with BMI correlated with AF incidence[205].

Preclinical and clinical studies have supported the epidemiological observations and help shed light on the mechanistic association between obesity and AF. In an ovine model of obesity, increasing weight correlated with increased atrial volumes, inflammatory infiltrates, TGFβ1 (transforming growth factor-β1), PDGF (platelet-derived growth factor), and fibrosis[110]. Obese sheep had heterogeneity of activation and conduction velocity slowing, rate-dependent conduction slowing, spontaneous AF episodes, easier AF induction, and longer AF episodes[111]. A clinical study of 63

patients undergoing AF ablation reported that elevated BMI was associated with short atrial effective refractory period (ERP) and slower atrial conduction velocity, findings that promote AF[206].

Pericardial and epicardial fat have been shown to have arrhythmogenic properties[207], potentially through exerting inflammatory effects on the atria that can promote AF[208, 209]. Cross sectional epidemiological studies have demonstrated an independent association between pericardial fat and the prevalence of AF[210, 211]. A meta-analysis including 352 275 individuals showed a strong and graded association between increasing epicardial fat and AF[212]. Mechanistically, Lin et al showed that incubation of rabbit left atrial cardiomyocytes with adipocytes prolongs action potential duration and promotes afterdepolarization-related spontaneous activity under adrenergic stimulation, while altering a range of ion currents, causing higher arrhythmogenesis in left atrial myocytes[213]. Electro-anatomical remodelling of the atria (areas of low voltage, conduction slowing, and greater fractionation of electrograms) were recently seen to be more pronounced in regions adjacent to epicardial fat depot (assessed using MRI) in patients undergoing AF ablation[214]. Nagashima et al showed higher prevalence of epicardial fat in persistent AF patients compared to those with paroxysmal AF, and also noted that areas with highest dominant frequency during AF were adjacent to epicardial fat locations.

The causative link between obesity and AF is further supported by multiple studies that show AF improvement by weight reduction. In the LEGACY trial (Long-Term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort), patients who achieved ≥10% of sustained weight loss enjoyed a 6-fold arrhythmia-free likelihood compared with those who lost <3% or gained weight[215]. In a sub-analysis

of LEGACY, the REVERSE-AF study demonstrated that patients who had the least percent of body weight loss had the highest progression to persistent AF (48%), while 88% of those achieving ≥10% weight reduction who started with persistent AF became paroxysmal or had no AF[216]. Weight loss through bariatric surgery for the morbidly obese patients (body mass index ≥40 kg/m2 or ≥35 kg/m^2 with obesity-related complications) was independently associated with lower recurrence after catheter ablation in a recent study[217].

The causal role of weight loss in AF reversal has been recently demonstrated by Mahajan and colleagues using an obese ovine model. Weight reduction by 30% was associated with reduction in left atrial pressure, inflammation ($p < 0.001$), endothelin-B receptor expression, and atrial fibrosis. Electrically, this manifested as an increase in atrial ERP, improved conduction velocity, decreased conduction heterogeneity, and decreased AF inducibility[218].

1.3.6 Physical activity

Physical activity and AF have an intricate relationship owing to the non-linear association between AF and physical activity per se[219], in addition to physical activity altering AF risk through modification of its other, established risk factors[220, 221]. With the increased risk of AF at the lower end of physical activity spectrum, a protective effect throughout most physical activity categories, and an increased risk in the higher end, a 'U-shaped' association has been described[222, 223].

Sedentary lifestyle has been shown to increase AF risk in multiple observational studies. A pooled estimate from 7 such studies including 93,995 participants quantified that risk to be more than double compared to physically active controls (pooled odds ratio (OR) 2.47 [95% CI 1.25–3.7])[224]. Increased fitness is inversely

and independently associated with the risk of developing AF[225]. A recent meta-analysis corroborated the protective effect of self-reported physical activity against AF and confirmed a step-wise association[219]. Elliott et al studied over 400,000 individuals from the UK Biobank observational cohort and found that higher self-reported physical activity had a protective effect against AF[226]. Objectively-measured physical activity has also been shown to reduce AF risk[219], and a dynamic risk of AF was demonstrated to be related to physical activity measured via accelerometer-derived parameters from implantable loop recorders[227]. Bonnesen et al very recently demonstrated that within-individual 1-hour decrease in physical activity during the last week conferred ~25% increased risk of AF onset[227].

There is concern however that physical activity is not always protective against AF, and may in fact predispose to AF[223, 228-230]. This increased risk appears to be mostly related to the higher end of physical activity range such as in athletic or endurance training[230, 231]. Molina et al reported a nearly 9-fold increase in AF risk in marathon running men compared to sedentary controls[232]. In an intriguing study of Swedish men participating in 90 km cross-country skiing event, a faster finishing time and a high number of completed races were associated with higher risk of arrhythmias[230], mainly due to AF[233]. The physiological adaptation related to intense physical training, including increased vagal tone[234] and atrial dilatation[235], can potentially explain the elevated AF risk. Intense endurance training in animal models produces atrial dilatation and structural, autonomic and electrical changes that promote AF[236, 237], with reversal of remodelling shown with exercise cessation[237].

In AF patients, there is evidence from small but randomised controlled trials that exercise training improves symptoms and quality of life[238-240]. Further, the CARDIO-

FIT (Cardiorespiratory Fitness on Arrhythmia Recurrence in Obese Individuals With Atrial Fibrillation) study was a prospective cohort study of 308 individuals with AF and elevated BMI (≥27 kg/m^2) which sought to assess the role of cardiorespiratory fitness improvement on rhythm control. Pathak et al noted a significant symptomatic improvement in symptom burden and symptom severity reduction for participants who managed to improve their fitness by ≥2 METs. Additionally, arrhythmia-free survival with and without rhythm control strategies was greatest in those with ≥2 METs gain compared to those with METs gain of <2[241].

1.3.7 Cardiac Disease

1.3.7.1 Coronary Artery Disease

Coronary artery disease has long been recognised as a risk factor of AF. Krahn et al reported in 1995 that among ~4000 male air crew recruits observed continuously for 44 years, the risk for AF was increased with myocardial infarction (MI) or stable coronary artery disease (relative risk 3.6, 2.21-2.84)[242]. In 1997, an analysis of the Cardiovascular Health Study of 5,201 adults aged ≥65 years demonstrated that coronary disease was independently associated with increased incident AF (relative risk 1.48, 95% CI 1.13-1.95)[243]. In a community-based cohort study of 3,220 patients hospitalised with incident MI from 1983 to 2007 in Olmsted County, Minnesota, the cumulative incidence of AF after MI at 5 years was 19%[244]. More recently, the Global Use of Strategies To Open occluded coronary arteries (GUSTO-III) investigators reported that 906 (6.5%) patients out of 13,858 with sinus rhythm at enrolment developed AF, with heart failure, hypotension, third degree heart block, and ventricular fibrillation as independent predictors of new AF[245]. Importantly, new onset AF was associated with a 49% increased risk of death after adjusting for all potential

confounders (odds ratio 1.49, 95% CI, 1.17-1.89)[245]. A recent meta-analysis of nearly 10,000 patients demonstrated that older age and increased baseline heart rate were related to greater risk of new-onset AF[246].

Across the spectrum of acute coronary syndrome, Lau et al found that patients with new-onset AF more often had left main coronary artery disease, resulting in a greater rate of surgical revascularization when they studied the ACACIA prospective registry of 3,393 patients, of whom 4.4% developed AF. Interestingly, intermediate-risk, rather than high risk acute coronary syndrome or ST elevation myocardial infarction (MI) patients had the highest risk for a composite endpoint of all death, myocardial infarction, and stroke (odds ratio 3.9, 2.0 and 1.4 for intermediate, high risk and ST-elevation MI respectively)[247].

The mechanisms behind the association between coronary disease and AF are multifactorial, and comprise shared upstream risk factors, heart failure related to coronary disease and direct atrial ischaemia[248, 249]. In a canine model, Sinno et al demonstrated that direct atrial ischaemia resulted in severe conduction slowing promoting AF maintenance[250]. Left ventricular infarction, despite the associated atrial stretch, hemodynamic change, and neurohumoral activation, contributes only partially to the AF substrate compared to direct atrial ischaemia. This was elucidated in an ovine study by Alasady et al, where MI was induced by occlusion of the left circumflex artery (LCX), from which atrial branches arise in sheep, or left anterior descending artery (LAD). The LCX group demonstrated greater conduction slowing and heterogeneity, along with greater AF vulnerability and longer AF duration, compared to the LAD occlusion group or the sham-operated controls[251]. In humans, Alasady et al reported that atrial branch disease, as assessed by invasive coronary

angiography in the setting of acute MI, was independently associated with the risk of AF development with 7 days[252].

1.3.7.2 Heart Failure

Heart failure (HF) and AF have a bidirectional relationship, in that HF is both a risk factor for AF and an adverse cardiovascular outcome of AF[163]. Multiple studies have confirmed the epidemiological link between AF and HF. Data from major registry studies show that 23-65% of HF patients have concurrent AF[154] and that the risk of AF increases with the increased left ventricular dysfunction and worsening HF symptoms[253, 254]. In the Framingham Heart Study, 37% of individuals with new AF had HF, and 57% of individuals with new HF had AF between 1980 and 2012[14]. Another report from the Framingham study showed that of participants who developed both conditions, a fifth were diagnosed with the two conditions simultaneously, two-fifths had AF diagnosed first and two-fifths HF first[255]. Further, AF occurs in two thirds of HF with preserved ejection fraction (HFpEF) patients at some point in the natural history[256]. The co-development of AF and HF has been shown to be associated with increased morbidity and mortality in multiple studies[14, 255, 257-259].

While the epidemiological link between AF and HF is established, the causative pathophysiological mechanisms are not well determined. Some of the causative links ought to be related to the multiple shared upstream risk factors such as age, hypertension, diabetes, obesity, and cardiac disease[154]. However, HF increases the AF risk directly through multiple mechanisms, including structural remodelling, autonomic and neuroendocrine dysfunction, and dysregulation of cellular ionic channels[260].

One of the first studies to provide mechanistic insights between heart failure and atrial fibrillation was published in 1999 by Li et al. Using rapid ventricular pacing in a canine heart failure model, the authors observed marked increase in AF inducibility, duration and conduction heterogeneity. Further, histopathological examination revealed extensive atrial fibrosis in the heart failure group, compared to the AF group or controls[261]. Lau et al used the cardiotoxic chemotherapy agent doxorubicin to induce cardiomyopathy in sheep. They confirmed the development of systolic dysfunction which was associated with left atrial dilatation, increased atrial fibrosis, electrical disturbances, and higher propensity for AF[262]. In a separate study, tachypacing in dogs for 4-6 weeks resulted in fibrosis and conduction abnormalities that were not reversible after 5 weeks of recovery[263]. Further, pacing-induced HF in dogs showed increased angiotensin II content contributing to arrhythmogenic atrial structural remodelling, and ACE inhibition interfered with signal transduction leading to the AF substrate[121], supporting the mechanistic role of the renin-angiotensin-aldosterone system in AF development. Dysregulation in ionic haemostasis promoting arrhythmogenesis has been shown in experimental studies[264, 265]. B-type Natriuretic Peptide (BNP), which is released from cardiac myocytes in response to volume expansion and is a well-recognised marker for HF severity[266], has been shown to be associated with increased calcium sparks in cardiomyocytes isolated from the pulmonary veins of rabbits[267].

Human studies examining the mechanistic role of HF in AF are relatively scarce. Extensive atrial fibrosis at autopsy was noted in patients with dilated cardiomyopathy[268], and Akkaya et al showed that AF patients with HF present with a higher degree of atrial fibrosis on MRI, highlighting a causal relationship between LV dysfunction and atrial structural remodelling leading to AF initiation and

maintenance[269]. Sanders et al sought to determine the electrophysiological and electroanatomic properties of the atria in patients with symptomatic congestive heart failure and reduced systolic function, in comparison to age-matched controls free of structural heart disease. They found that HF was associated with changes in atrial ERP, regional conduction slowing, and greater number of electrograms with fractionation or double potentials that were associated with areas of low voltage and electrical silence (scar). Given the detected collective changes conducive to AF, it was perhaps not surprising to then observe that patients with HF had increased propensity for AF which was more sustained[109].

1.3.7.3 Valvular Disease

The Framingham Heart Study reported that valve disease was independently associated with increased AF risk, more so for women than men (OR 3.4 and 1.8 respectively)[270]. In the developing world, rheumatic heart disease, particularly mitral stenosis, is strongly associated with AF with over 40% of afflicted individuals developing AF[271]. In a retrospective study of 940 patients followed-up for 11 years, AF risk was associated with aortic stenosis and mitral regurgitation (hazard ratio of 3.73 and 2.52, respectively, $p<0.0001$ for both)[272].

Atrial stretch has been implicated as the likely mechanism through which mitral valve disease mediates AF risk. In a canine model of mitral regurgitation, Verheule and colleagues reported increasing left atrial volumes and increased AF vulnerability[273]. Johns et al studied the structural and electrophysiological atrial remodelling in patients with severe mitral stenosis. They found that patients with atrial remodelling was characterised by left atrial enlargement, loss of myocardium, and scarring associated with widespread conduction abnormalities and heightened susceptibility

for AF[274]. In a follow-up study, the same authors showed that much of the remodelling reverses after mitral commissurotomy, further confirming the causative role of mitral stenosis in AF substrate and maintenance[275].

1.3.8 Diabetes

Diabetes and elevated blood glucose have been associated with increased risk of atrial fibrillation in a number of epidemiological studies. The Framingham Heart Study showed that diabetes was associated with a 40% and 60% increased AF risk for men and women respectively[141]. There appears to be a dose-response with regards to diabetes and AF risk supporting a causal association. Cumulative exposure to diabetes seems to affect the risk of AF[276], and elevated serum glycated haemoglobin levels, a long-term measure of glucose control, may be associated with an increased risk of AF[277]. A recent unique meta-analysis utilised machine learning-assisted screening, identifying 29 studies comprising over 10 million individuals, reported a pooled ~49% greater risk of developing AF in diabetics compared with individuals without diabetes. This risk was attenuated to 26% but remained significant when controlling for hypertension, obesity and heart disease[278], supporting the notion that diabetes is a strong, independent risk factor for AF.

Diabetes mediates AF risk by a number of mechanisms that involve structural, ultrastructural, and electrical remodelling. Animal models of diabetes provide strong support to the association between diabetes and myocardial fibrosis, a hallmark of the AF substrate[279]. In rat models of diabetes, significantly increased diffuse fibrotic deposition is noted in diabetic rats compared to controls, as well as conduction slowing, regional heterogeneity of conduction, and increased atrial arrhythmogenicity[280, 281]. The profibrotic process in diabetes is complex and involves

advanced glycation end products[282] and mitochondrial dysfunction resulting in persistent oxidative stress effects[283]. Additionally, preclinical studies suggest that hyperglycaemia aggravates ionic remodelling[284] and that heterogeneous sympathetic innervation exists in diabetic atria with more pronounced AF susceptibility in response to sympathetic stimulation, suggesting the presence of neural remodelling in diabetes and implicating the autonomic system in AF pathogenesis in diabetes[285].

Extensive myocardial fibrosis and stiffening can lead to diastolic dysfunction, which is commonly seen in patients with diabetes[286]. In the Strong Heart Study of cardiovascular disease in American Indians, diabetes was seen to have independent adverse cardiac effects, including increased left ventricular mass and wall thicknesses, reduced myocardial function, and increased arterial stiffness[287]. Rutter et al also showed that left ventricular mass, wall thickness and atrial dilatation increased with worsening glucose intolerance in participants of the Framingham Heart Study[288].

Patients with impaired fasting glucose were found to have significantly prolonged conduction times, with reductions in both left atrial emptying volume and emptying fraction[289], while diabetic patients undergoing catheter ablation for AF had significantly lower right atrial and left atrial voltages than patients without diabetes[290]. Further, electromechanical delay, an independent predictor of both new and recurrent AF[291], has been shown to be significantly higher in patients with diabetes compared with healthy control subjects[292]. Additionally, high levels of serum glycated haemoglobin were associated with an increased risk of recurrence of atrial tachyarrhythmia in patients with diabetes and paroxysmal AF undergoing ablation[293].

1.3.9 Other modifiable lifestyle risk factors

Alcohol has long been recognised as a risk factor for AF development, with the term 'holiday heart' coined in the late 1970s[294]. Alcohol was the most commonly reported trigger of AF episodes (35%) in nearly 1000 participants in the Health eHeart study[295]. Gallagher et al showed in a meta-analysis that high levels of alcohol intake were associated with a 34% elevation in the risk of incident AF regardless of gender[296]. The temporal relationship between alcohol consumption and AF occurrence has been recently demonstrated using continuous ECG recordings and ankle-worn transdermal ethanol sensors in 100 participants with paroxysmal AF[297].

Animal studies show that alcohol causes ionic remodelling and acute alterations in current densities conducive to AF[298-300]. Five standard drinks of whiskey resulted in shortened effective refractory period and slowed intra-atrial conduction, in a first-of-a-kind study of 14 patients studied before and after ingestion of alcohol back in 1978[301]. Contemporary studies demonstrate that atrial electrical and mechanical changes are associated with high alcohol consumption[302, 303], and that these changes are acutely mediated by autonomic modulation and mechanical dysfunction[304]. Abstinence from alcohol reduced arrhythmia recurrences in regular drinkers with atrial fibrillation in a recent randomised controlled trial, further supporting the mechanistic link between alcohol and AF[305].

Tobacco use has been associated with increased AF risk. In the ARIC study ever smokers (current or past) had a 58% higher adjusted AF risk, and current smokers had double the risk compared to non-smokers[306]. A meta-analysis found a dose-dependent relationship between smoking and AF risk that was most prominent in active compared with former smokers[307]. In a dog model, nicotine induced interstitial

fibrosis and increased AF susceptibility, possibly caused by downregulation of microRNAs 133 and 590[308], and human studies demonstrated that AF is associated with increased fibrosis[309]. Additionally, the increased AF risk due to smoking may be partly explained by the increased risk of myocardial ischaemia and lung disease, both of which have been linked to AF[310, 311].

1.3.10 Summary

This section discussed a number of AF risk factors in some detail, and highlighted the role for upstream therapy in AF management by addressing these conditions as crucial contributors to AF initiation and maintenance.

It is important to appreciate the important inter-play between these risk factors, which often co-exist. In fact, there is increasing recognition of AF as being part of a clinical syndrome, that often includes excess weight, hypertension, (pre)diabetes and often, cardiac disease such as heart failure with preserved ejection fraction[154]. In most patients, and in addition to traditional pharmacological treatments, managing these risk factors requires a wholistic approach to lifestyle modification[312].

1.4 Sleep-Disordered Breathing and AF

1.4.1 Introduction and historical perspective

Sleep-disordered breathing (SDB) is an umbrella term that encompasses a range of disorders, most falling into the categories of obstructive sleep apnoea (OSA) or central sleep apnoea (CSA) which may manifest as Cheyne-Stokes respiration[313, 314].

OSA is characterized by recurrent collapse of the pharyngeal airway during sleep, resulting in substantially reduced (hypopnea) or complete cessation (apnoea) of airflow despite ongoing breathing efforts. Most respiratory events culminate in a brief awakening from sleep, leading to a cyclical breathing pattern and fragmented sleep[315].

Observations of periodic breathing in sleep were first reported in the 1870s, where several cases of obstructed apnoeas were reported as “fruitless contractions of the inspiratory and expiratory muscles against glottic obstruction with accompanying cyanosis during sleep”[316]. The term ‘Pickwickian Syndrome’ was first coined by Sir William Osler in 1918 to describe the association of obesity, hypersomnolence, and cyanosis. The term was acquired from Charles Dickens’s first novel “The Posthumous Papers of the Pickwick Club” in which a character named “Joe the fat boy” had similar physical features and always fell asleep in the middle of tasks[317]. However, the description of obstructive sleep apnoea as a clinical entity was first made in the mid-1960s using polygraphic studies of patients with Pickwickian Syndrome, which documented episodes of repetitive cessation of breathing during sleep. These were postulated to cause repetitive arousals that may have been responsible for subsequent daytime sleepiness[318, 319].

In 1978, Remmers and colleagues described the mechanisms of OSA in a landmark paper[320]. They proposed the “balance of forces” theory, in which they model the upper airway as a tube, with forces that would collapse it (negative intraluminal pressure and increased tissue (extraluminal) pressure) being balanced against forces that maintain its patency (contraction of pharyngeal dilator muscles)[321]. This laid the foundation for the pioneering work by Sullivan and colleagues that

demonstrated the safety and efficacy of continuous positive airway pressure (CPAP) for the first time[322]. The authors described how low levels of pressure served as a pneumatic splint for the nasopharyngeal airway, and completely prevented upper airway occlusion during sleep in five patients with severe OSA resulting in uninterrupted sleep[322]. Four decades later, and CPAP is still recognised as the mainstay of OSA treatment[323].

Central sleep apnoea (CSA), in contrast to OSA in which ongoing respiratory efforts are observed, is characterized by a lack of drive to breathe during sleep, resulting in insufficient or absent ventilation and compromised gas exchange[314]. CSA is common among patients with heart failure[324], and periodic breathing in heart failure patients was reported as early as the 19th century by Cheyne and Stokes[325]. However, considerable overlap exists between OSA and CSA in terms of pathogenesis and pathophysiology, that the distinction is often difficult[326].

1.4.2 Evaluation and Management of SDB

As discussed, SDB is a spectrum of sleep-related breathing disorders, with most characterised by repetitive narrowing or closure of the upper airway (OSA), or compromised neuromuscular ventilatory control resulting in diminished or absent respiratory effort without airway collapse (CSA)[314, 327]. OSA and CSA often co-occur in the same individual, complicating diagnosis and treatment[421].

For the diagnosis of sleep apnoea to be made, the International Classification of Sleep Disorders (ICSD) requires objective demonstration of five or more respiratory disturbance events (obstructive and mixed apneas, hypopneas, or respiratory effort-related arousals) per hour of sleep, along with symptoms of SDB (eg, associated sleepiness, fatigue, insomnia, snoring, subjective nocturnal respiratory disturbance,

or observed apnea), or a medical or psychiatric disorder known to be associated with SDB (hypertension, coronary artery disease, atrial fibrillation, congestive heart failure, stroke, diabetes, cognitive dysfunction, or mood disorder). Alternatively, fifteen respiratory disturbance events per hour of sleep regardless of symptoms or associated medical/psychiatric conditions suffice to make the diagnosis[328].

The number of apnoeas and hypopneas experienced throughout sleep, indexed by the number of hours of sleep, defines he apnoea-hypopnea index (AHI), while the respiratory disturbance index (RDI) incorporates respiratory effort-related arousals in addition to AHI[313]. Sleep apnoea severity is typically quantified using the AHI. Based on expert consensus, an AHI less than 5 events per hour is considered normal, 5 to 14.9 is considered mild, 15 to 29.9 is considered moderate, and at least 30 is considered severe OSA[329].

1.4.2.1 Polysomnography

Attended in-lab polysomnography (PSG) is the gold standard test for sleep disorders[313]. A typical laboratory-based polysomnogram includes measures of[330]:

- airflow through the nose using a nasal cannula connected to a pressure transducer or through the nose and mouth using a thermal sensor
- respiratory effort using thoracic and abdominal inductance bands
- oxygen haemoglobin saturation by finger pulse oximetry
- snoring using a microphone affixed over the trachea or by filtering out low-frequency signals from the nasal cannula-pressure transducer system
- sleep stage and arousal using electroencephalogram, electro-oculogram, and chin electromyogram
- ECG
- body position
- leg movement

Strictly speaking, apnoea in adults is scored when there is a drop in the peak signal excursion by ≥ 90% of pre-event baseline, while a hypopnea is scored when the peak airflow signal excursions drop by ≥ 30% of pre-event baseline for ≥ 10 seconds in association with either ≥ 3% arterial oxygen desaturation or a cortical arousal[331]. An alternative definition of hypopnea is allowed which requires the association of airflow reduction with a 4% oxygen desaturation without consideration of cortical arousals[331]. Depending on which definition is used, the AHI may be considerably different in a given individuals and introduces complexity in the evaluation of evidence regarding the diagnosis of OSA[331].

1.4.2.2 Home Sleep Apnoea Testing (HSAT)

Home sleep apnoea testing (HSAT) is increasingly used to diagnose sleep apnoea, and consists of measures of airflow, respiratory effort, and oxygen saturation, but not measures of sleep or leg movements. The sensors are self-applied by the patient at home following instruction from a technologist or via an instructional video[330]. Reflecting the lack of precise sleep data, the AHI cannot be calculated, and the main metric from a HSAT is the Respiratory Event Index (REI), which is the sum of apnoeas and hypopneas divided by the estimated sleep time[332].

HSAT is an attractive option for sleep apnoea testing due to the lower cost and burden[332] in addition to adequate diagnostic sensitivity and specificity[330]. However, in patients with a high prior probability of disease, as many as 25% to 50% of study results negative for OSA were false-negative[333, 334]. Therefore, in laboratory polysomnography is generally recommended to evaluate patients with complex comorbidities[335].

Traditionally, sleep studies have been categorized as Type I, Type II, Type III or Type IV. Unattended studies fall into categories Type II through Type IV. Type II studies use the same monitoring sensors as full PSGs (Type I) but are unattended, and thus can be performed outside of the sleep laboratory. Type III studies use devices that measure limited cardiopulmonary parameters; two respiratory variables (e.g., effort to breathe, airflow), oxygen saturation, and a cardiac variable (e.g., heart rate or electrocardiogram). Type IV studies utilize devices that measure only 1 or 2 parameters, typically oxygen saturation and heart rate, or in some cases, just air flow[335].

1.4.2.3 Questionnaire-Based Tools

A number of screening questionnaires exist that can be used to assess sleep apnoea risk. They include assessment of symptoms and risk factors such as obesity, increased neck girth, and hypertension[332]. They include the Berlin Questionnaire, developed for use in the primary care setting[336], and the STOP-Bang questionnaire, developed for preoperative screening[337, 338]. The reported sensitivity is 77%-89%, but with low specificity around 34%[339].

The Epworth Sleepiness Scale (ESS) is a tool for grading the propensity for dozing in 8 different situations, and is widely used in both clinical practice and research to assess for excessive daytime sleepiness (EDS)[340]. Sleep apnea screening questionnaires appear to have poorer diagnostic accuracy in certain groups, such as in women[341, 342] and heart failure patients[435]. International guidelines stress that sleeping questionnaires should not be used for the diagnosis of sleep apnoea on their own[335].

1.4.2.4 Measures derived from Cardiac Implantable Electronic Devices (CIEDs)

Rate-responsive CIEDs use minute ventilation sensors to adjust heart rate and have demonstrated the capability to detect breathing variations by using transthoracic impedance measurements[343, 344]. Estimation of apnoeas and hypopneas can then be made by cessation of inspiratory flow or reduction of tidal volume by 30% respectively[345].

The DREAM study compared the utility of an algorithm using transthoracic impedance and minute ventilation sleep apnoea monitoring (SAM) algorithm against gold-standard PSG. The authors found that an algorithm-optimised respiratory disturbance index (SAM-RDI) of 20 events/hr yielded a sensitivity of 88.9% and specificity of 84.6% for detection of severe (AHI≥30) sleep apnoea[343]. Multiple studies have since demonstrated the feasibility of CIED-based sleep apnoea testing[343, 346-349], with good diagnostic accuracy that was confirmed in a recent meta-analysis[350]. Longitudinal data have helped provide valuable insights into the dynamic nature of sleep apnoea, as detected by wide variation in the night-to-night sleep apnoea severity[351, 352].

1.4.2.5 Novel Tools

Advances in technology and signal processing have facilitated a number of emerging SDB assessment tools. Peripheral arterial tonometry (PAT) uses finger pneumo-optic plethysmograph to detect fluctuations in peripheral arterial pulse waveform, which has been shown to decrease transiently in patients with OSA with a timing and periodicity linked to the arterial oxyhemoglobin desaturation and arousal response of

the apneic cycle[353]. The WatchPAT device (Itamar Medical, Ltd) uses a proprietary algorithm that combines PAT, oximetry, heart rate monitoring, and actigraphy to provide an estimate of total sleeping time, and to calculate a respiratory disturbance index[354]. Studies have demonstrated a good correlation between sleep indices calculated by in-lab PSG and those calculated using PAT devices have a reasonable (r=0.889)[355].

A novel wireless wearable patch that measures sleep breathing patterns using an inbuilt microphone and an accelerometer to record movement has recently shown promise in a pilot study (75% sensitivity and 71% specificity for detecting sleep apnoea events compared to gold standard PSG), and highlights the potential for acoustic sensors, alone or in combination with other technologies for SDB assessment[356].

The wide availability of smartphones, their multiple in-built sensors and their ability to track sleep in a non-invasive manner make them an attractive choice for SDB evaluation. However, studies assessing the utility of application-based sleep apnoea assessment have shown contradicting and largely poor correlation to PSG-derived parameters[357].

1.4.2.6 Treatment Options for SDB

Effective treatment of SDB includes behavioural measures, medical devices and surgery[330].

1.4.2.6.i Lifestyle Measures:

Behavioural measures include abstinence from alcohol, avoiding supine sleep position, regular aerobic exercise, and weight loss[330, 358, 359]. A 10% weight gain was

associated with a 32% increase in AHI in the Wisconsin, but a 10% weight loss resulted in a 26% decrease in AHI[360]. In the Action for Health in Diabetes study, 264 patients with overweight or obesity with type 2 diabetes mellitus and OSA were randomised to undergo a lifestyle intervention consisting of weight loss through diet and exercise or a diabetes education control. At the 1-year follow-up, the lifestyle intervention resulted in a 10.2-kg greater reduction in weight and a 9.7–event per hour greater reduction in AHI[361]. Exercise, even without significant weight loss, has been shown to improve OSA severity by 24-34%[362, 363].

1.4.2.6.ii Continuous Positive Airway Pressure (CPAP)

CPAP is established as first-line therapy in patients with symptomatic OSA of any severity, and for those with moderate or severe OSA due to its impact on both symptoms and quality of life[332]. As discussed previously, positive pressure functions as a pneumatic splint that maintains airway patency overnight.

CPAP can normalise AHI in up to 90% of users[364], but the benefit is highly dependent on adherence to therapy[365]. Adherence to CPAP therapy decreases significantly over time[366]. Approximately 20-35% of patients stop using CPAP long term, and factors that have been linked to improved adherence include higher AHI, higher BMI and sleepiness[367-369]. Education about risks of OSA and the expected benefits of CPAP therapy; monitoring of CPAP use with reinforcement and support for technical problems; and behavioural interventions, including cognitive behavioural therapy and motivational enhancement therapy have been shown to improve compliance[330, 370].

1.4.2.6.iii Mandibular Advancement Devices

Adjustable mandibular-advancement splints are effective treatment options for individuals with mild to moderate OSA who are unable to use CPAP[371]. These devices consist of plates made to fit the upper and lower teeth. Positions of these plates can be adjusted, allowing advancement of the mandible relative to the maxilla, resulting in increased upper airway volume and, consequently, reduced airway collapsibility[330]. A 2015 meta-analysis of 34 randomized clinical trials found that these devices were associated with a mean reduction in AHI of 13.6 (95% CI, 12.0-15.3) events per hour[372].

1.4.2.6.iv Other Treatment Options

Positional therapy involves avoiding a supine sleep position and is an effective treatment option for patients with positional sleep apnoea, who constitute a substantial proportion of patients with OSA[373]. The prevalence of OSA that may improve on proper positioning is 50% to 60%, while the prevalence of OSA that appears only on sleeping on the back and disappears on sleeping in any position other than on the back is 25% to 30%[373]. A recent Cochrane review concluded that while positional therapy may have better adherence than CPAP, CPAP has a greater effect on improving AHI compared with positional therapy in positional OSA[373].

Surgical procedures for managing OSA aim to modify upper airway soft tissue, including palate, tongue base, and lateral pharyngeal walls[330]. Evidence to support surgical options are mostly derived from observational studies but the relatively small randomised trials support observational data[374]. In the largest randomised trial comparing uvulopalatopharyngoplasty (n=32) to controls (n=33), surgery was associated with mean reduction in AHI from 53.3 to 21.1 events per hour with no

significant reduction in the control group. Other less studied procedures include lateral wall pharyngoplasty, tongue reduction procedures, and maxillomandibular advancement, which all require careful patient selection to ensure favourable anatomy[330, 375].

Hypoglossal nerve stimulation is a newer surgical procedure that increases pharyngeal dilator muscle tone during sleep. The procedure involves placement of an electrode on the medial branch of the hypoglossal nerve to enhance tongue protrusion, a pressure sensor placed between internal and external intercostal muscles to detect inspiratory effort, and a small neurostimulator implanted in the chest wall that triggers the hypoglossal electrode in response to respiratory effort[330]. The Stimulation Therapy for Apnea Reduction (STAR) demonstrated that upper-airway stimulation led to reduction in median AHI from 29.3 to 9.0 events per hour, along with improvement in subjective measurements of the severity of obstructive sleep apnoea[376].

1.4.3 Epidemiology of SDB and AF

SDB is a widely common disorder and population-based epidemiological studies have noted a steady increase in prevalence over time[377, 378]; it is now estimated that 1 billion people aged between 30 and 69 years have OSA globally[379]. Further, these estimates are likely to be conservative given that OSA tends to be underdiagnosed in the community[380]. The worldwide increase in obesity[381], a major risk factor for OSA[382], has undoubtedly contributed to the rise in OSA prevalence[383]. Significant socioeconomic cost[384-387], morbidity[388] and mortality[389, 390] are associated with SDB. An 18-year follow-up in the population-based Wisconsin Sleep Cohort showed that the adjusted hazard ratio for cardiovascular mortality in patients with untreated OSA

was 5.2 (95% CI: 1.4,19.2). Observational studies suggest that the treatment of OSA significantly reduces the risk of cardiovascular complications and mortality[389, 391], further implicating OSA as a mediator of that risk.

It has long been recognised that OSA is associated with cardiac arrhythmias, particularly AF[392, 393]. Detailed sleep study assessments indicate that sleep apnoea in AF patients is predominantly obstructive rather than central[394]. The prevalence of OSA in AF patients is not well characterised. Stevenson et al reported that 62% of a relatively small cohort of AF patients (n=90) had significant OSA compared to 38% in an age- and sex-matched control group as detected by sleep studies (P = 0.01). The trade-off of larger, registry based studies such as the Outcomes Registry for Better Informed Treatment of AF (ORBIT-AF), which reported an OSA prevalence of 18% in 10,132 AF patients[395], is that screening for SDB tends not to be systematic, making such estimates less reliable. In general, the available reports of SDB prevalence in AF range between 18% and 74%, compared to 3-49% in the general population[39]. Selection bias, diverse measurement techniques and inconsistent definitions likely contribute to the reported variation.

There are multiple shared risk factors between AF and SDB, such as obesity[391], diabetes and hypertension[396]. However, there is epidemiological evidence of an association between AF and SDB independent of those factors. Data from the Olmsted County Study were reported by Gami et al in 2007 in a landmark study, which showed that among 3,542 AF-free individuals who underwent sleep studies at baseline, a diagnosis of OSA conferred a two-fold increased risk of AF incidence compared to controls (HR, 2.18; 95% CI, 1.34–3.54) after adjusting for body mass index, neck circumference, hypertension, and diabetes mellitus[397]. This figure was

recently reproduced in a meta-analysis which arrived at a very similar pooled estimate of AF risk due to OSA from 9 studies comprising ~20,000 individuals (OR; 2.120, 95% CI: 1.845–2.436, p <0.001)[398].

Participants in the Sleep Heart Health Study with severe sleep-disordered breathing were four times more likely to develop AF (OR 4.02; 95% CI 1.03-15.74) after adjusting for age, sex, body mass index, and prevalent coronary heart disease [393]. In another study, OSA was found to be more prevalent in AF patients than in high-risk cardiovascular patients comparable in age, gender, body mass index, and rates of diabetes, hypertension, and congestive heart failure, further supporting a causal association that goes beyond common upstream risk factors[399]. In one analysis of the Multi-Ethnic Study of Atherosclerosis (MESA), Lin et al used Cox proportional hazards with extensive adjustment for potential confounders and confirmed that physician-diagnosed sleep apnoea was independently associated with incident AF over ~8.5 years (hazard ratio = 1.76, 95% CI: 1.03, 3.02)[400]. Moreover, SDB has been demonstrated to be an independent predictor of post-operative AF[401, 402].

A dose-response relationship between SDB and AF, which lends support to a causal link[403], has been shown in a number of studies. For example, Cadby et al showed that in whole-population hospital data from Western Australia which included nearly 7,000 patients followed-up for ~12 years, OSA diagnosis was independently associated with incident AF, with an adjusted excess AF risk of 48%, 51% and 73% in mild, moderate, and severe OSA respectively[404]. Further, Gami et al showed that apnoea-hypopnea index (AHI), a measure of OSA severity, was predictive of incident AF, although this particular analysis was not corrected for potential confounders[397]. Conversely, the prevalence of AF is also noted to increase with increased OSA

severity[405], and a large population-based study of Japanese men aged 40–74 years reported a stepwise increase based on SDB severity too[406].

1.4.4 Mechanisms underlying AF in SDB

There are multiple consequences of SDB that can contribute to AF initiation and maintenance. These include intrathoracic pressure swings, deficient gas exchange, and recurrent arousals which subsequently result in haemodynamic, inflammatory and autonomic changes conducive to AF. Further, chronic SDB promotes AF by inducing atrial structural and electrical remodelling as well as autonomic imbalance and hyperinnervation.

1.4.4.1 Airway obstruction and intrathoracic pressure changes

Forced inspiration against an occluded upper airway, as is the case with OSA, leads to substantially negative intrathoracic pressure and increased transmural pressures[407], promoting myocardial stretch particularly in the thin-walled atria[408] and increasing left ventricular afterload[409, 410]. On the right side of the heart, negative intrathoracic pressure augments venous return and pre-load[411], and the OSA-associated hypoxia causes pulmonary vasoconstriction which increases right-ventricular afterload[408]. This leads to right ventricular overload, stretch, and leftward septal displacement in diastole which results in reduced left ventricular filling[408, 412].

The Müller manoeuvre simulates OSA and involves forced inspiration against a closed mouth and nose in order to make a substantially negative pressure in the chest. Orban and colleagues studied the effects of the Müller manoeuvre on healthy adults and found that the negative intrathoracic pressure led to left ventricular end-systolic dimension increase in association with a decrease in left ventricular ejection

fraction and increased left ventricular afterload[413]. Direct cardiac chamber pressure measurements in humans using high-fidelity micromanometer catheters confirmed that the Müller manoeuvre increased right-to-left pressure gradient across the atrial septum, likely as a result of greater blood return to the right atrium from extra-thoracic veins[414]. The important contribution of increased venous return in atrial distension was demonstrated by Iwasaki et al, who showed that inferior vena caval balloon occlusion prevented left atrial dilatation during obstructive apnoeas in a rat model of OSA, with an associated substantial (83.3%) AF prevention[415].

In multiple animal studies, simulation of sleep apnoea has consistently resulted in cardiac remodelling and AF vulnerability. Linz et al published a series of preclinical experiments in a pig OSA model showing that negative tracheal pressure during tracheal occlusion reproducibly and reversibly promoted AF[416-420]. In rats, obstructive respiratory events mimicked by stopping the ventilator and closing the airway for 40 seconds resulted in substantial negative intrathoracic pressure, acute left atrial dilation, and increased AF inducibility[415]. Zhang et al showed that the atrial dimensions begin to increase shortly into simulated OSA experiments (3 hours) in a canine model. Further, they demonstrated gradual enlargement of the left atrium with prolongation of apnoea, along with associated ultrastructural atrial remodelling that will be discussed in more detail later[421].

Observations from human studies demonstrate that OSA is associated with greater cardiac structural remodelling, independent of other AF risk factors including, importantly, obesity. Otto et al described increased indexed left atrial volumes in otherwise-healthy obese patients with OSA compared to similarly-obese patients without OSA (16.3 +/- 1.2 ml/m in obese patients and 20.2 +/- 1.0 ml/m in those with

OSA, p = 0.02)[422]. Another study utilised 3-dimensional echocardiography and showed not only that OSA was associated with increased indexed left atrial volumes, but that this association correlated to the severity of OSA[423]. Yu et al reported a meta-analysis recently which confirmed the OSA association with increased left atrial diameter (weighted mean difference (WMD), 95% CI: 2.13 [1.48, 2.77]; $p < 0.001$) and left atrial diameter volume index (WMD, 95% CIs: 3.96 [3.32, 4.61]; $p < 0.001$)[424].

The role of intrathoracic pressure swings versus simple occlusion (and associated hypoxaemia/hypercapnoea) was elucidated by Linz et al who showed that tracheal occlusion without applied negative tracheal pressure, in contrast to tracheal occlusion with negative pressure up to -100 bar, caused comparable changes in blood gases but failed to shorten atrial refractoriness or enhance AF inducibility in pigs[419]. This suggests that intrathoracic pressure changes, likely through neurohumoral modulation, play an important role in AF pathogenesis. This notion is supported by data from human studies. For example, Ringler et al showed that blood pressure surges post apnoeic events, surrogate markers of increased sympathetic activity, were not related to hypoxaemia in OSA patients, and concluded that other factors associated with apnoea termination including changes of intrathoracic pressure may be responsible[425]. In addition to AF substrate formation, airway obstruction can also trigger AF. Simulated obstructive apnoea and hypopnea in humans resulted in frequent ectopy[417] and disturbances in cardiac repolarisation - changes that were not seen in simulated central apnoea or in normal breathing, highlighting the importance of airway obstruction in arrhythmogenesis[426].

1.4.4.2 Altered gas exchange and oxidative stress

The repetitive episodes of apnoea and hypopneas in SDB are typically associated with a desaturation–reoxygenation sequence[427]. This triggers chemoreflex receptors resulting in enhanced sympathetic nerve activity, particularly towards the end of an apnoeic event[428, 429]. Increased sympathetic drive due to hypoxaemia per se has been shown in healthy adults[430] and was demonstrated to correlate with the degree of nocturnal hypoxaemia[431]. The increased sympathetic drive causes increased heart rate and blood pressure[432, 433], which increases myocardial oxygen demand at a time when systemic oxygenation levels are lowered due to the apnoea/hypopnoea episodes, resulting in myocardial ischaemia and promoting atrial fibrosis and remodelling[434], an integral part of the AF substrate[435].

Periods of hypoxia are associated with reduced antioxidant mechanisms, while periods of reoxygenation are associated with increased production of reactive oxygen species, the two combined lead to increased oxidative stress similar to ischaemia-reperfusion injury[436]. This is likely to be mediated through imbalance between hypoxia-inducible factor-1 subunits (HIF-1α and HIF-2α)[437]. Oxidative stress and inflammation are linked to AF through myocardial injury, atrial remodelling and AF substrate promotion[438].

While other comorbidities common to AF and SDB can also increase oxidative stress such as obesity[439], a number of studies found that SDB in itself is associated with increased oxidative stress[440-442]. Ntalpascha et al recruited 18 patients with severe SDB and 13 controls comparable in age, BMI, and blood pressure, and all were free of comorbidities known to increase oxidative stress. They found significant differences in the overnight oxidised/reduced glutathione ratio, a biomarker of

oxidative stress and indicator of cellular health, between those with OSA and controls suggesting that OSA has a causal association with increased oxidative stress[441]. Further, a larger study including 128 patients found that the severity of OSA was independently associated with oxidative stress measured through quantification of urinary biomarkers[443].

Inflammation and endothelial dysfunction play an important part in atrial remodelling, and thus AF[444]. The proinflammatory cytokines tumour necrosis factor-α and interleukin (IL)-6 are increased in patients with OSA,[445] and have been shown in a meta-analysis to be associated with increased AF risk and AF recurrence[446]. In a rat model of OSA, longer apnea-hypopnea duration is related to more systemic inflammatory and endothelial dysfunction, as well as hypertension and cardiac remodeling[447]. Shamsuzzaman et al. reported significantly higher levels of plasma C-reactive protein (CRP) in patients with OSA than in control subjects (0.33 versus 0.09 mg/dl) and CRP levels were independently associated with the OSA severity as well[448]. Moreover, repeated apnoea-related hypoxia significantly enhances superoxide production in OSA, with rapid and long-lasting decrease in superoxide release with CPAP therapy[449]. CPAP treatment also leads to reduced levels of CRP and IL-6[450] and improved endothelial function in humans[451]. The elevation of inflammatory and endothelial dysfunction markers associated with SDB, along with their improvement with SDB treatment[452], strongly suggest a causal link.

In isolated superfused left atria of the rabbit, the inducibility of tachyarrhythmias by single early premature stimuli was highly increased by hypoxia, and was likely facilitated by the observed moderate shortening of the wavelength and increase in inhomogeneity in conduction[453]. Another study using isolated rabbit pulmonary veins

showed that hypoxia and reoxygenation significantly increased pulmonary vein spontaneous rate and induced PV burst firings[454]. Ghias et al showed that apnea-induced hypoxemia, in the absence of arousals or inspiratory effort, significantly reduced atrial refractory periods, thus lowering the threshold for development of AF[455]. However, the role of hypoxaemia has been questioned by Stevenson et al who showed that atrial electrophysiology is altered by acute hypercapnia but not hypoxaemia in a sheep model of OSA[456]. The authors found that isolated hypercapnia resulted in atrial effective refractory period prolongation. Refractoriness rapidly returned to baseline, but recovery of conduction was delayed following correction of hypercapnia. Even though AF vulnerability was reduced during hypercapnia, it increased significantly with subsequent return to eucapnia[454].

Additionally, it is important to consider that intermittent hypoxaemia also indirectly contributes to AF through increasing the risk of multiple AF risk factors, including hypertension[457], heart failure[458, 459] (with RAAS activation implicated[416, 460]), obesity[461], and diabetes[462-464] - the contribution of each to AF risk has been covered earlier in this chapter.

1.4.4.3 Autonomic Changes

Normally, sleep is characterized by cardiovascular quiescence with metabolic and sympathetic reduction, accompanied by increased vagal tone during non-rapid eye movement (nREM) sleep[465, 466]. Despite surges in sympathetic activity during REM sleep, the average blood pressure and heart rate remain below waking levels[465]. SDB, likely through recurrent arousals[467] and chemoreflex triggers[429] disrupts this equilibrium with potentially significant consequences[465, 468].

Patients with obstructive sleep apnoea have high baseline sympathetic tone when awake as demonstrated by measured muscle nerve sympathetic activity[469], with further increases in sympathetic activity and blood pressure during sleep[429]. Elevation of daytime catecholamines was noted by Fletcher et al in 1987, who studied patients with severe apnoea before and after treatment (tracheostomy then) and found significant elevation in baseline daytime norepinephrine and normetanephrine levels in apnoeic patients when compared either with controls or with their own post-tracheostomy values[470]. Similar findings were made by Peled and colleagues who also demonstrated that the minimal oxygen saturation level was a significant predictor of increased norepinephrine levels[471].

Animal studies confirm the role of autonomic nervous system (ANS) in AF development and help elucidate the underlying mechanisms. Linz et al showed that in a pig model, negative tracheal pressure during obstructive apneas led to pronounced shortening of atrial refractoriness promoting AF. These electrophysiological changes were mainly mediated by sympatho-vagal dysbalance, since they could be influenced by atropine, bilateral vagotomy or beta-receptor blockade[416, 418-420, 472]. Yu et al found that obstructive apnoeas in dogs caused hyperactivity of ganglionic plexi (GPs) and of the extrinsic ANS with associated shortening of atrial effective refractoriness and triggering AF[473]. A more recent study by Tavares et al in a canine model of sleep apnoea demonstrated a close mechanistic association between the cardiac autonomic nervous system and apnoea-induced AF. The authors performed simultaneous nerve recordings from bilateral vagal nerves, left stellate ganglion, and anterior right GP. They observed a consistent sequence of events secondary to apnoea including: increases in GP activity; progressively increasing phasic bursts of vagal activity, which closely

correlate with heart rate and blood pressure oscillations; and tonic increase in sympathetic activity, which correlates with steady increases in heart rate and systolic blood pressure[474]. Further, denervation of GP sensory neurons (afferent denervation) resulted in decreases in sympathetic and GP nerve activity, and prevented atrial refractoriness reduction and AF inducibility[474]. In addition to increased ANS activity associated with SDB, animal studies of chronic SDB show evidence of autonomic remodelling with increased nerve densities, sympathetic nerve hyperinnervation, and enhanced protein expression of β1, β2, and M2 receptors[475-477].

1.4.5 Atrial Structural Remodelling in SDB

Several studies examined the effects of repeated obstructive apnoeas over several weeks to mimic the remodelling caused by SDB in humans. Zhao et al utilised a canine model of OSA where they stopped the ventilator and closed the airway for 4 hours per day over 12 weeks. They observed atrial structural remodelling characterised by apoptosis, interstitial fibrosis and altered expression of important channel proteins, which was associated with reduction in atrial refractoriness and enhanced AF inducibility and duration[477]. Zhang et al demonstrated that chronic OSA in dog caused atrial dilatation, increased glycogen and collagen volume fractions, increased apoptosis ratio in atrial myocytes, mitochondrial changes, and disordered myofilament and disc arrangement, providing a basis for the AF substrate[421]. In rodents, a chronic OSA model showed that 2-weeks of simulated OSA cause proteins changes in the atria which suggest impairment of energy metabolism and enhancement of hypertrophy[478].

In a rat model of AF, OSA was associated with atrial conduction slowing attributed to connexin-43 downregulation and increased atrial fibrosis, which promoted the persistence of AF[479]. Connexin-43 was specifically seen to be downregulated with chronic intermittent hypoxia in another rodent study of SDB[475]. A very recent unique rat model of SDB study was published, which simulated night-to-night SDB variability by applying intermittent negative upper airway pressure for 1 minute followed by a 9-minute resting period, and repeated this sequence for 24 events/4 h every second day throughout 3 weeks. Atrial histological analysis revealed increased cardiomyocyte diameters, reduced connexin 43 expression, and increased interstitial fibrosis formation which were associated with longer inducible AF episodes[480]. Dai et al focused on an interesting consequence of SDB, by demonstrating the epicardial adipose tissue (EAT) remodelling in a chronic SDB canine model. They elegantly show that chronic OSA induced infiltration of EAT into the left atrium, enhanced the profibrotic effect of EAT on the adjacent atrial myocardium and induced profibrotic cytokine secretion from EAT, alterations that were significantly attenuated by metoprolol[481].

In human, multiple studies have demonstrated left atrial enlargement related to SDB as discussed above[422-424]. Some studies have shown cardiac structural and functional remodelling related to SDB beyond left atrial enlargement, including left ventricular dilatation, increased left ventricular mass and left ventricular systolic and diastolic dysfunction[482]. These changes were observed independent of obesity[483] and seem to correlate with the severity of OSA and the degree of left ventricular diastolic impairment[484]. A vicious loop of ventricular dysfunction, sleep-disordered breathing, and atrial fibrillation is therefore plausible[485]. Utilising the late gadolinium enhancement (LGE) technique on MRI to detect atrial fibrosis, de Oliveira and

colleagues demonstrated that patients with OSA and AF showed significantly more atrial LGE (95% vs. 30%, p < 0.001), and that atrial LGE was an independent predictor of AF in multivariate analysis (P < 0,001)[486].

1.4.6 Atrial Electrical Remodelling in SDB

Multiple animal studies have demonstrated that AF induced by SDB is related to shortening of the (protective) atrial effective refractory period (AERP). For example one study in pigs showed that negative tracheal pressure shortened AERP significantly (157.0 ± 2.8 to 102.1 ± 6.2 ms; P <.0001) and enhanced AF inducibility during AERP measurements from 0% at baseline to 90% (P <.00001)[419]. These changes may be due to the (ultra)structural changes described above, as well as ionic channel remodelling[487]. Additional electrical mechanisms implicated in AF pathogenesis in SDB include conduction slowing and an increase in heterogeneity of refractory periods, which are conducive to maintenance of arrhythmia as previously discussed[453].

Advancement in electroanatomical mapping techniques has helped provide important insights from human studies regarding the role of SDB in AF arrhythmogenesis. Dimitri et al studied 20 patients with moderate SDB (AHI ≥15/hr) undergoing ablation for paroxysmal AF and compared them to 20 reference patients with no OSA who were comparable in the prevalence of baseline AF risk factors. The authors found that OSA is associated with significant atrial remodelling characterized by atrial enlargement, reduction in voltage, site-specific and widespread conduction abnormalities, and longer sinus node recovery[435]. The conduction abnormalities entailed lower atrial voltage, slower atrial conduction (and longer P-wave duration), greater number and duration of complex electrograms along the crista terminalis,

longer P-wave duration, and more widespread complex electrograms in both atria. Notably, no difference in ERP was seen.

Anter et al later confirmed the above findings in a group of 86 paroxysmal AF patients undergoing AF ablation, half of which with moderate-to-severe SDB. The authors found that patients with SDB had lower atrial voltage amplitude, slower conduction velocities, and higher prevalence of electrogram fractionation. Additionally, they sought to investigate AF triggers in this cohort of patients and found that at baseline, pulmonary veins (PVs) were the most frequent triggers for AF in both groups; however, after PV isolation patients with SDB had increased incidence of additional extra-PV triggers (41.8% versus 11.6%; P=0.003)[488].

The degree of electro-anatomical remodelling was very recently seen to correlate with the severity of SDB in patients with paroxysmal, but not persistent, AF. Nalliah et al used high-density left atrial mapping (mean 2351 ± 1244 points) in a cohort of 66 consecutive AF patients. An independent correlation was seen between polysomnography-detected severity of SDB, quantified by AHI, and multiple measures of electrical remodelling including inverse correlation to global voltage, and positive correlation with the number of low voltage areas, voltage heterogeneity and number of fractionation of electrograms. Interestingly, the association of AHI with remodelling was most apparent among paroxysmal AF but not persistent AF, as significant remodelling was observed across all SDB categories in persistent AF (1.67 ± 0.55 mV vs. 1.50 ± 0.66 mV vs. 1.55 ± 0.67 mV, P = 0.82)[489].

1.4.7 Clinical Implications of SDB in AF

1.4.7.1 SDB and AF outcomes

Concomitant SDB seems detrimental to AF patients, being associated with worsening AF-related symptoms, increasing risk of hospitalisation, AF complications and reduced efficacy of AF treatments. Data from 10,132 patients enrolled in The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) study, showed that patients with OSA (N=1841, 18%) were more symptomatic (22% vs 16% for severe/disabling symptoms on the EHRA scale; P < .0001) despite a higher proportion of OSA patients receiving rhythm-control therapy (35% vs 31%; P = .0037). Further, OSA was an independent predictor of higher risk of hospitalization (hazard ratio [HR], 1.12; 95% CI, 1.03-1.22; P = .0078)[395].

OSA is associated with increased cardioembolic complications such as stroke in patients with AF[490, 491]. Data from the European Sleep Apnea Database (ESADA) identified Indices of hypoxia during sleep were associated with increased CHA_2DS_2-VASc score[490], while a previous observational study by Szymanski et al showed an association between CHA_2DS_2-VASc scores and OSA severity assessed by AHI[492]. A more recent analysis of the ORBIT-AF registries, found that after adjustment, the presence of OSA was significantly associated with major adverse cardiovascular events (HR: 1.16 [95% CI: 1.03–1.31], P = .011). OSA was also an independent risk factor for stroke and systemic embolism beyond the CHA_2DS_2-VASc risk factors (HR: 1.38 [95% CI 1.12–1.70], P = .003)[493].

The earliest report of the detrimental association between sleep apnoea and reduced AF treatment efficacy came from Kanagala and colleagues in 2003. They observed a

higher recurrence rate of AF post successful cardioversion in patients with PSG-diagnosed but untreated OSA compared to those with treated OSA or controls free of OSA (82%, 42% and 53%, pairwise P=0.013 and 0.009, respectively)[494]. More recently, Monahan et al studied the effect of OSA on the efficacy of antiarrhythmic drugs (AAD) in a prospective cohort study. Defining 'response' as patients remaining on the same AAD therapy for ≥6 months with ≥75% reduction in symptomatic AF burden, they found that patients who do not respond to antiarrhythmic drug therapy were significantly more likely to have severe OSA rather than mild OSA (52% vs. 23%; P=0.05), and those with severe OSA were much less likely to respond to antiarrhythmics than patients with mild OSA (39% vs. 70%; P=0.02)[495].

With regards to catheter ablation for AF, a large cohort study comprising 3000 patients undergoing AF ablation found that those OSA experienced higher rates of periprocedural haematomas compared to non-OSA patients (5% vs 1.5%, P<0.001)[496]. However, other confounding factors were not accounted for in this analysis, particularly BMI which was significantly higher in the OSA group (31±3 vs 26±5 Kg/m^2, P<0.001). In another study by Sauer et al, OSA was more prevalent in the group of patients who experienced acute pulmonary vein reconnection following catheter ablation (11.9% vs 5.2%, P=0.02). Indeed, OSA was an independent predictor of acute pulmonary vein reconnection (relative risk 2.16 (1.32, 3.94))[497].

Numerous studies evaluated the impact of OSA on AF recurrence post catheter ablation. However, most studies evaluated that impact within the context of CPAP use. Therefore, patients not compliant with CPAP therapy provide a unique insight into the effect of OSA per se on AF outcomes, which appears to be unfavourable. For example, Naruse et al found that this group of patients (concomitant AF, OSA,

and no CPAP use) had a higher AF recurrence (53%) than in the no-OSA (22%) and CPAP (30%) groups during a mean follow-up period of 18.8±10.3 months (P<.01)[498]. The authors also found that concomitant OSA (HR 2.61; 95% CI 1.12–6.09; P<.05) was an independent predictor of AF recurrence. A meta-analysis of five studies involving 3743 patients found that patients with OSA had a 31% greater risk of AF recurrence after catheter ablation than did patients without OSA, and this risk increased by 57% in patients with OSA not undergoing CPAP therapy.[499]

1.4.7.2 SDB Treatment and AF Outcomes

Holmqvist et al, in their report of the ORBIT-AF registry mentioned above, found that OSA had no effect on progression of AF compared to patients with no OSA. However, within patients with concomitant AF and OSA, patients who received CPAP treatment were much less likely to progress to permanent forms of the arrhythmia compared with no treatment (HR: 0.66, 95% CI, 0.46, 0.94; P=0.021)[395].

Therapy with CPAP appears to have the ability to reduce the risk of AF recurrence after catheter ablation to a level similar to that in patients without OSA[500]. In a prospective study of 720 patients, Neilan et al found that he cumulative incidence of AF recurrence after catheter ablation was 51% in patients with SA and 30% in patients without SA. However, when OSA was treated, 35% of patients experienced recurrence (compared to 68% in patients with untreated SA)[501]. Similarly, Fein et al found that the AF recurrence rate of CPAP-treated patients was similar to the group of patients without OSA (HR: 0.7, p = 0.46), and that AF recurrence following PVI in CPAP nonuser patients was significantly higher (HR: 2.4, p < 0.02) and similar to that of OSA patients managed medically without ablation (HR: 2.1, p = 0.68)[502]. Further, treatment with CPAP is associated with a lower incidence of newly

diagnosed AF after ablation for typical atrial flutter, suggestive that CPAP has a protective role against AF triggers and/or substrate progression[503].

Multiple meta-analyses have identified a protective effect of CPAP against arrhythmia recurrence[499, 504-506]. Very recently, an updated meta-analysis found that CPAP therapy reduced the risk of AF recurrence or progression by 63%[504], while a previous meta-analysis estimated that 18% of cases with recurrent AF could be attributed to not receiving CPAP in OSA patients undergoing catheter ablation[507].

It is important to note that while CPAP has been shown to be beneficial, this is based largely on relatively small observational studies, which are not universally consistent in their findings. Srivali et al reported on outcomes from 429 patients with OSA and AF who had undergone catheter ablation, and found no effect of PAP treatment of SDB on time to recurrence of AF post-AF intervention[508]. In meta-regression analysis, benefits of CPAP were stronger for younger, obese, and male patients[506].

To date, only two reported randomised controlled trials have been reported to investigated the impact of CPAP therapy on AF. The first by Caples et al randomised 25 patients with persistent AF and OSA (AHI≥5/hr) (after screening 1757 patients) to receive positive airway pressure or usual care post DC cardioversion. Patients with sleepiness, significant cardiac or respiratory disease were excluded. The authors found no difference in the proportion of patients experiencing AF recurrence or time to recurrence[509]. More recently, Traaen and colleagues reported the results of their randomised trial of CPAP use in 108 patients with paroxysmal AF and moderate-to-severe OSA (AHI≥15/hr). Using implantable loop recorders to assess AF burden, the authors found that the mean time in AF decreased from 5.6% at baseline to 4.1% during the last 3 months of CPAP intervention and from 5.0% to 4.3% in the control

group, a difference that was not statistically significant and reflects the underpowering of the study. Of note, this study recruited fewer than a fifth of screened patients (18.7%), which highlights the logistical and ethical challenges in conducting randomised trials that can potentially lead to withholding treatment in patients who are likely to benefit from the most[332].

1.4.7.3 SDB Treatment and Cardiovascular Outcomes

A key limitation when studying the effect of CPAP therapy on cardiovascular outcomes is the ethical requirement of excluding patients with severe sleepiness or hypoxemia, for whom CPAP is an established treatment to improve symptoms and quality of life, yet this is the group most likely to derive maximal benefit from CPAP treatment[332]. Studies of short-term CPAP treatment on daytime blood pressure control have been mixed, although the consensus seems to be that sustained, long-term treatment with CPAP can help reduce blood pressure[510]. The HIPARCO randomised controlled trial demonstrated that CPAP treatment for 12 weeks compared with control resulted in a decrease in 24-hour mean and diastolic blood pressure and an improvement in the nocturnal blood pressure pattern[511]. Huang and colleagues identified BMI, baseline mean blood pressure and CPAP compliance to be independent predictors of blood pressure improvement with CPAP use[512]. A patient-level data meta-analysis of four randomised studies including 1206 patients found that CPAP treatment reduced subjective sleepiness and SDB severity, but not to have a beneficial effect on blood pressure in patients with minimally symptomatic SDB, except in patients who used CPAP for >4 h/night[513].

The MOSAIC study randomised 391 patients with SDB (AHI ≥ 7.5/hr) with no excessive daytime sleepiness to 6-months of CPAP therapy or standard of care. The

investigators found that CPAP therapy improved ESS scores by 2 points (95% CI −2.6 to −1.4), but failed to improve the 5-year calculated vascular risk. Notably, 22% of those randomised to receive CPAP therapy reported stopping treatment, and that the median CPAP use for the entire CPAP arm was only 2:39 hours per night[514]. The Spanish Sleep and Breathing Network conducted a randomised trial between 2004 and 2006 which evaluated CPAP therapy in 723 patients with moderate-to-severe SDB (AHI ≥ 20/hr) but with no excessive daytime sleepiness, and found no statistically significant difference in the incidence of hypertension or cardiovascular events. The authors acknowledged that the study may have had limited power to detect a significant difference[515].

For secondary prevention of cardiovascular events, McEvoy and colleagues more recently conducted the SAVE study, which randomised 2717 patients with moderate-to-severe OSA and coronary or cerebrovascular disease to receive CPAP treatment plus usual care, or usual care alone. The primary endpoint was a composite of 'hard' endpoints of death from cardiovascular causes, myocardial infarction, stroke, or hospitalisation for unstable angina, heart failure, or transient ischemic attack. The investigators found no difference in the primary endpoint after a mean follow-up of 3.7 years. Remarkably, CPAP significantly reduced snoring and daytime sleepiness and improved health-related quality of life and mood. Similar to MOSAIC, the CPAP adherence was low at an average of 3.3 hours per night. The prespecified subgroup analysis showed that those with CPAP adherence >4 h per night had a lower risk of stroke (HR: 0.56; 95% CI: 0.32-1.00) and total cerebrovascular events (HR: 0.52; 95% CI: 0.30-0.90)[516]. Peker et al studied patients with newly-revascularised coronary artery disease and SDB but without excessive daytime sleepiness and found no effect on the primary outcome of repeat revascularisation, myocardial

infarction, stroke, or cardiovascular mortality in in the 122 patients randomised to CPAP therapy. Again, in a prespecified subgroup analysis, those with better CPAP adherence (≥4 hrs/night) had a lower risk of stroke (HR: 0.56; 95% CI: 0.32-1.00) and total cerebrovascular events (HR: 0.52; 95% CI: 0.30-0.90)[517]. The importance of adherence to CPAP therapy were further emphasised in a recent meta-analysis which showed that utilisation of CPAP in patients with OSA was not associated with improved cardiac outcomes except in patients who used CPAP for >4 hours[518].

Chapter 2: Self-Reported Daytime Sleepiness and Sleep-Disordered Breathing in Patients with Atrial Fibrillation

2.1 Introduction

SDB affects up to 74% of all patients with AF[39] and is an independent predictor of stroke.[519] Treatment of SDB can improve arrhythmia-free survival of AF following pharmacological treatment or catheter ablation.[520] This important interplay between AF and SDB has been recognised in the international AF management guidelines; current guidelines from the European Society of Cardiology and Consensus from the Heart Rhythm Society both recommend screening for signs and symptoms of SDB in patients with AF, and to consider initiation of SDB therapy to improve AF treatment outcomes.[74, 521]

Excessive daytime sleepiness (EDS) is an important clinical consequence of SDB that can significantly impair the quality of life of its sufferers.[522] Assessing self-reported daytime sleepiness is advocated in international sleep medicine guidelines to aid the assessment of symptom burden of patients with sleep apnea prior to and on therapy, and is often used to triage patients for SDB investigation and treatment[523] While treatment with positive-airway-pressure (PAP) is considered the standard of care for patients with moderate-to-severe SDB to improve daytime sleepiness, the indication to start PAP is less certain in patients with mild SDB.[523] However, the goals of SDB treatment may not be interchangeable between Sleep-Clinic and AF-Clinic populations, as the primary aim in treating SDB in AF patients is not just to improve EDS, but to control AF symptoms and maintain sinus rhythm. The

fact that only a minority of people with SDB in population-based studies[524] and in cardiovascular clinics[525-527], including those symptomatic of persistent AF referred for electrical cardioversion,[528] report daytime sleepiness further complicates this common clinical scenario.

The hypothesis of this study is that self-reported daytime sleepiness does not correlate with the presence or severity of SDB in AF patients, and that self-reported daytime sleepiness lacks the sensitivity and specificity to identify SDB or guide SDB management. This was tested on a cohort of ambulatory AF patients referred from ther AF-Clinic for formal overnight sleep studies as part of their work-up for AF management.

The aims of the study were: (i) to investigate the correlation between daytime sleepiness and presence and severity of SDB; (ii) characterise the population with moderate-to-severe SDB (i.e. patients most likely to be treated with PAP by sleep medicine physicians); and (iii) assess the distribution of EDS and AF-related symptoms and potential implication for AF and SDB management.

2.2 Methods

2.2.1 Study design and population

The study included consecutive patients with symptomatic AF referred from the Centre for Heart Rhythm Disorders at the University of Adelaide to undergo polysomnography (PSG) as part of their AF work-up. Referrals to the Adelaide Institute for Sleep Health from January 2009 to March 2017 were screened and patients without AF or with incomplete PSG data were excluded **(Figure 1)**. The

study protocol was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital (R20180831) and registered on Australian New Zealand Clinical Trials Registry (Trial ID. ACTRN12618001859279).

2.2.2 Patient characteristics

AF was confirmed by at least one 12-lead electrocardiogram (ECG). Type of AF was defined according to the 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation.[74] Demographic and anthropometric data were collected for all patients. Clinical risk factors were actively screened-for and the CHA_2DS_2-VASc score was calculated accordingly.[138]

Transthoracic echocardiography was performed to assess left atrial and ventricular dimensions and left ventricular systolic function. All measurements were performed according to the recommended protocols for cardiac chamber quantification by the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[529] In patients with AF during echocardiography, all measurements were averaged over a minimum of 5 cardiac cycles.

2.2.3 Assessment of daytime sleepiness

To assess the degree of subjective daytime sleepiness, the Epworth Sleepiness Scale (ESS) was administered to all participants before polysomnography. The Epworth Sleepiness Scale is a validated questionnaire that requires subjects to rate their likelihood of falling asleep in several common situations.[340] Scores range from 0 (least sleepy) to 24 (sleepiest). Normal daytime sleepiness was defined as an

Epworth Sleepiness Scale score between 0 and 10. Excessive daytime sleepiness (EDS) was defined as a score of 11 or higher.

2.2.4 Assessment of SDB-severity

AF patients underwent standard overnight polysomnography (PSG; Somte, Compumedics) which included continuous recordings of electroencephalography (EEG), electro-oculography (EOG), and chin electromyography (EMG) for sleep staging. PSG data were scored by an experienced sleep technician and reviewed and reported by a registered sleep physician according to methods described in the American Academy of Sleep Medicine manual for the scoring of sleep and associated events.[530] The apnea-hypopnea index (AHI) was calculated as the total number of apneas plus hypopneas divided by the total sleep time. SDB was considered present if the AHI was ≥5. SDB-severity was determined according to categories AHI: AHI 5-14.9, mild SDB; AHI 15-29.9, moderate SDB; AHI≥30, severe SDB; AHI≥15, moderate-to-severe SDB)[530].

2.2.5 Assessment of AF symptom burden

A subgroup of patients also underwent AF symptom burden assessment using the AF severity scale (AFSS). The AFSS is a validated scale that has been previously described and utilised in quantifying symptom burden in AF patients.[215, 241, 531-533] The AFSS ranges from 3.25 (single minimally symptomatic episode lasting minutes) to 30 (continuous highly symptomatic episode lasting >48hours). It encompasses 3 domains of AF: event frequency (scored 1-10), duration (scored 1.25-10), and global episode severity (scored 1-10).

2.2.6 Statistical analysis

Continuous variables were tested for normality in distribution and are presented as mean ± standard deviation or median and inter-quartile range as appropriate. Categorical variables are presented as count and proportion. Group differences were tested using Student t or one-way analysis of variance tests for normally distributed variables, while Mann-Whitney U and Kruskal-Wallis H tests were used for nonparametric variables. Differences in proportions were tested using X^2 or Fisher's exact test where appropriate.

Binary logistic regression analysis was used to test the univariate relationship of baseline characteristics and the presence of moderate-to-severe SDB, with alpha value set at 0.1 to conditionally include a given variable in a multivariate forward stepwise conditional model. Hosmer and Lemeshow's goodness of fitness test was then applied to the multivariate model. Linear correlation was used to test the relationship between daytime sleepiness and degree of SDB as defined by AHI and is reported as Spearman's coefficient of correlation and coefficient of determination (R^2). To test the utility of the Epworth Sleepiness Scale to predict the presence of SDB, we used receiver operating characteristic (ROC) analysis that allowed assessment of sensitivity and specificity of all possible cut-offs of the predictor variable. Significance was set at $p<0.05$. All statistical analysis was performed using SPSS statistical software for Windows (Version 24; IBM corp.).

2.3 Results

2.3.1 Study population

The study included a total of 442 patients, of whom 306 (69.2%) were men. Mean age was 60±11 years and mean BMI was 30.5±5.2 kg/m^2. One hundred sixty-nine patients (38.2%) had non-paroxysmal AF. Baseline characteristics are reported in **Table 1**. When stratified for the presence and type of SDB, nearly one third of the studied population had no SDB (n=150, 33.9%), one third had mild SDB (n=143, 32.3%) and one third had moderate-to-severe SDB (n=149, 33.7%). This latter group consisted of 76 patients (17.2%) with moderate and 73 patients (16.5%) with severe SDB respectively (**Figure 2**). Seventy-seven patients (26.4%) had predominant central sleep apnea. The proportion of patients with predominant central sleep apnea was higher in mild SDB (32.2%) as opposed to the moderate (27.6%) or severe SDB (13.7%) groups, p=0.01. **Table 2** summarises PSG findings in the population stratified by the presence and type of SDB.

2.3.2 Correlation between Epworth Sleepiness Scale score and SDB

The studied population reported low levels of daytime sleepiness regardless of the presence or severity of SDB. The median Epworth Sleepiness Scale score for the population was 5 [3-8] and did not differ significantly when the population was stratified by SDB severity (p=0.18) (**Table 2**). **Figure 3** depicts the Epworth Sleepiness Scale score distribution using a scatterplot of all the cases, ranked by Epworth Sleepiness Scale score and stratified by SDB severity.

There was a statistically significant, but very weak correlation between Epworth Sleepiness Scale and AHI (Spearman's rho correlation coefficient=0.12, 95% CI:

0.02-0.21, p=0.01), with only 1% of the variation in reported daytime sleepiness potentially explained by the severity of SDB (adjusted R^2=0.01, p=0.02) (**Figure 4**). However, there was no correlation when correcting for presence of SDB, gender or obesity (R=0.14, 0.14 and 0.12 respectively, p=ns).

2.3.3 Utility of Epworth Sleepiness Scale to predict SDB

Epworth Sleepiness Scale performed very poorly as a predictor for SDB regardless of the degree of SDB or the cut-offs of Epworth Sleepiness Scale used. Using ROC analysis, the AUC was 0.54, 0.48, 0.53, and 0.57 for any SDB, mild SDB, moderate SDB and severe SDB respectively (p=ns) (**Figure 5**). When combining the moderate and severe categories (AHI≥15), the AUC reached statistical significance (p=0.04) but remained low at 0.56 (95% CI: 0.5 – 0.62). Using the conventional threshold of Epworth Sleepiness Scale score ≥ 11 to define EDS, the test had a sensitivity of 12% and specificity of 89.3% for detection of SDB (AHI≥5) with a negative predictive value (NPV) of 34.3% and a positive predictive value (PPV) of 68.6%. In comparison, to detect moderate-to-severe SDB (AHI≥15) with the same EDS threshold, Epworth Sleepiness Scale had a slightly better sensitivity of 14.8% and specificity of 90.1% with a NPV of 43.1% and a PPV of 67.5%. **Table 3** shows the sensitivity and specificity values of ESS at various thresholds to detect any or moderate-to-severe SDB.

2.3.4 Characterising AF patients with moderate-to-severe SDB: patients likely receiving PAP treatment

Out of the 292 patients with any SDB (AHI≥5), 149 (51%) had moderate-to-severe SDB (AHI≥15) and would likely be considered for PAP treatment. The mean age for

this population was 61±10 years and 114 (76.5%) were men. The moderate-to-severe SDB group had higher BMI and a higher proportion of patients with obesity (**Table 4**). There was no observed difference in the left ventricular ejection fraction between these two groups, but the group with moderate-to-severe SDB had larger left atrial diameter (4.1±1.0 vs 3.8±0.9 cm, p<0.001) and volume (61.8±25.2 vs 69.9±31 cm^3, p<0.02). Baseline medications were comparable between the groups other than for ACEi/ARB (107 (71.8%) vs 81 (56.6%)) and diuretics (38 (25.5%) vs 16 (11.2%)), which were used more frequently in patients with moderate-to-severe SDB when compared to mild SDB.

The multivariable regression model constructed to assess the utility of baseline clinical characteristics to identify patients with moderate-to-severe SDB was a good fit for the data (X^2=3.8, df=8, p=0.87). We found that male gender, obesity, diabetes mellitus and history of stroke/TIA were independently associated with increased likelihood of having moderate-to-severe SDB. Male gender (OR: 2.3, 95% CI: 1.4-3.8, p=0.001) and diabetes mellitus (OR: 2.3, 95% CI: 1.2-4.4, p=008) were associated with double the likelihood to have moderate-to-severe SDB. Obesity was associated with a three-fold increased risk of moderate-to-severe SDB (OR: 3.5, 95% CI: 2.3-5.5, p<0.001) while history of cerebrovascular disease increased the odds of having moderate-to-severe SDB by a factor of 4.6 (95% CI:1.7-12.3, p=0.002). Additionally, annual increments in age increased the likelihood of moderate-to-severe SDB diagnosis by ~2.5% (OR: 1.023, 95% CI: 1.001-1.045, p=0.04). The model adjusted for type of AF and history of hypertension.

2.3.5 Excessive daytime sleepiness and AF-symptom burden: potential role in AF and SDB management

Only a small proportion of patients with diagnosed SDB reported EDS (11.9%). A comparable proportion of patients with no SDB also reported EDS (10.7%). There was a non-significant trend towards increased prevalence of EDS within SDB as the severity of SDB increased (X^2= 0.48) (**Figure 3**). This finding remained consistent in patients with predominant central sleep apnea (EDS prevalence of 10.9%, 23.8%, and 20% for mild, moderate and severe SDB respectively, p=0.36). In AF patients with mild SDB where the presence of EDS might influence the decision to start PAP, most patients (90.1%) did not report EDS, and this group represents almost a third of the whole population in this study (130/442 patients (29.4%)).

AFSS questionnaire results were available for 306 patients. Mean AFSS score was 13.6±5.8 (out of a maximum of 30) and did not differ when the population was stratified by the presence and degree of SDB (**Figure 6**). There was no correlation between AF symptom burden and reported sleepiness (R=-0.01, p=0.7) or AF symptom burden and SDB (R=0.23, p=0.7). AFSS did not differ across SDB categories when corrected for EDS or predominant-central-sleep-apnea (p=0.07 and 0.5 respectively). Patients with mild SDB were not less symptomatic with their AF than those with moderate-to-severe SDB (mean AFSS: 13.3±5.9 vs 14.1±5.5, p=0.3).

2.4 Discussion

In this cohort of ambulatory AF patients referred for formal overnight sleep studies, we found: (i) SDB to be prevalent, with nearly a third of the patients having

moderate-to-severe SDB, a third with mild SDB and a third with no SDB; (ii) self-reported daytime sleepiness to correlate very poorly with objective measures of SDB; (iii) EDS to be low, regardless of the presence or severity of SDB; and (iv) certain clinical features are more helpful than EDS to identify patients with moderate-to-severe SDB (i.e. patients most likely to be treated with PAP by sleep medicine physicians irrespective of the presence of AF).

Albuquerque et al observed that excessive daytime sleepiness did not correlate with the severity of SDB in a selected group of 151 patients with persistent AF referred for electrical cardioversion.[528] Our study extrapolates these findings to a larger, consecutively-recruited, symptomatic AF population being considered for rhythm-control therapy, irrespective of the type of AF or the presence or absence of SDB-related symptoms. The studied population is thus more representative of the patients encountered in a typical ambulatory setting.

Given the lack of correlation between daytime sleepiness and SDB, it was not surprising to see that the Epworth Sleepiness Scale performed very poorly as a prediction tool for SDB, regardless of the severity of SDB being tested or the thresholds of the scale utilised. The Epworth Sleepiness Scale may have a role in establishing a baseline daytime sleepiness level, which can help monitor treatment response and potentially guide PAP therapy in selected patients if EDS is present.[523] However, in light of our findings, we stress the importance of not relying on subjective daytime sleepiness to select patients for overnight sleep studies. Had EDS been used as a prerequisite for screening for SDB in our studied population, up to 88% of the patients with any SDB and ~85% of patients with moderate-to-severe SDB would have been missed. While daytime sleepiness and SDB seem to

correlate in the general population,[524] the lack of a similar correlation in AF patients is interesting. It is possible that increased sympathetic tone in AF patients[38, 534] counteracts sleepiness due to SDB as seen in stroke or heart failure patients.[525] It is also plausible that patients with SDB and AF have blurred perception of their symptoms and are unable to specifically attribute them to one condition or another.[535]

From a sleep-medicine perspective, PAP treatment is likely to be recommended for severe SDB regardless of EDS and for moderate and possibly even mild SDB if EDS is present.[523] However, from a heart-rhythm management perspective, the current literature is scarce regarding rhythm-management outcomes in patients with AF and concomitant mild SDB, as most of the published studies are observational and use a relatively high AHI threshold for defining SDB.[520] This can pose a real management dilemma in the treatment of AF patients with mild SDB and no EDS as currently no evidence-based treatment indication is available, neither from the sleep-medicine nor from the heart-rhythm management perspective. Our study demonstrates that this is not an uncommon scenario when AF patients are referred to sleep studies irrespective of the presence or absence of SDB symptoms, with nearly one third (29.4%) of the studied population falling in this category. Contributing to this dilemma is the finding that those patients do not seem to be any less symptomatic with their AF than their counterparts with moderate-to-severe SDB.

It is prudent to be able to identify AF patients with significant SDB as these are the patients most likely to benefit from SDB treatment from a rhythm-management perspective.[435, 536, 537] Our study demonstrates that the clinical features of obesity, male gender, history of cerebrovascular disease or diabetes can help predict the

presence of moderate-to-severe SDB and potentially guide patient selection for investigation of SDB. While polysomnography remains the gold-standard for diagnosing SDB, simpler methods such as overnight oximetry can provide a more widely-accessible option for patient screening.[538, 539] Further studies are warranted to investigate whether PAP treatment of patients with AF and SDB, irrespective of EDS, can improve rhythm-management outcomes, and to determine the level of SDB severity for which PAP treatment is beneficial. Meanwhile, adopting an aggressive AF risk factor management strategy, which includes PAP initiation in AF patients with severe SDB or those with moderate SDB and EDS, has been shown to long-term arrhythmia-free survival following catheter ablation for AF.[138]

2.5 Limitations

The studied population represents patients with symptomatic AF referred for specialist management of their arrhythmia. Therefore, our results may differ had the subjects been enrolled from a Sleep Clinic and then tested for AF. However, the large number of patients, the consecutive data collection and the resultant diverse population allow for the generalisation of this study's findings to the population seen in the cardiac outpatient clinic. In our study, only Epworth Sleepiness Scale was used to test for daytime sleepiness. There may be other questionnaires that can potentially detect SDB more accurately than Epworth Sleepiness Scale such as Berlin Questionnaire or STOP-BANG.

2.6 Conclusions

In this ambulatory AF cohort, SDB is common (66%) but most AF patients reported low levels of daytime sleepiness. Therefore, the lack of excessive daytime

sleepiness should not preclude patients from being investigated for the potential presence of concomitant SDB. Clinical features, rather than daytime sleepiness, were predictive of patients with moderate-to-severe SDB most likely to benefit from PAP treatment. A significant proportion (32%) have only mild SDB, but evidence is lacking regarding treating SDB in those patients both from sleep-medicine and heart-rhythm management perspectives. Whether AF management outcomes improve by treating concomitant mild or moderate SDB, particularly with no excessive daytime sleepiness, warrants further study.

2.7 Tables and Figures

Table 1

Baseline clinical characteristics per sleep-disordered breathing (SDB) category. Continuous variables are presented as mean ± standard deviation while categorical variables are presented as number (proportions).

Characteristics	No SDB	Mild SDB	Moderate SDB	Severe SDB	p
Number of patients	**150**	**143**	**76**	**73**	
Male	**89 (59.3)**	**103 (72)**	**57 (75)**	**57 (78.1)**	**0.01**
Age, years	**56.9±11.8**	**62.1±10.1**	**60.7±9.8**	**61.7±11**	**0.001**
Weight, kg	**87.6±15.5**	**88.6±13.9**	**96.5±17.9**	**102.5±20.2**	**<0.001**
BMI, kg/m2	**29.1±4.6**	**29.4±4.3**	**31.3±5**	**34.5±5.7**	**<0.001**
Obesity	**47 (31.3)**	**54 (37.8)**	**39 (51.3)**	**54 (74)**	**<0.001**
Hypertension	**100 (66.7)**	**102 (71.3)**	**53 (69.7)**	**59 (80.8)**	**0.2**
DM (or glucose intolerance)	**10 (6.7)**	**13 (9.1)**	**12 (15.8)**	**18 (24.7)**	**0.001**
Dyslipidaemia	**59 (39.6)**	**69 (48.6)**	**34 (44.7)**	**42 (57.5)**	**0.1**
Coronary artery disease	**12 (8)**	**12 (8.4)**	**4 (5.3)**	**13 (17.8)**	**0.04**
Cerebrovascular disease	**3 (2)**	**5 (3.5)**	**5 (6.6)**	**8 (11)**	**0.02**
CHA_2DS_2Vasc	**1.5±1.2**	**1.8±1.2**	**1.8±1.2**	**2.2±1.1**	**0.001**
Non-paroxysmal AF	**40 (26.7)**	**62 (43.4)**	**38 (50)**	**29 (39.7)**	**0.002**
Previous AF ablation	**20 (13.3)**	**30 (21)**	**11 (14.5)**	**11 (15.3)**	**0.3**
Excess alcohol (>30g/week)	**37 (24.7)**	**30 (21)**	**17 (22.4)**	**9 (12.3)**	**0.2**

Smoking: none-smoker	**111 (74)**	**108 (75.5)**	**52 (68.4)**	**52 (71.2)**	**0.3**
Ex-smoker	**6 (4)**	**5 (3.5)**	**0 (0)**	**1 (1.4)**	
Current-smoker	**33 (22)**	**30 (21)**	**24 (31.6)**	**20 (27.4)**	
EF, %	**61.3±8.7**	**61.1±8.2**	**61.4±9.9**	**59.5±10.8**	**0.6**
Impaired LVF (EF<40%)	**4 (2.7)**	**4 (2.8)**	**4 (5.3)**	**3 (4.1)**	**0.7**
LVIDd, cm	**4.9±0.9**	**4.8±1**	**5.1±0.9**	**5±0.7**	**0.02**
LA volume, cm^2	**62.2±31**	**61.8±25.2**	**72±34.5**	**67.8±27.1**	**0.02**
LA diameter, cm	**3.7±1**	**3.8±0.9**	**4.1±1**	**4.1±0.9**	**<0.001**
NOAC	**32 (21.3)**	**50 (35)**	**26 (34.2)**	**22 (30.1)**	**0.053**
Warfarin	**42 (28)**	**41 (28.7)**	**28 (36.8)**	**29 (39.7)**	**0.2**
Aspirin	**41 (27.3)**	**38 (26.6)**	**12 (15.8)**	**16 (21.9)**	**0.2**
Beta-blockers	**78 (52)**	**67 (46.9)**	**36 (47.4)**	**41 (56.9)**	**0.5**
Digoxin	**8 (5.3)**	**5 (3.5)**	**5 (6.6)**	**8 (11)**	**0.2**
Flecainide	**59 (39.3)**	**40 (28)**	**19 (25)**	**17 (23.3)**	**0.03**
Sotalol	**13 (8.7)**	**19 (13.3)**	**12 (15.8)**	**10 (13.7)**	**0.4**
Amiodarone	**5 (3.3)**	**8 (5.6)**	**7 (9.2)**	**3 (4.1)**	**0.3**
Statin	**38 (25.3)**	**52 (36.4)**	**24 (31.6)**	**41 (56.2)**	**<0.001**
ACEi/ARB	**74 (49.3)**	**81 (56.6)**	**51 (67.1)**	**56 (76.7)**	**0.001**
CCB	**47 (31.3)**	**41 (28.9)**	**20 (26.3)**	**31 (43.1)**	**0.1**
Diuretics	**15 (10)**	**16 (11.2)**	**14 (18.4)**	**24 (32.9)**	**<0.001**
MRA	**6 (4.2)**	**11 (7.8)**	**7 (9.5)**	**7 (9.6)**	**0.4**

Abbreviations: DM=diabetes mellitus, EF=ejection fraction. LVF=left ventricular function. LA=left atrium. NOAC=non-vitamin K oral anticoagulants. ACEi=angiotensin converting enzyme inhibitors. ARB=angiotensin receptor blockers. CCB=calcium channel blockers. MRA=mineralocorticoid receptor antagonist.

Table 2

Polysomnography characteristics per sleep-disordered breathing (SDB) category. Continuous variables are presented as median [25th-75th percentile] or mean ± standard deviation. Categorical variables are presented as number (proportions).

Characteristic	No SDB	Mild SDB	Moderate SDB	Severe SDB	p
Epworth Sleepiness Scale score	4 [3-7]	4 [3-7]	5 [3-9]	6 [3-9]	0.2
Apnoea-hypopnoea index	2.1 [1-3.6]	9.5 [6.6-11.8]	21 [18-24.3]	44 [36-65]	<0.001
Predominant central sleep apnoea	51 (34)	46 (32.2)	21 (27.6)	10 (13.7)	0.01
Total sleep time, minutes	326 [264-373]	329.5 [274.5-377]	318 [275.5-364.5]	277 [185-324.4]	<0.001
Non-rapid eye movement sleep, %	82.9±8.4	89.2±60	93.8±93.7	87.7±8.8	0.001
Rapid eye movement sleep, %	16.5±6.9	17.8±18.5	18±12.9	12.4±8.9	0.001
Sleep efficacy, %	72±17	72.6±14.9	70.7±15	64.7±16.6	0.003

Table 3

Sensitivity and specificity of Epworth Sleepiness Scale (ESS) to detect any or moderate-to-severe sleep-disordered breathing (SDB) using various apnoea-hypopnoea-index (AHI) thresholds.

ESS	Any SDB (AHI≥5)		Moderate-to-severe SDB (AHI≥15)	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
3	79.8	24.7	81.2	23.2
4	66.4	41.3	68.5	38.6
5	52.7	50.7	56.4	50.9
6	44.5	62.0	49.0	61.1
7	36.6	68.0	39.6	67.2
8	28.4	75.3	34.2	76.5
9	21.9	81.3	27.5	82.6
10	16.4	86.7	20.8	87.4
11	12.0	89.3	14.8	90.1
12	8.2	90.7	9.4	91.8

Table 4

Baseline clinical characteristics of the studied atrial fibrillation (AF) population. P values provided are for the differences between the no or mild and moderate-to-severe SDB groups. Continuous variables are presented as mean ± standard deviation and categorical variables as number (proportion).

Characteristics	Total population	No or mild SDB (AHI<15)	Moderate-to-severe SDB (AHI≥15)	P
Number of patients	442	143	149	
Male	306 (69.2)	103 (72)	114 (76.5)	0.4
Age, years	60±11	62.1±10.1	61.2±10.4	0.4
Weight, kg	91.9±17.2	88.6±13.9	99.4±19.2	<0.001
BMI, kg/m2	30.5±5.2	29.4±4.3	32.9±5.6	<0.001
Obesity	194 (43.9)	54 (37.8)	93 (62.4)	<0.001
Hypertension	314 (71)	102 (71.3)	112 (75.2)	0.5
Diabetes mellitus	53 (12)	13 (9.1)	30 (20.1)	0.008
Dyslipidaemia	204 (46.4)	69 (48.6)	76 (51)	0.7
Coronary artery disease	41 (9.3)	12 (8.4)	17 (11.4)	0.4
Cerebrovascular disease	21 (4.8)	5 (3.5)	13 (8.7)	0.06
CHA_2DS_2Vasc score	1.8±1.2	1.6±1.2	2±1.2	0.005
Non-paroxysmal AF	169 (38.2)	62 (43.4)	67 (45)	0.8
Previous AF ablation	72 (16.3)	30 (21)	22 (14.9)	0.2
Excess alcohol (>30g/week)	93 (21)	30 (32)	26 (17.4)	0.4
Smoker: non-smokers	323 (73.1)	108 (75.5)	104 (69.8)	0.07

Ex-smoker	107 (24.2)	30 (21)	44 (29.5)	0.08
Current-smoker	12 (2.7)	5 (3.5)	1 (0.7)	0.08
Ejection fraction, %	60.1±10.1	61.1±8.2	60.5±10.4	0.4
LVIDd, cm	4.9±0.9	4.8±1	5.1 ±0.8	0.004
LA diameter, cm	3.9±0.9	3.8±0.9	4.1±1	<0.001
LA volume, cm^2	64.7±29.4	61.8±25.2	69.9±31	0.007
NOAC	130 (29.44)	50 (35)	48 (32.2)	0.6
Warfarin	140 (31.7)	41 (28.7)	57 (38.3)	0.08
Aspirin	107 (24.24)	38 (26.6)	28 (18.8)	0.1
Beta-blockers	222 (50.2)	67 (46.9)	77 (51.7)	0.4
Digoxin	26 (5.9)	5 (3.5)	13 (8.7)	0.06
Flecainide	135 (30.5)	40 (28)	36 (24.2)	0.5
Sotalol	54 (12.2)	19 (13.3)	22 (14.8)	0.7
Amiodarone	23 (5.2)	8 (5.6)	10 (6.7)	0.7
Statins	155 (35.1)	52 (36.4)	65 (43.6)	0.2
ACEi/ARB	262 (59.34)	81 (56.6)	107 (71.8)	0.007
CCB	139 (31.4)	41 (28.7)	51 (34.2)	0.3
Diuretics	90 (20.4)	16 (11.2)	38 (25.5)	0.002
MRA	31 (7)	11 (7.7)	14 (9.4)	0.6

Abbreviations: LA=left atrium. NOAC=non-vitamin K oral anticoagulants.

ACEi=angiotensin converting enzyme inhibitors. ARB=angiotensin receptor blockers.

CCB=calcium channel blockers. MRA=mineralocorticoid receptor antagonist.

Figure 1

Patient selection flow diagram.

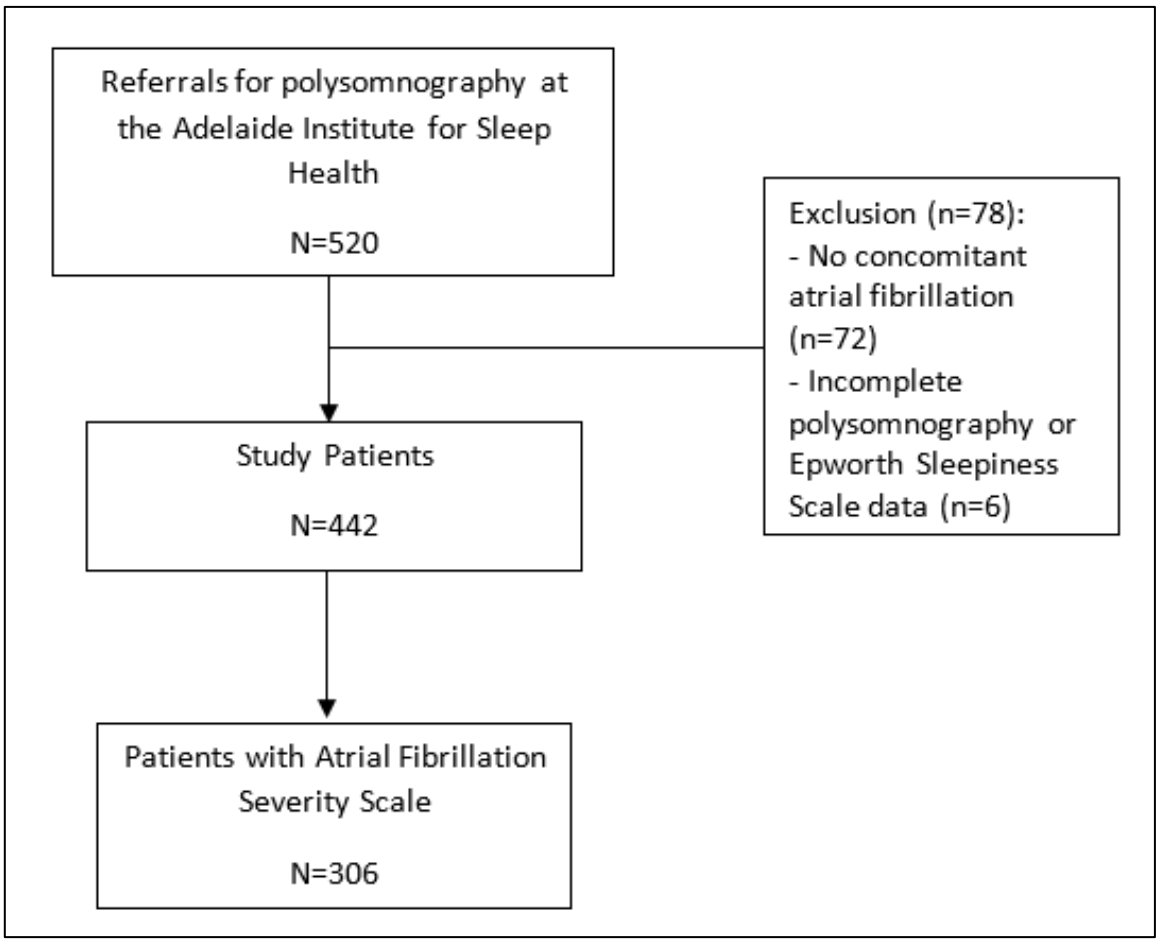


Figure 2

Distribution of patients per sleep-disordered breathing (SDB) category.

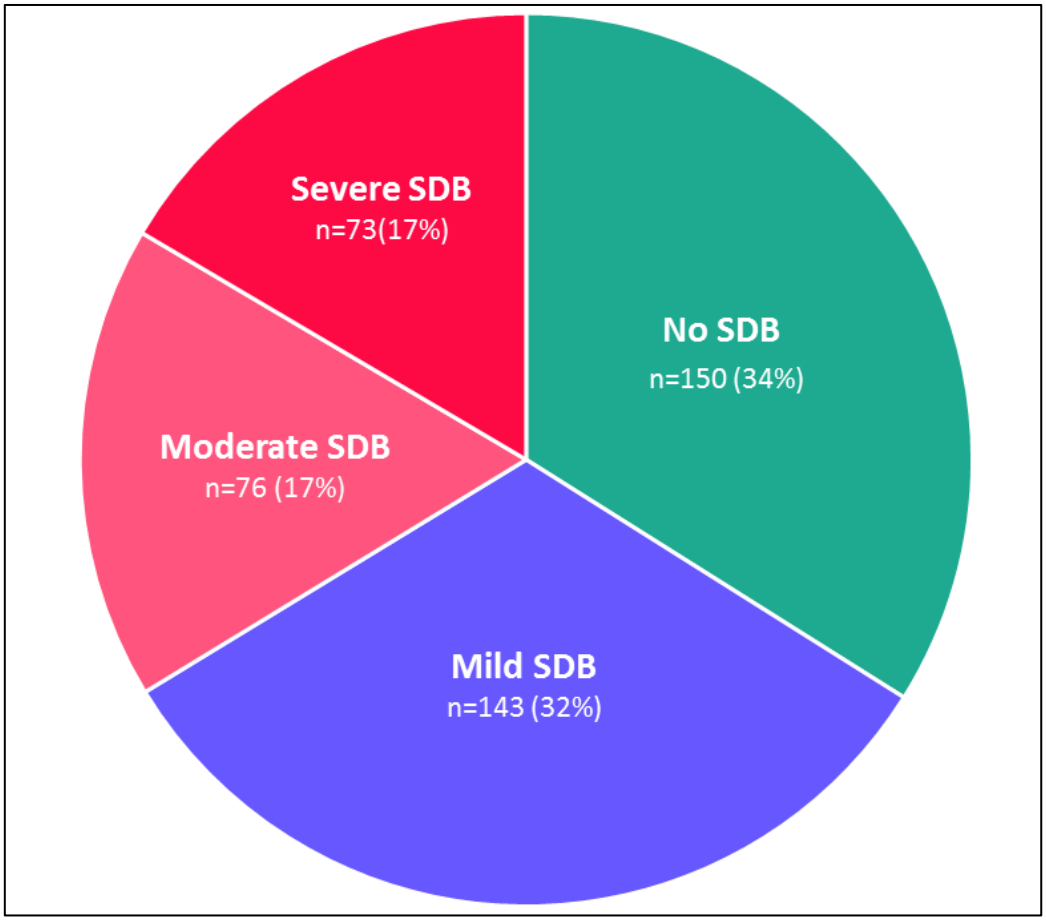


Figure 3

Scatter-plot of all cases stratified by presence and severity of sleep-disordered breathing (SDB). Y-axis represents the severity of sleepiness as assessed by Epworth Sleepiness Scale with identical-score cases stacked horizontally. Blue dotted line represents the thresholds for excessive daytime sleepiness (EDS).

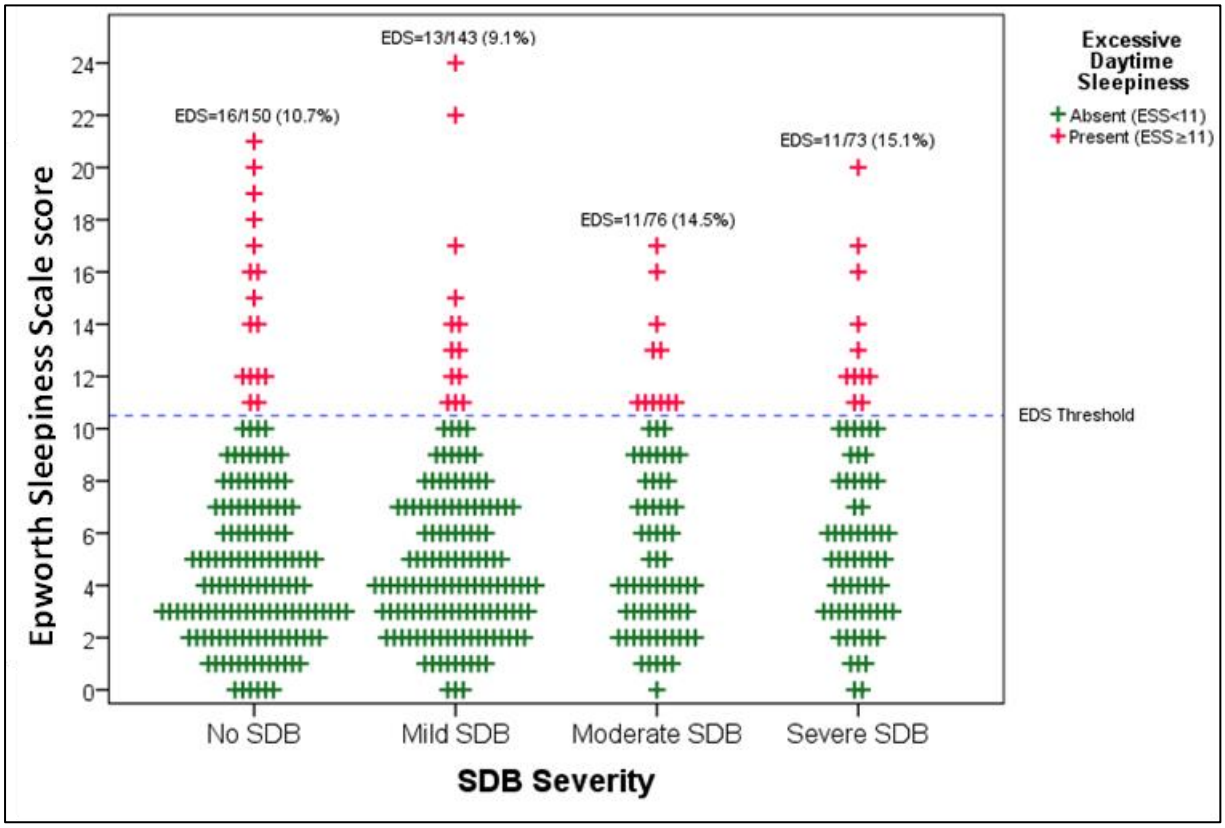


Figure 4

Correlation between Epworth Sleepiness Scale score and apnoea-hypopnoea index (AHI).

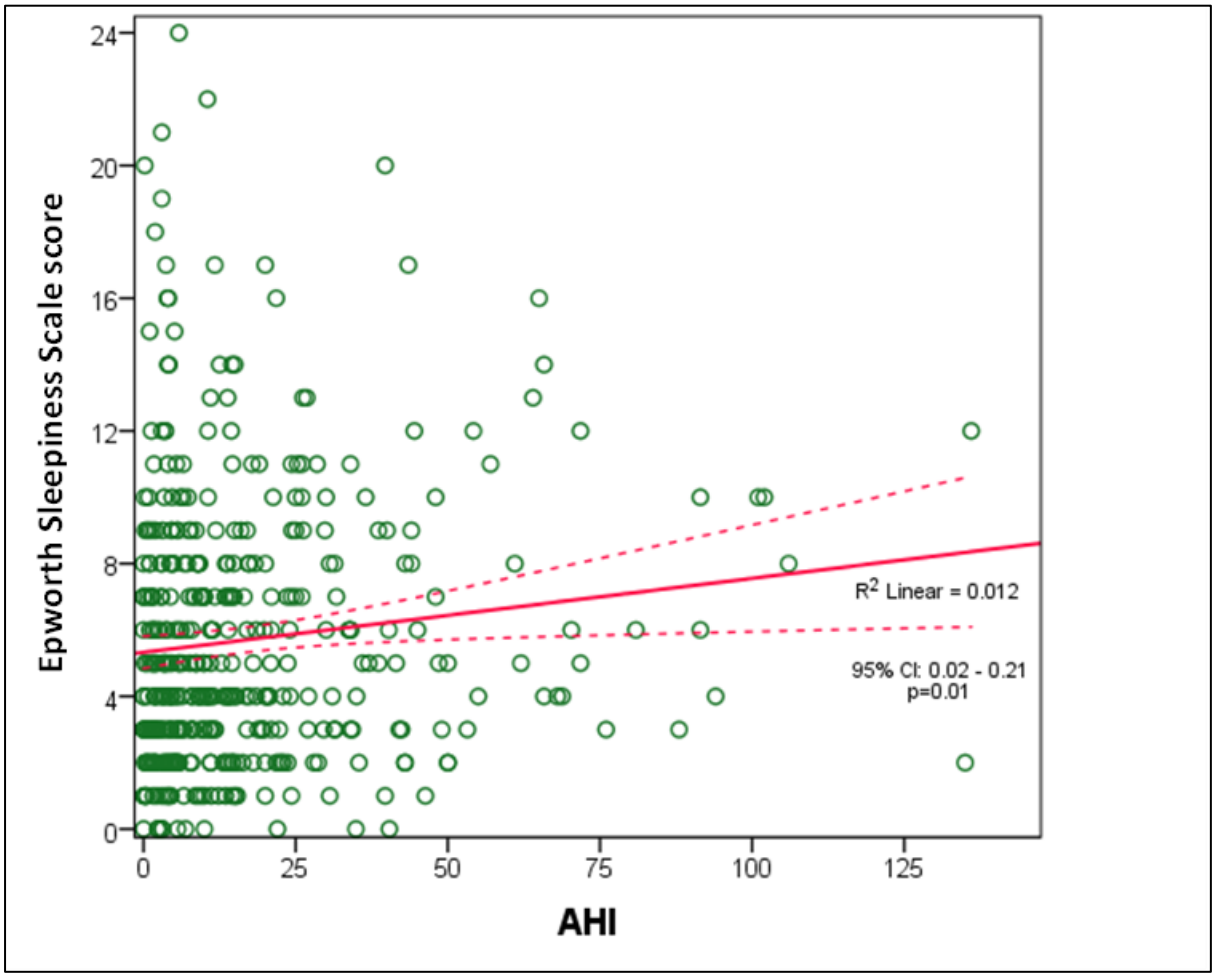


Figure 5

Receiver-operating-characteristic (ROC) curve analyses for the utility of Epworth Sleepiness Scale (ESS) to detect (clockwise from top left): Any sleep-disordered breathing (SDB), moderate SDB, severe SDB and moderate-to-severe SDB. Area under the curve (AUC) for any SDB=0.54 (95% CI: 0.48-0.6, p=0.17), AUC for moderate SDB=0.53 (95% CI: 0.45-0.6, p=0.47), AUC for severe SDB=0.57 (95% CI: 0.5-0.64, p=0.06) and AUC for moderate-to-severe SDB=0.56 (95%CI=0.5-0.62, p=0.04).

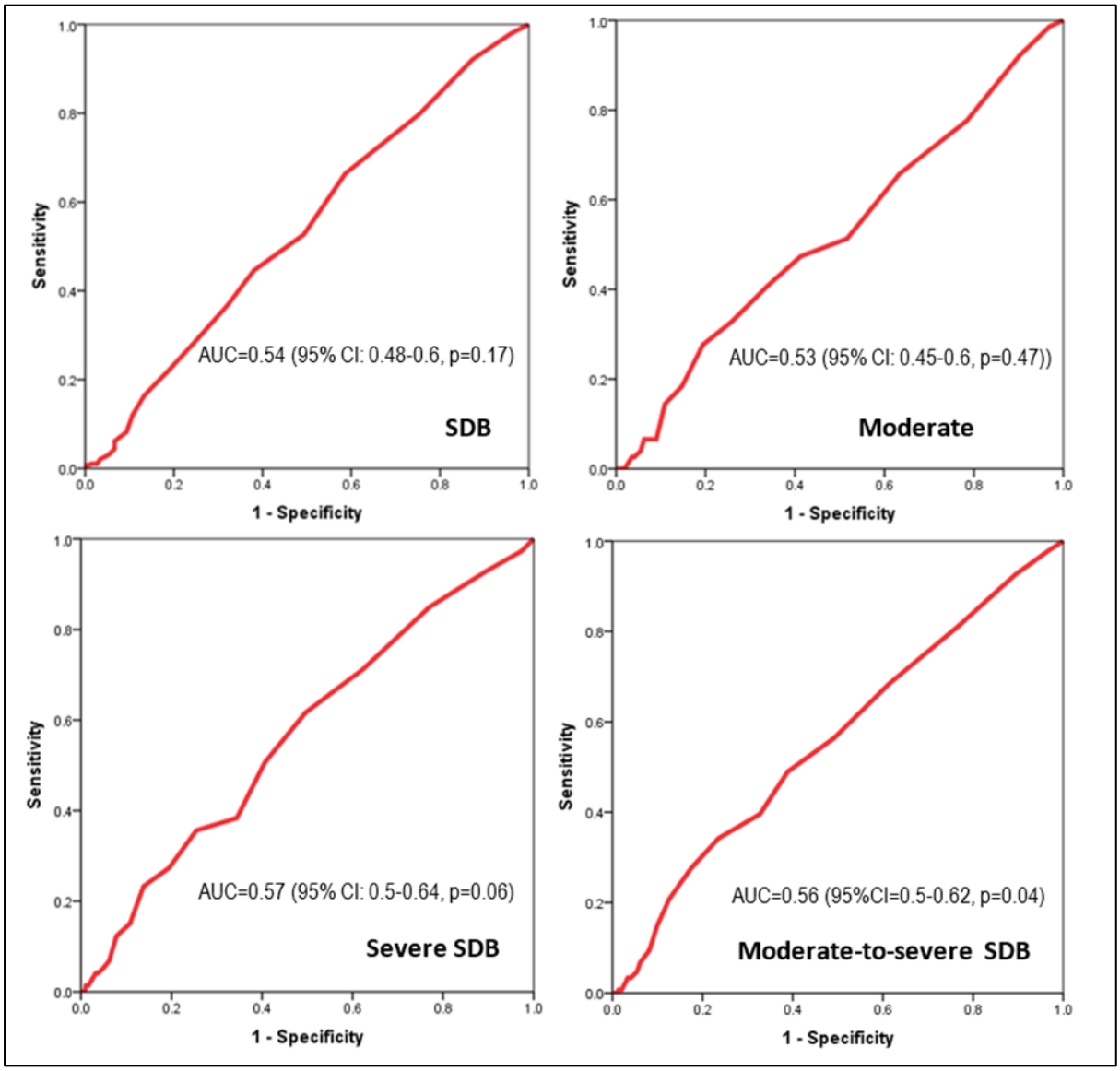
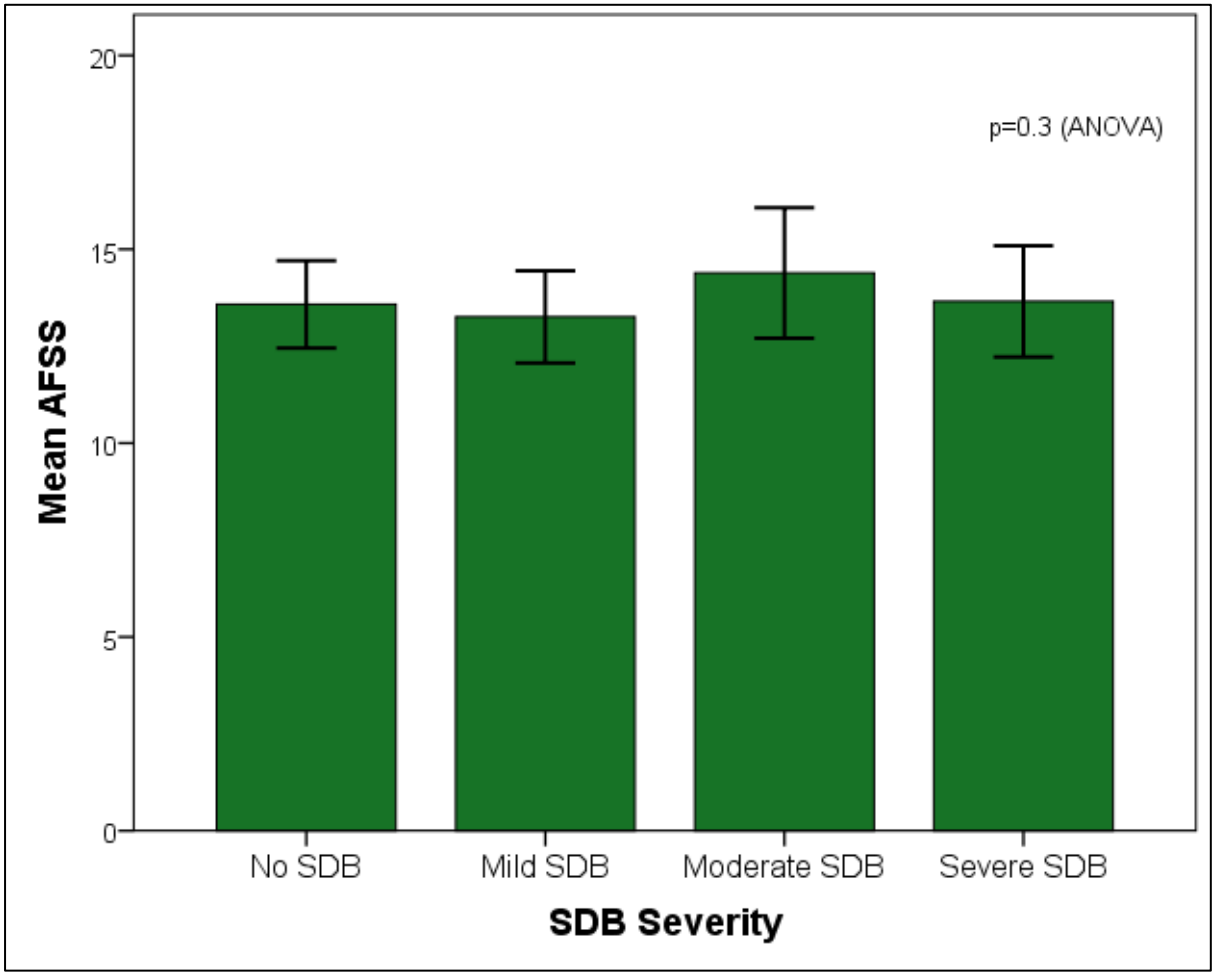


Figure 6

Mean (95% CI) atrial fibrillation severity scale (AFSS) by sleep-disordered breathing (SDB) category: No SDB: 13.6 (12.4-14.7). Mild SDB: 13.3 (12.1-14.4). Moderate SDB: 14.4 (12.7-16.1). Severe SDB: 13.7 (12.2-15.1). One-way analysis of variance (ANOVA), p=0.3.



Chapter 3: Prevalence and Assessment of Sleep-Disordered Breathing in Patients with Atrial Fibrillation: A Systematic Review and Meta-Analysis

3.1 Introduction

AF is the most common sustained cardiac arrhythmia in adults and is associated with substantial morbidity and mortality[540]. SDB, of which OSA is the main subtype, is increasingly recognised as an important modifiable risk factor for AF[541]. While there are multiple shared upstream risk factors between SDB and AF, there is evidence that the two conditions have a negative synergistic effect, and that their co-existence portends poorer outcomes[542]. Conversely, treatment of SDB has been shown to be associated with improved AF-related outcomes[543], leading international AF management guidelines to recommend identification and management of concomitant SDB in AF patients[544].

There are multiple challenges in detecting concomitant SDB in AF, such as lack of conventional SDB symptoms in AF patients[545]; healthcare access- and cost-related obstacles[546], together with a poor understanding of the true prevalence of SDB in the AF population[541]. Overcoming the latter would allow for an assessment of the extent of the problem that is comorbid SDB in AF, and thus enable heightened clinical awareness and informed healthcare and research resource allocation.

We therefore undertook this systematic review and meta-analysis in order to: 1) quantify the prevalence of SDB in AF; 2) assess the variability in SDB testing in available studies, where described; and 3) examine the association between baseline characteristics and the increased risk of concomitant SDB.

3.2 Methods

3.2.1 Literature Search

This systematic review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement and reported according to the MOOSE guidelines[547]. The electronic literature search was carried out through August 2020 with the aid of an experienced librarian and included MEDLINE (via PubMed), EMBASE, and CINAHL. The search strategy was designed for each database, using relevant text words and Medical Subject Headings that consisted of terms relating to AF and SDB or sleep apnoea. The search was limited to human studies but without language or year restrictions. Details of the search strategy are provided in **Table 1.**

The search results were evaluated by two independent reviewers (Kadhim Kadhim and Melissa Middeldorp) to find eligible articles. Disagreements were resolved by consensus. First, references were imported into EndNote X9 and duplicates were removed by an automated method. Second, irrelevant items identified by their reference type (conference abstracts, editorials, case reports, reviews and letters) were excluded. Then, assessment based on title and/or abstract identified references eligible for full text review. Articles were included in the study if they: 1) reported on the proportion of patients with SDB in an AF population; 2) included a minimum of 100 adult (≥18 years) participants; and 3) reported on the method of SDB ascertainment. Standardised classification of the types of sleep studies was adopted[313]. Level 1 sleep studies were classified as attended polysomnography, level 2 as unattended polysomnography, level 3 as ambulatory polygraphy and level 4 as pulse oximetry.

For the meta-analysis, further requirements were needed: 1) systematic use of a level 1-3 SDB test in all the studied sample; 2) clear definition of test cut-offs used to establish SDB diagnosis; and 3) that the AF population was not pre-selected prior to SDB testing (e.g. by using the Berlin Questionnaire).

3.2.2 Data extraction and outcomes

Data were extracted by two reviewers independently (KK and MEM) using bespoke electronic data collection forms (Microsoft Access 2016) based on the Cochrane Consumers and Communication Review Group's data extraction template and refined accordingly. For each study, the following parameters were extracted: authors, year, study design, sample size, setting (inpatient or outpatient), follow-up period, outcome measures and dates of study start/end. For the population studied, several baseline characteristics were extracted including age, male sex, body mass index (BMI), type of AF and the prevalence of diabetes, hypertension and previous stroke or transient ischemic attack (TIA). In cases where the variables of interest were only provided for subgroups, categorical variables for the studied populations were summed across subgroups, and combined means ± standard deviations (SD) were calculated using the recommended formulae from the Cochrane Handbook for Systematic Reviews of Interventions[548]. The outcomes of interest were the number of patients diagnosed with SDB, the method of SDB assessment and diagnostic cut-offs used.

3.2.3 Analysis

Data synthesis was performed by summarizing study and population characteristics. Dichotomous outcomes were summarized as numbers and proportions, while continuous variables were reported as means ± SD or median and interquartile range (IQR) as appropriate. The prevalence of patients diagnosed with SDB was calculated as the proportion of those with SDB in the studied population, and the standard error (SE) of the estimate was calculated. Pooled prevalence was calculated using random effects modelling and inverse variance estimates. To explore factors associated with increased SDB prevalence, we included studies where SDB was diagnosed using poly(somno)graphy and reported on SDB prevalence using clear definitions. Those factors were chosen *a priori* by authors' consensus based on existing literature, and related data were pooled to calculate odds ratio (OR), weighted mean difference (WMD), and 95% confidence intervals (95% CIs) using the DerSimonian–Laird random-effects model.

The percentage of variability across the pooled estimates attributable to heterogeneity beyond chance was estimated using the I^2 statistic and by calculating the *P* value for heterogeneity. Subgroup analysis was planned *a priori* stratified by type of AF (persistent AF only versus mixed AF (i.e. paroxysmal and paroxysmal or persistent) and level of SDB test (1-3). Analyses were performed in Review Manager 5.4 (Cochrane Collaboration, Oxford, UK) and R Version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria). For all analyses, a *P* value of <0.05 was considered statistically significant.

3.2.4 Assessment of methodological quality

The methodological quality of each paper was assessed independently by the authors (KK and MEM), and disagreements were resolved by consensus or arbitration of a supervisor. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomised studies in meta-analyses was utilised. The NOS uses predefined criteria and awards stars for each study: 4 for quality of patient selection, 2 for comparability between cases and controls and 3 stars for the adequate ascertainment of exposure, which in our study is the ascertainment of SDB. Given that our analysis related to prevalence, studies were regarded as single-arm only and therefore the section relating to comparability was omitted, with a maximum of 7 stars per study (**Figure 1)**. We considered studies with 6-7 stars as good quality, 4-5 stars as moderate quality and ≤3 stars as weak quality.

3.3 Results

3.3.1 Search Results

The literature search resulted in 2758 potentially relevant records from the three electronic databases. After assessment and exclusion, 33 studies comprising 23,894 patients were included in the qualitative analysis **(Figure 2).** None of the studies were randomised trials, and 5 were case-control studies (**Table 2).** Eighteen studies (55%) included patients undergoing AF ablation, four studies (12%) reported on patients undergoing electrical cardioversion and, in the remainder, (11 studies, 30%) no specific AF intervention was reported. Most studies were of good quality (N=20), 8 were of moderate quality and 5 were deemed to have poor methodological quality pertaining to our study's questions **(Table 3).**

3.3.2 SDB Prevalence

Thirteen studies comprising 2,660 patients met the inclusion criteria for SDB prevalence meta-analysis. For an SDB diagnostic cut-off of AHI ≥ 5/hr, 10 studies with 2,278 AF patients were included. The pooled prevalence of SDB was 78% (95% CI: 70-86%). The prevalence of SDB in the persistent AF subgroup was 83% (95% CI: 72-93%) and 76% in the mixed AF subgroup (95% CI: 65-86%) with no significant difference between subgroups (Chi^2 for subgroup difference *P*=.35). The individual study prevalence ranged from 46% to 92% (**Figure 3A).**

For moderate-to-severe SDB (AHI ≥ 15), data from 11 studies (N=2,379 patients) were meta-analyzed yielding an estimated pooled prevalence of 40% (95% CI: 32-48%, *P*<.001). The SDB prevalence in the persistent AF subgroup did not differ from that of the mixed subgroup (41% vs 40%, *P*=0.95) (**Figure 3B).** For both AHI cut-offs analyses, there was a high degree of heterogeneity observed (I^2 = 96% and 94% respectively, *P*<.001 for both) which did not significantly change across the subgroups. Explorative sensitivity analyses failed to identify potential sources of this heterogeneity (**Figure 4).**

3.3.3 SDB Ascertainment

Most studies (N=22, 67%) used a level 1-4 test to ascertain the presence of SDB in a total of 7409 (31%) patients (**Figure 5).** Pulse oximetry was used in 3 (9%) studies which included 571 (2.4%) patients.

Questionnaire-based tools (Berlin-Questionnaire or STOP-BANG) were used in 8 (24%) of studies which included 2487 patients (19% of the population). Three studies

relied on self-reports and 1 study used international classification of disease (ICD) coding. **(Table 2).**

3.3.4 SDB Diagnostic Thresholds

For studies where a level 1-4 sleep test was used (N=22), the main SDB definition used was AHI ≥ 5 in 12 (55%) studies, followed by AHI ≥ 15 (N=4, 18%). One study used AHI ≥ 10 as the cut-off, one used ≥ 30, and one study did not provide a clear definition of SDB. These studies ranged in their reported prevalence between 10-92%.

The three studies using level 4 pulse oximetry used 3 different oxygen-desaturation index (ODI) thresholds (5, 10 and 15/hr) with variable oxygen desaturation threshold (3% in 1 study, 4% in 2) **(Table 2).**

The most common questionnaire-based assessment was Berlin-Questionnaire (BQ), which was used in 7 of the 8 studies where questionnaires were utilized. The prevalence of SDB using a high risk BQ (defined as 2 positive categories out of 3) ranged between 3-58% **(Table 2).** For explorative purposes, the pooled prevalence of SDB using questionnaires was 33% (95% CI: 0.18-0.47, *P<.001*) (**Figure 6).**

3.3.5 SDB Correlates

Table 2 summarizes the association between selected baseline characteristics and SDB, stratified by the severity of SDB. Age, body mass index (BMI), hypertension and diabetes were significantly associated with the presence of SDB, regardless of its severity. Analysis based on age was possible for 7 studies comprising a total of 1825 patients and found that SDB patients were older than controls (weighted mean difference (WMD)= 5.72 years, 95% CI: 3.03-8.42, P<.001) but with high

heterogeneity (I^2 = 83%). Interestingly, that association weakened with AHI ≥ 15/hr (WMD=2.30 years, 95% CI: 0.27-4.33, P=0.03). Male gender was associated with double the risk of having SDB (pooled odds ratio (OR)=2.01, 95% CI: 1.60-2.52, P<.001, I^2=0%) but that association was not statistically significant for moderate-to-severe SDB. Similarly, non-paroxysmal AF was strongly associated with SDB when a cut-off of AHI ≥ 5/hr was used but that association became insignificant when tested across the studies with AHI ≥15/hr as the threshold **(Table 4).**

3.4 Discussion

Our study's principal finding is that SDB is highly prevalent in patients with AF. Three-in-four AF patients have concomitant SDB of any degree, and nearly half suffer with moderate-to-severe SDB. We also found that while the majority of studies use poly(somno)graphy to test for SDB, wide variation exists in the diagnostic cut-offs used, and a significant proportion of studies rely on questionnaire-based tools to assess for the presence of SDB**.**

The association between SDB and AF has been increasingly studied. Gami et al demonstrated a significantly increased risk of incident AF in younger patients (<65 years old) with OSA compared to controls[397], and Tung et al showed that central sleep apnoea (CSA) is independently associated with increased AF risk.[549] This risk appears to be mediated by the severity of SDB in a dose-response fashion, with another study showing that more severe forms of OSA are associated with higher risk of developing AF[404]. Conversely, our study demonstrates that SDB exists in a significantly large proportion of AF patients highlighting the important interaction between the two conditions. That interaction can potentially be explained by the number of shared upstream risk factors for both conditions, such as age and

metabolic syndrome.[550], both were found to be increasing the risk of SDB in the AF population in our study. However, there is evidence to suggest that this relationship may go beyond association, with plausible pathophysiological mechanisms that contribute to AF initiation and maintenance.[541, 551] This is further supported by the findings that targeted therapies of the underlying conditions improves the chances of sinus rhythm maintenance in patients with AF in observational studies.[532, 552]

International AF management guidelines recommend SDB assessment and treatment of concomitant SDB in order to improve treatment success and quality of life for patients[540, 553]. However, detection of SDB can be challenging. The gold-standard test of polysomnography is time- and resource-intensive, and its availability may be limited in many healthcare settings. Consequently, simpler tests have been developed and validated aiming to increase availability, such as home sleep-apnoea tests (HSAT). These however come at the expense of some loss of accuracy, which should be balanced against efficiency and patient care[313]. This perhaps explains the inter-study variation seen in terms of SDB prevalence, owing to the use of different tests and diagnostic cut-offs. Additionally, the main metric used in the diagnosis of SDB is AHI, which provides an indexed number of apnoeic and hypopnoeic events, but fails to sufficiently reflect many of the relevant SDB characteristics such as the type (central versus obstructive), extent and duration of each event, the total nocturnal hypoxaemic burden or variability based on sleep stages or sleeping positions[554]. Given the significant nightly variation in SDB severity, the overall SDB prevalence and that of moderate-to-severe SDB may well be under-represented. When longer-term SDB monitoring is used, for example by pacemaker-based respiratory disturbance indices (RDI), up to 85% of patients with paroxysmal AF had

at least one night of RDI 20/hour indicative of severe SDB, but only 32% of patients had consistently raised RDI[352].

Importantly, the variation in SDB assessment found in our qualitative analysis was remarkable, consequently hindering the interpretation of existing studies exploring the role of SDB in AF since comparability across those studies may be limited. The American Academy of Sleep Medicine strongly recommends against the use of clinical tools and questionnaires to diagnose SDB in the absence of PSG or HSAT, since these are prone to error[313]. This is at odds with our findings, with some studies relying solely on questionnaire-based tools, mainly the Berlin Questionnaire, to diagnose OSA. This casts doubts on the validity of those studies' findings and is not conducive to furthering our understanding of the complex relationship between SDB and AF. These studies have been excluded from our quantitative analysis.

Assessing the scale of the problem that is concomitant SDB and AF is the first step to addressing it, both from a clinical perspective and for research purposes. Previous smaller observational studies have had conflicting findings, with some reporting an SDB prevalence as low as 3%[555], and others as high as 92%[556]. Ours is the first study to systematically quantify the prevalence of SDB in the AF population utilising data from nearly 2500 patients. Our findings support that concomitant SDB is highly prevalent in AF patients. Future large-scale prospective studies can be instrumental in furthering our understanding of the true prevalence of SDB in AF, by implementing longitudinal assessment methods.[557]

3.4.1 Limitations

We observed high heterogeneity in the SDB prevalence in our study, which probably reflects the variation in SDB diagnostic approaches. Despite the large number of

patients included, the number of studies is relatively low which limits the ability to explore the factors behind the observed heterogeneity, for example using meta-regression. While we adhered to a clear and systematic inclusion criterion, it is possible that selection bias exists in the original studies which would subsequently introduce bias in our findings. However, short of a large prospective study in an unselected AF population using polysomography, and to the best of our knowledge, our study provides the first comprehensive assessment of SDB prevalence in the AF population. Finally, we focused on SDB diagnosed by AHI thresholds, but did not investigate the prevalence of central versus obstructive sleep apnoea, or the neuropsychological consequences of SDB, hypoxemia, arousals or sleep quality, which all have been individually related to AF prevalence[558].

3.4.2 Conclusions

SDB is highly prevalent in the AF population, with over three quarters of AF patients having concomitant SDB of any degree, and nearly half with moderate-to-severe SDB. Wide variation exists in the diagnostic tools and thresholds used to detect concomitant SDB in AF. Prospective, systematic testing for SDB in unselected cohorts of AF patients may be required to define the true prevalence of SDB in this population.

3.5 Tables and Figures

Table 1

Search strategy.

Pumbed:	(((((Atrial fibrillation[Title/Abstract]) OR Atrial arrhythmia[Title/Abstract]) OR AF[Title/Abstract]) OR Atrial fibrillation[MeSH Terms])) AND ((((Sleep-disordered breathing[Title/Abstract]) OR Sleep apnoea[Title/Abstract]) OR Sleep apnea[Title/Abstract]) OR Sleep Apnea Syndromes[MeSH Terms])
Embase:	('atrial fibrillation':ab,ti OR 'heart atrium arrhythmia':ab,ti) AND ('sleep disordered breathing':ab,ti OR 'sleep apnea':ab,ti OR 'sleep apnoea':ab,ti OR 'sleep-disordered breathing':ab,ti) AND [embase]/lim
CINAHL:	((TI atrial fibrillation or afib or af) OR (AB atrial fibrillation or afib or af) OR (MH "Atrial Fibrillation") OR (MH "Arrhythmia, Atrial+")) AND ((TI sleep apnea or apnea or obstructive sleep apnea) OR (AB sleep apnea or apnea or obstructive sleep apnea) OR (TI sleep disordered breathing) OR (AB sleep disordered breathing) OR (MH "Sleep Apnea Syndromes+"))

Table 2

Study characteristics of the included studies.

	Study	Study Design	Dates	Sample Size	Age, years, mean ± SD or median [IQR]	Men (%)	PAF (%)	BMI, Kg/m^2, mean ± SD or median [IQR]	SDB Prevalence (%)	Consecutive screening	SDB ascertainment	SDB definition
1	Abumuamar 2019[559]	Cohort	Jun 2016 - Mar 2017	100	63 ± 13	70	29	29 ± 6	85	Y	PSG – level 2	AHI ≥ 5
2	Albuquerque 2012[528]	Cohort	Jun 2004 - Apr 2009	151	69.1 ± 0.9	76.2	0	34.1 ± 0.7	81.5	Y	PSG – level 1	AHI ≥ 5
3	Bitter 2009[560]	Cohort	Jan 2006 - Dec 2007	150	66.1 ± 1.7	73.3	0	29.2 ± 2.1	74	Y	PG – level 3	AHI ≥ 5
4	Calvo 2016[561]	Case-control	Not reported	115	46 ± 10	87	60	26 ± 3	34.8	Y	BQ‡	BQ ≥ 2
5	Chilukuri 2009[562]	Cohort	Not reported	210	58 ± 10	79.5	56.7	29 ± 5	43.8	Y	BQ	BQ ≥ 2

6	Farrehi 2015[563]	Cohort	Jan 2011 - Oct 2011	247	62.5 ± 10.3	73.3	49.4	51.80*	87	Y	Self-report & SB	Self-report &/or SB ≥ 3
7	Fox 2016[556]	Cohort	Not reported	138	67.8 ± 10.3	67.3	0	28.7 ± 4.8	92	Y	PG – level 3	AHI ≥ 5
8	Gami 2004[399]	Case-control	Not reported	151	71 ± 12	64.2	0	29 ± 6	49	Y	BQ†	BQ ≥ 2
9	Groh 2019[295]	Cohort	Mar 2017	957	63 [52 – 74]	66.9	100	N/A	17.3	N	Self-reported	Not provided
10	Guo 2019[564]	Cohort	Jan 2008 - Dec 2014	2720	59.7 ± 9.7	70.8	NA	20.40*	29.1	N	ICD-9/10	Not provided
11	Hojo 2019[565]	Cohort	Aug 2013 - Sep 2015	100	62.9 ± 11.7	71	89	24.3 ± 3.5	34	Y	PG – level3§	AHI ≥ 15
12	Holmqvist 2015[542]	Cross-sectional	Jun 2010 – Aug 2011	10321	75 [67 – 82]	58	51	29 [25-34]	17.8	N	Clinical registry	Not provided
13	Jongnarangsin 2008[566]	Cohort	Jul 2005 - Jul 2006	324	57 ± 11	75.9	72.2	43*	9.9	N	PSG - undetermined	Not provided
14	Kadhim 2019[567]	Cohort	Jan 2009 - Mar 2017	442	60 ± 11	69.2	61.8	30.5 ± 5.2	66.1	Y	PSG – level 1	AHI ≥ 5

15	Kaitani 2016[568]	Cohort	Dec 2011 - May 2014	246	65 [59-70]	76.8	64.2	23.6 [22-25]	71.5	Y	PO – level 4	ODI (3%) ≥ 5
16	Kawakami 2016[569]	Cohort	Aug 2010 - Jun 2014	124	62 ± 10	68.5	66.9	24 ± 3.2	44.4	Y	PG – level 3	AHI ≥ 15
17	Kimura 2015[570]	Cohort	Not reported	134	59.6 ± 9.4	88.8	61.9	24.8 ± 3.2	23.9	Y	PO – level 4	ODI ≥ 15
18	Kohno 2018[571]	Cohort	Not reported	197	60 ± 9	94.9	56.3	25 ± 3	68.5	Y	PG – level 3	AHI ≥ 10
19	Matiello 2010[572]	Cohort	Jan 2005 - Dec 2007	174	52.5 ± 11.4	77.6	56.3	27.3 ± 3.3	24.1	Y	BQ‡ & PG – level 3	BQ ≥ 2 and AHI>10
20	Mazza 2009[573]	Cohort	Jan 2004 - Mar 2006	158	69 ± 12	53.2	0	28.2 ± 5.3	31	Y	PSG - undetermined	AHI ≥ 15
21	Mohanty 2014[574]	Case-control	Aug 2008 - April 2011	1257	62.2 ± 10.8	72.6	30.2	29.3 ± 6.2	18.9	N	BQ	BQ ≥ 2
22	Naruse 2013[498]	Cohort	Aug 2009 - Jan 2011	153	60 ± 9	83.7	53.6	25 ± 3.5	75.8	Y	PSG – level 1	AHI ≥ 5
23	Park 2014[555]	Cohort	May 2010 - Apr 2012	155	56 ± 10.6	73.5	100	24.8 ± 3.2	2.6	Y	BQ	BQ ≥ 2

24	Patel, D 2010[496]	Case-control	Jan 2004 - Dec 2007	3000	57 ± 11	77.2	54.3	27.1 ± 5.1	21.3	N	PSG – undetermined	AHI ≥ 15
25	Patel, NJ 2017[575]	Case-control	Not reported	132	67 ± 13	68.2	0	35 ± 9	37.9	N	PSG – undetermined	AHI ≥ 30
26	Shah 2014[576]	Cohort	Sep 2005 - Jun 2011	403	57 [49-64]	72	34.2	28.7 [25.7-31.8]	18.6	Y	PSG – undetermined	AHI ≥ 5
27	Shapira-Daniels[577] 2020	Cohort	Jan 2015 – Dec 2016	188	62 ± 11.3	65.4	45.7	29.2 ± 5.5	82.4	Y	PG – level 2	AHI ≥ 5
28	Szymanski 2014[578]	Cohort	Not reported	266	57.6 ± 10.1	65	69.5	29.7 ± 5	45.5	Y	PG – level 3	AHI ≥ 5
29	Takagi 2020[579]	Cohort	Apr 2016 - Dec 2018	111	64.4 ± 9.7	80.2	63.1	24.7 ± 4.6	91.9	Y	PG – level 3¶	AHI ≥ 5
30	Tang 2009[580]	Cohort	Jan 2007 - Nov 2007	178	57.2 ± 11.4	68.5	100	25.6 ± 3.3	58.4	Y	BQ†	BQ ≥ 2
31	Tanigawa 2018[581]	Cohort	Not reported	191	55.7 ± 8.7	90.6	55	24.8 ± 2.9	16.8	Y	PO – level 4	ODI (4%) > 10

32	Traaen 2020[394]	Cohort	Aug 2015 - Dec 2018	579	59.9 ± 9.6	72.9	100	28.5 ± 4.5	82.7	Y	PG – level 3	AHI ≥ 5
33	van Oosten 2012[582]	Cohort	Jan 2008 - Dec 2009	122	68.3 ± 10.4	75.4	73.8	30.4 ± 5.8	27	N	PSG – undetermined	AHI ≥ 5

* reported as proportion of obesity (BMI >30 Kg/m^2), †: a subset also underwent polysomnography as a validation cohort. ‡: high risk BQ underwent P(S)G. § patients with AHI 10-40 underwent level 2 PSG. ¶: moderate-to-severe AHI patients underwent level 1 PSG.

Abbreviations: AHI: apnoea-hypopnea index. BMI: body mass index. BQ: Berlin Questionnaire. ODI: oxygen desaturation index. PAF: paroxysmal atrial fibrillation. PSG: polysomnography. PG: polygraphy. PO: pulse oximetry. SB: STOP-BANG questionnaire. SDB: sleep-disordered breathing.

Table 3

Quality assessment summary of the included studies.

	Study	Representativeness	Outcome	Total	
1	Abumuamar 2019	***	***	6	Good
2	Albuquerque 2012	***	***	6	Good
3	Bitter 2009	****	***	7	Good
4	Calvo 2016	*	**	3	Poor
5	Chilukuri 2009	***	**	5	Moderate
6	Farrehi 2015	***	*	4	Moderate
7	Fox 2016	***	***	6	Good
8	Gami 2004	**	***	5	Moderate
9	Groh 2019	**	*	3	Poor
10	Guo 2019	***	**	5	Moderate
11	Hojo 2019	****	***	7	Good
12	Holmqvist 2015	***	**	5	Moderate
13	Jongnarangsin 2008	***		3	Poor
14	Kadhim 2019	****	***	7	Good
15	Kaitani 2016	***	***	6	Good
16	Kawakami 2016	***	***	6	Good
17	Kimura 2015	****	***	7	Good
18	Kohno 2018	****	***	7	Good
19	Matiello 2010	***	***	6	Good
20	Mazza 2009	***	***	6	Good
21	Mohanty 2014	**		2	Poor
22	Naruse 2013	***	***	6	Good
23	Park 2014	***	*	4	Moderate
24	Patel 2010	***	*	4	Moderate
25	Patel 2017	*	**	3	Poor

26	Shah 2014	****	***	7	Good
27	Shapira-Daniels 2020	****	***	7	Good
28	Szymanski 2014	****	***	7	Good
29	Tang 2009	****	*	5	Moderate
30	Takagi 2020	****	***	7	Good
31	Tanigawa 2018	****	***	7	Good
32	Traaen 2020	****	***	7	Good
33	vanOosten 2012	****	**	6	Good

Table 4

Univariate association between baseline characteristics and the presence of SDB, stratified by SDB severity

Factor	N of Studies	N of Patients	Statistical method	Pooled Estimate [95% CI]	P value	Heterogeneity Tau^2	Heterogeneity I^2
AHI ≥ 5/hr							
Age	7	1825	WMD	5.72 [3.03, 8.42]	<.001	9.95; Chi^2 = 36.24, df = 6 (P=<.001)	I^2 = 83%
Male	7	1825	OR	2.01 [1.60, 2.52]	<.001	0.00; Chi^2 = 4.29, df = 6 (P=.64)	I^2 = 0%
Body mass index	7	1825	WMD	2.26 [1.86, 2.66]	<.001	0.00; Chi^2 = 2.37, df = 5 (P=.80)	I^2 = 0%
Hypertension	6	1675	OR	2.12 [1.49, 3.00]	<.001	0.07; Chi^2 = 8.40, df = 5 (P=.14)	I^2 = 40%
Non-paroxysmal AF	4	996	OR	1.88 [1.40, 2.52]	<.001	0.00; Chi^2 = 2.14, df = 3 (P=.54)	I^2 = 0%
Diabetes	6	1675	OR	2.50 [1.58, 3.98]	0.001	0.08; Chi^2 = 4.90, df = 5 (P=.43)	I^2 = 0%

Stroke/TIA	5	1487	OR	2.23 [0.97, 5.13]	0.06	0.35; Chi² = 6.75, df = 4 (P=0.15)	I² = 41%
AHI ≥ 15/hr							
Age	4	1398	WMD	2.30 [0.27, 4.33]	0.03	2.78; Chi² = 9.40, df = 3 (P=.02)	I² = 68%
Male	4	1398	OR	1.39 [0.90, 2.17]	0.14	0.11; Chi² = 7.22, df = 3 (P=0.07)	I² = 58%
Body mass index	4	1398	WMD	2.72 [1.98, 3.47]	<.001	0.23; Chi² = 4.99, df = 3 (P=.17)	I² = 40%
Hypertension	4	1398	OR	1.73 [1.35, 2.21]	<.001	0.00; Chi² = 1.88, df = 3 (P=.60)	I² = 0%
Non-paroxysmal AF	2	553	OR	0.87 [0.12, 6.49]	0.89	1.99; Chi² = 17.41, df = 1 (P<0.001)	I² = 94%
Diabetes	4	1398	OR	2.28 [1.35, 3.86]	0.002	0.12; Chi² = 5.06, df = 3 (P=.17)	I² = 41%
Stroke/TIA	4	1398	OR	1.33 [0.57, 3.09]	0.51	0.46; Chi² = 8.24, df = 3 (P=.04)	I² = 64%

Figure 1

Modified Newcastle-Ottawa Quality Assessment Scale.

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories.

Selection

1) Representativeness of the exposed cohort
   a) Truly representative of the average atrial fibrillation (AF) population*
   b) somewhat representative of the average AF population *
   c) selected group of AF patients
   d) no description of the derivation of the cohort

2) Selection of the non-exposed cohort
   a) drawn from the same community as the exposed cohort *
   b) drawn from a different source
   c) no description of the derivation of the non-exposed cohort

3) Ascertainment of exposure
   a) secure record (eg surgical records) *
   b) structured interview *
   c) written self-report
   d) no description

4) Demonstration that outcome of interest was not present at start of study
   a) yes *
   b) no

Outcome

1) Sleep-disordered breathing (SDB) was assessed by:
   a) independent blind assessment *
   b) record linkage *
   c) self-report
   d) no description

2) Was SDB systematically assessed?
   a) yes (select an adequate follow up period for outcome of interest) *
   b) no

3) Adequacy of assessment: SDB was diagnosed using a sleep study?
   a) Yes – details provided *
   b) Yes – but method not clear *
   c) No sleep studies
   d) no statement

Figure 2

PRISMA chart of study selection.

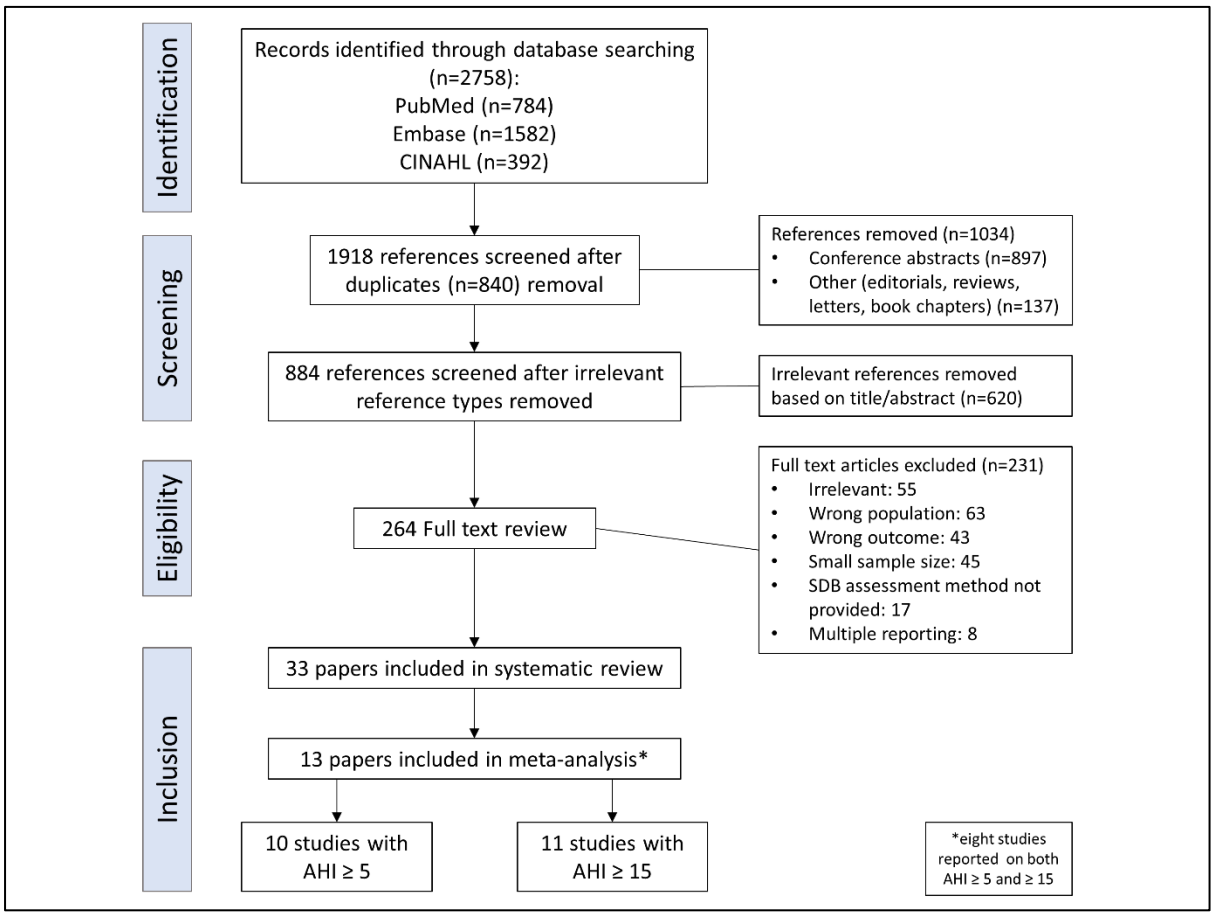


Figure 3

Forest plot of prevalence of SDB in AF patients stratified by type of AF (persistent AF only versus paroxysmal or persistent AF).

A: for any SDB. **B:** for moderate-to-severe SDB.

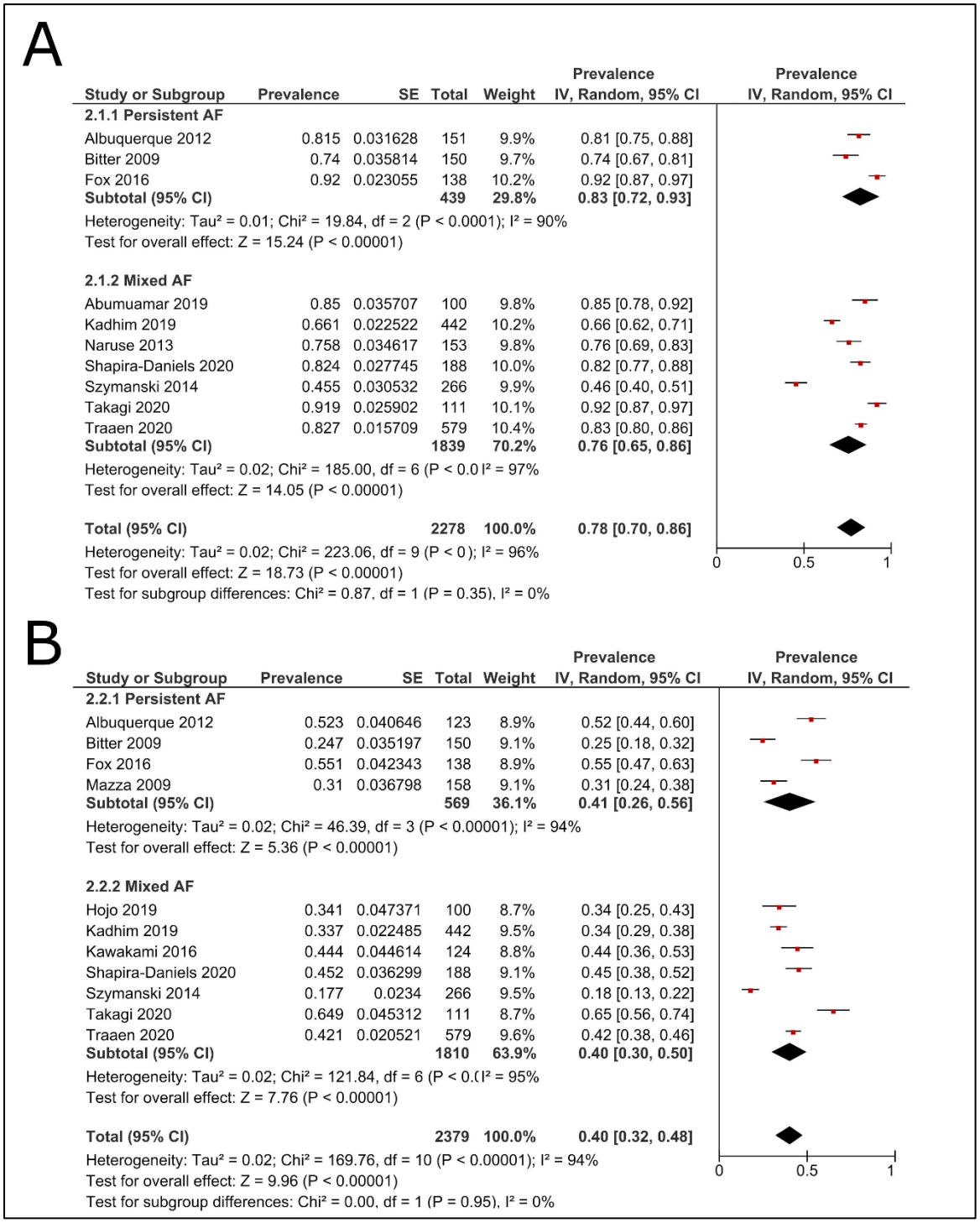


Figure 4

Sensitivity analysis: Forest plot of prevalence of SDB in AF patients stratified by SDB test type. A: for any SDB. B: for moderate-to-severe SDB.

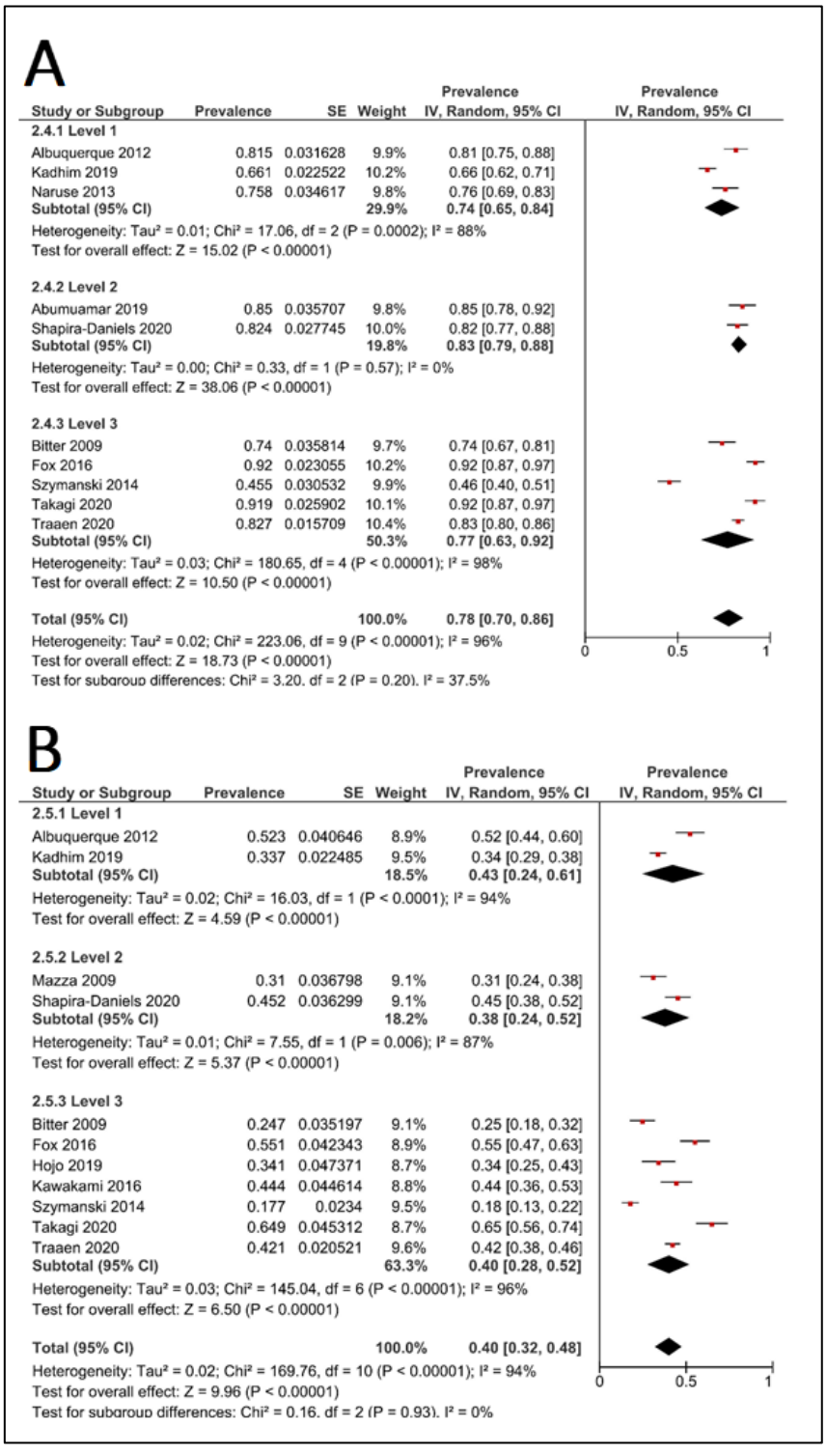


Figure 5

Graphical representation of the SDB ascertainment methods used. A: stratified by the number of studies. B: stratified by the population included across studies.

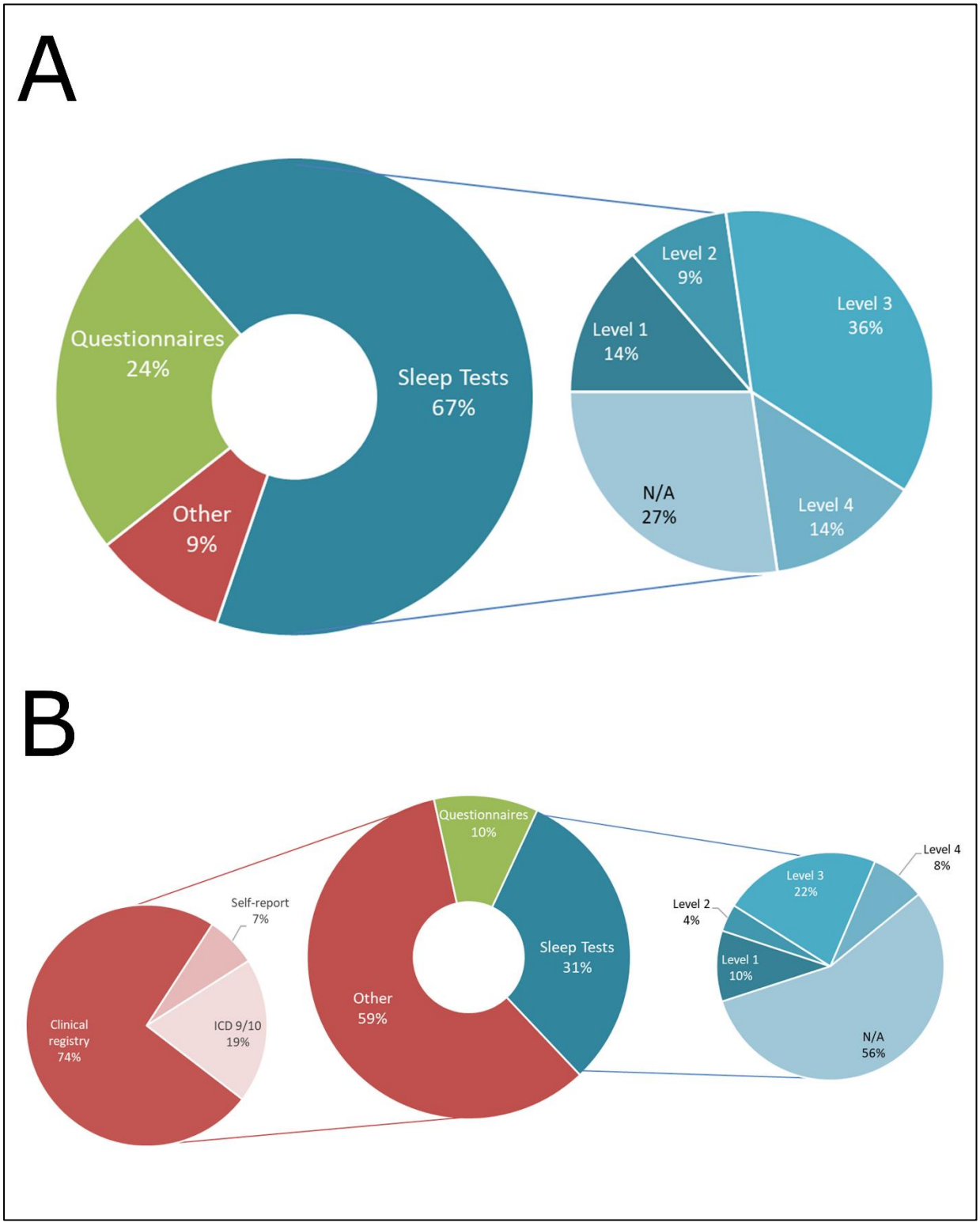
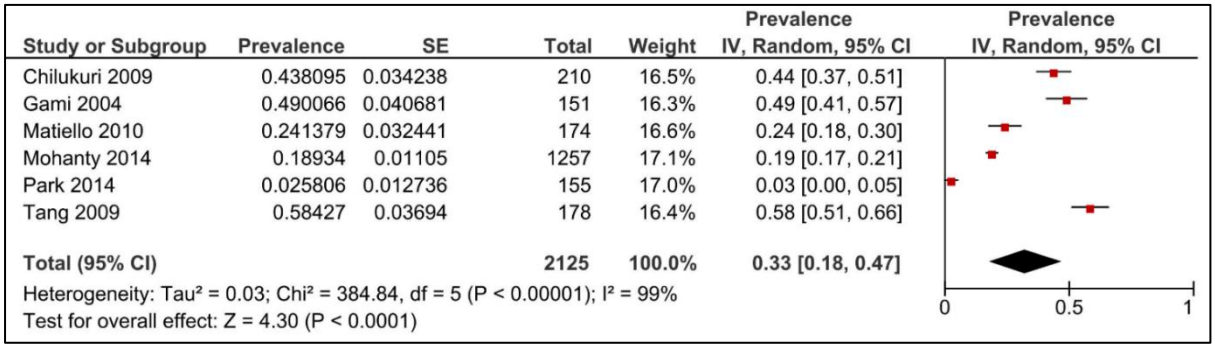


Figure 6

Prevalence of SDB estimated by questionnaires.



Chapter 4: Utility and Accuracy of Overnight Oximetry for the Diagnosis of Sleep-Disordered Breathing in Atrial Fibrillation Patients

4.1 Introduction

SDB, particularly obstructive sleep apnea, is highly prevalent in patients with AF. It has been reported to be much higher (between 18% and 74%) compared to populations without AF (between 3% and 49%).(1-5) SDB reduces the efficacy of catheter-based and pharmacological antiarrhythmic therapy.(6,7) Treatment of SDB by continuous positive airway pressure (CPAP) seems to lower the rate of AF recurrence after electrical cardioversion and improves catheter-ablation success rates in AF patients.(8,9) With accumulating evidence, the 2017 HRS/EHRA/ECAS/APHRS/SOLAECE Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation(10) as well as the guidelines for the management of atrial fibrillation of the 2016 European Society of Cardiology(11) mention SDB as a relevant modifiable risk factor for AF and recommend screening for SDB in patients with AF, including those who are being evaluated to undergo an AF ablation procedure.

The gold standard for the diagnosis of SDB is an overnight polysomnography (PSG). The presence and severity of SDB is determined using the apnea-hypopnea index (AHI) which represents the total number of apnea and hypopnea events per hour of sleep.(12,13) Limited access to PSG, its high cost, time commitment and variable patient compliance constrain PSG as effective tool for systematic SDB screening. In

addition, the burgeoning prevalence of AF further limits the use of PSG as a means of screening for SDB.

Simpler and less expensive strategies such as overnight oximetry monitoring might be a good alternative to PSG to allow broad and systematic SDB screening in the large number of AF patients. While overnight oximetry is already considered as a screening tool for SDB in the general population,(14-16) its diagnostic accuracy in AF patients is unknown. We sought to assess the diagnostic utility of different measures derived from overnight pulse oximetry in predicting SDB in AF patients when compared to the AHI which is derived from the gold-standard PSG.

4.2 Methods

Prospectively collected data on 439 consecutive patients with paroxysmal and persistent AF who underwent PSG between 2012 and 2017 as part of their clinical AF work-up in the Centre for Heart Rhythm Disorders at the University of Adelaide were analyzed. The study was approved by the Institutional Committee on Human Research at the University of Adelaide and all patients gave written informed consent before study enrolment.

4.2.1 Patient characteristics

The diagnosis of AF was confirmed with at least one available electrocardiogram (ECG) documentation. AF was defined as per the 2017 HRS/EHRA/ECAS/APHRS/SOLAECE Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation.(10) Paroxysmal AF was defined as self-terminating episodes of AF within 48 hours (or cardioverted within 7 days). Persistent

AF was defined as AF episodes that last over 7 days and longstanding persistent was defined as continuous AF lasting for ≥ 1 year.(10)

The following clinical characteristics were collected: gender, age, body mass index (BMI), previous pulmonary vein isolation and prior electrical cardioversion. The presence of hypertension, diabetes, hyperlipidemia, a history of cerebrovascular disease (stroke or transient ischaemic attack) and the CHA2DS2-VASc score were extracted from patients' clinical records. In addition, pharmacological therapy at the time of PSG was recorded and included anticoagulants (vitamin K antagonist, VKA; new oral anticoagulants, NOACs), antihypertensives (ACE-inhibitors/Angiotensin receptor blocker, ARB; calcium channel blockers CCBs; diuretics), statins and beta-blockers, digoxin, flecainide, amiodarone and sotalol.

4.2.2 Assessment of daytime sleepiness

To assess the degree of subjective daytime sleepiness, the Epworth Sleepiness Scale (ESS) was administered to all participants the evening before polysomnography. The ESS is a validated questionnaire that requires subjects to rate their likelihood of falling asleep in several common situations.(17) Scores range from 0 (least sleepy) to 24 (sleepiest). Normal daytime sleepiness was defined as an ESS score between 0 and 10. Excessive daytime sleepiness was defined as a score of 11 or higher.

4.2.3 Polysomnography

AF patients underwent standard overnight polysomnography (Somte PSG, Compumedics) which included continuous recordings of electroencephalography (EEG), electro-oculography (EOG), and chin electromyography (EMG) for sleep

staging. Nasal and oral thermistors were used to measure airflow and inductance plethysmography was used to measure rib cage and abdominal motion. The ECG and SpO2 were also continuously monitored. A minimum of 4 hours valid recording time was required. PSG data was scored by an experienced sleep specialist and reviewed and reported by a registered sleep physician according to methods described in the American Academy of Sleep Medicine manual for the scoring of sleep and associated events.(18)

4.2.3.1 Scoring of the apnea-hypopnea index

Apnea was defined as a drop in peak nasal airflow by ≥ 90% of pre-event baseline of more than 10 seconds duration. Apnea was scored as obstructive if apnea criteria were met in association with continuation of, or increase in, inspiratory effort during the event. Central apnea was defined as apnea according to the above definition in the absence of associated inspiratory effort. Hypopnea was defined as a 30% reduction in the airflow signal or thoraco-abdominal movement compared to the baseline value of the immediately preceding breaths lasting more than 10 seconds accompanied by either a fall of ≥3% in saturation or an arousal. A desaturation was therefore not a requisite criterion if an arousal was present with reduction in airflow. Hypopneas were classified as obstructive if there was either snoring at the time of the event or an increase of inspiratory flattening of nasal airflow, or occurrence of associated thoracoabdominal paradox during, but not before, the event; central hypopnea was scored if none of the obstructive hypopnea criteria were met. The AHI was calculated as the total number of apneas plus hypopneas divided by the total sleep time. SDB-severity was determined according to categories of the PSG derived apnea-hypopnea index (AHI) (AHI 15-29/h, moderate SDB; AHI ≥15/h,

moderate-to-severe SDB; AHI ≥30/h, severe SDB). SDB was classified according to the predominant type of apneas (>80% central events as predominant central sleep apnea; >80% obstructive events as predominant obstructive sleep apnea).

4.2.3.2 Scoring of oximetry derived measures

Digital oximetry signals of the complete recording time were extracted from the PSG for further processing by a novel fully automated MATLAB® based computer algorithm. Missing data were excluded by the algorithm. Acute desaturations were defined as episodic, monotonous drops in oxygen saturation levels by at least four percent that were followed by an onset of a resaturation to two-thirds of oxygen saturation level prior to desaturation within a period of 150 seconds. The requirement of a resaturation after a scored desaturation event is not implemented in the current AASM (18) scoring rules but allows the discrimination between episodic desaturation events and transient sustained drifts of baseline oxygen saturation as well as the determination of the onset and end of the desaturation event. In addition to mean nocturnal oxygen saturation (mean SpO2) and time spent below 90% oxygen saturation (T90), the oxygen desaturation index (ODI) as count of desaturations per hour recording time was determined.

4.2.4 Statistical analysis

Descriptive statistics are presented as mean ± standard deviation or median and inter-quartile range (in square brackets) for non-normally distributed variables. An ANOVA was applied to normally distributed variables across the three groups (AHI <15/h; AHI 15-29/h; AHI ≥30/h). Kruskal-Wallis H compared ranked data for

significantly skewed distributions. Categorical variables are presented as number and percentage and were analyzed with chi-square across the three groups. The main group effect p-value was reported for the between group comparison.

The primary objective of this study was to assess the diagnostic accuracy of oximetry derived parameters (T90, mean nocturnal oxygen saturation and ODI) and other demographic/clinical characteristics in the diagnosis of SDB as assessed via gold standard PSG. We ran two different prediction models for 1) the prediction of moderate-to-severe SDB (AHI ≥15/h) and 2) the prediction of severe SDB (AHI ≥30/h). Logistic regression was used to develop predictive models of either at moderate-to-severe (AHI ≥15/h) or severe (AHI ≥30/h) SDB. All parameters were assessed for their univariate relationships with SDB diagnosis and those with a relationship that resulted in a P value <0.10 were entered into a forward stepwise model. The final model was assessed for overall predictive value using receiver operating characteristic (ROC) analyses that allow assessment of sensitivity and specificity of all possible cut-offs of the predictor variable. The predictor cut-off with the best trade-off between sensitivity and specificity was calculated at the inflection point of the ROC curve.

All statistical analyses were performed using SPSS statistical software (Version 23; IBM corp) and significance was set at $p<0.05$.

4.3 Results

4.3.1 Patient characteristics

Patient characteristics are summarized in **Table 1**. The total sample of 439 subjects consisted of 69% men with 62, 35 and 3% having paroxysmal, persistent and long-standing persistent AF respectively. The mean age was 59.9±11.3 yrs. The median AHI was 9.5 [3.6-21.0]/h and the prevalence of moderate and severe SDB was 17.3% (n=76) and 16.6% (n=73), respectively. Most AF patients with moderate (n=55) and severe (n=67) SDB showed predominant obstructive sleep apnea. 21 patients with moderate SDB and 6 patients with severe SDB showed predominant central sleep apnea. Mean SpO2 was 93.9±1.7 %, and median ODI and T90 were 3.0 [0.8-8.2] /h and 0.5 [0.0-3.1] min, respectively.

4.3.2 Descriptive characteristics and their relationship to SDB severity

Age was not associated with the presence of moderate or severe sleep apnea (p=0.21). However, male gender trended towards being over-represented in severe SDB (p=0.07). 47% and 44% of the patients were overweight and obese, respectively. The presence of obesity was strongly related to severe SDB (p<0.001) as was the presence of non-paroxysmal AF (p<0.037) (**Table 1**).

ODI and T90 both increased with more significant sleep apnea (all p<0.001). Lower mean nocturnal SpO2 was associated with a greater severity of sleep apnea (p<0.001). The results showed a trend towards increased ESS as well as excessive

daytime sleepiness (ESS>10) in patients with more severe sleep apnea (p=0.10) (**Table1**).

There was a trend toward more warfarin use in moderate and severe SDB (p=0.08); however, NOAC therapy bore no relationship (p=0.56). Beta-blockers (p=0.44), digoxin (p=0.11), flecainide (p=0.13), amiodarone (p=0.23) and sotalol (p=0.49) were not related to the presence or severity of SDB. Similarly, electrical cardioversion (p=0.77) and the percentage of patients who had undergone an AF ablation procedure (p=0.81) did not differ amongst SDB sub-groups (**Table1**).

The presence of hypertension (p=0.001), diabetes (p<0.001), cerebrovascular disease (p=0.01) and the CHA2DS2-VASc score (p=0.001) were all significantly associated with SDB severity categories; however, hyperlipidemia trended toward being more prevalent as sleep apnea became more severe (p=0.10). Smoking status was not associated with the presence or severity of SDB (p=0.15) (**Table 1**).

4.3.3 Diagnostic accuracy of oximetry derived variables to predict SDB

Oximetry derived ODI, T90, and mean SpO2 were significantly correlated to the gold-standard of AHI (**Figure 1**; p<0.001); however, ODI displayed the strongest correlation (R=0.839). Additionally, T90, mean SpO2 and ODI were significantly correlated to each other (**Figure 2**; p<0.001 for all).

4.3.4 Prediction of moderate-to-severe SDB (AHI ≥15/h)

Demographic and risk factors such as BMI-categories (overweight, obesity), cerebrovascular disease, diabetes, hyperlipidemia, hypertension and gender were

univariately related to the presence of moderate-to-severe SDB (AHI ≥15/h) (statistical cut-off: $p<0.10$). All significant variables were entered into a forward stepwise prediction model together with ODI, T90 and mean SpO2, respectively. When modeled together with ODI, ODI and male gender remained significant. When modeled together with T90, T90, BMI category, diabetes, cerebrovascular disease and gender remained. When modeled together with mean SpO2, meanSpO2, BMI category, hypertension, diabetes, cerebrovascular disease and gender remained.

T90 and mean SpO2 alone (univariate, simple models) or in combination with additional variables (multivariate, complex models) had a clearly lower predictive value than ODI alone (**Figure 3**). ODI alone was able to detect moderate-to-severe SDB with an area under the ROC curve of 0.951 (95% CI: 0.929-0.972). The addition of male gender only marginally increased the area under the ROC curve at 0.954 (95% CI: 0.934-0.973). Using the simplest model (ODI alone), an ODI cut-off of 4.1 events per hour (as per inflection point on ROC curve) resulted in a 91% sensitivity and 83% specificity in discriminating between patients with and without moderate-to-severe SDB. In our sample, 11/145 patients who suffered from moderate-to-severe sleep apnea would have *not* been detected via ODI screening (ODI > 4.1 events/h correctly classified 134/145 patients with moderate-to-severe SDB). In contrast, 48/285 patients would have been sent for unnecessary PSG screening. The positive predictive value was: true positives / (true positives + false positives) = 134 / (134+48) = 73.6%. The negative predictive value was: true negatives / (true negatives + false negatives) = 237 / (237+11) = 95.5%. All 27 patients with moderate-to-severe predominant central sleep apnea were correctly classified by oximetry derived ODI.

4.3.5 Prediction of severe SDB (AHI ≥30/h)

Demographic and risk factors such as BMI categories (overweight, obesity), cerebrovascular disease, diabetes, hyperlipidemia, hypertension and gender were again univariately related to presence of severe SDB (AHI ≥30/h) (statistical cut-off: $p<0.10$). In forward stepwise selection, ODI together with hypertension; T90 together with BMI category, diabetes, cerebrovascular disease and gender; and mean SpO2 together with BMI category, hypertension, diabetes, cerebrovascular disease and gender formed the most complex models **(Table 2).**

T90 and mean SpO2 alone or in combination with additional variables had again a lower predictive value than ODI alone (**Figure 3**). ODI alone was associated with an area under the ROC curve of 0.932 (95% CI: 0.895-0.968), which marginally improved to 0.937 (95% CI: 0.911-0.963) with the introduction of hypertension (**Figure 3**). Using the simplest model, an ODI cut-off of 7.6 events per hour yielded a sensitivity and specificity for severe SDB of 89% and 83%, respectively, which did not appreciably improve in the most complex model.

Using ODI alone as a simple screening tool, 8/72 patients who suffered from severe sleep apnea would have *not* been detected via ODI screening, whereas ODI correctly classified 64/72 patients with severe SDB. In contrast, 60/358 patients would have been sent for unnecessary PSG screening. The positive predictive value was: true positives / (true positives + false positives) = 64 / (64+60) = 51.6%. The negative predictive value was: true negatives / (true negatives + false negatives) = 298 / (298+8) = 97.4%. All 6 patients with severe predominant central sleep apnea were correctly classified by oximetry derived ODI.

4.4 Discussion

This study evaluated the diagnostic performance and accuracy of a novel automated algorithm to analyze digital oximetry recordings in a large AF population to detect SDB. Oximetry derived ODI correlated with the gold standard AHI and could detect moderate-to-severe and severe SDB with good sensitivity and specificity in the studied population of 439 consecutive patients with AF. With a high negative predictive value of above 95%, ODI was particularly effective in ruling out moderate-to-severe and severe SDB in patients with SDB. ODI had a higher predictive value than other oximetry derived parameters such as T90 or mean nocturnal SpO2.

This is the first validation study demonstrating diagnostic accuracy of overnight oximetry derived ODI in patients with paroxysmal and persistent AF. Previous studies performed in the general population (14-16) or in smaller cohorts of patients with specific concomitant conditions such as a high cardiovascular risk or stroke (19,20) suggested a good performance of overnight oximetry to diagnose SDB. However, other studies have questioned the diagnostic utility of oximetry-derived parameters in these populations (21-25) supporting the need and clinical relevance of the present study.

Although the ODI can be used as a robust measure for the identification of AF patients with SDB, oximetry derived ODIs were lower than the PSG derived AHI, a finding which is consistent with other studies in non-AF patients.(26) The reason for differences between ODI and AHI in AF patients is multi-factorial. Underestimation of AHI by ODI might be due to a higher proportion of apneas and hypopneas not accompanied with desaturations, which are accounted for in the AHI but not in the ODI.(12,13) Comorbidities such as obesity might explain a part of this difference.(27)

Additionally, the ODI in our study was determined per recording time while AHI is recorded per sleep time which might result in lower ODIs particularly in patients with low sleep efficacy. Importantly, the difference between AHI and ODI was observed throughout all AHI groups and regression analysis revealed that the ODI-thresholds of 4.1/h or 7.6/h can be used to discriminate between AF patients with and without moderate-to-severe SDB or with and without severe SDB, respectively with good sensitivity and specificity. With a high negative predictive value, ODI is particularly effective in ruling out SDB in patients with AF. We tested, whether the consideration of additional demographic, risk factors or the presence of daytime sleepiness influences the diagnostic performance of oximetry derived parameters. Several variables were introduced in a stepwise prediction model, which clearly improved the diagnostic performance of T90 and mean SpO2 but had just a marginally impact on ODI. ODI alone had a better predictive value than T90 or mean SpO2 modelled together with additional variables. Therefore, it seems reasonable to use ODI alone as an effective tool to screen for and particularly to rule out SDB in patients with AF.

In the studied population, only patients with ECG documented AF were included. As expected, prevalence of comorbidities like hypertension, diabetes and obesity was strongly related to SDB severity, which was also reflected by the prescription of respective medication. This underlines the representative nature of the AF population used for this validation study. In this large AF population referred for PSG as part of the standard clinical work-up, a novel custom made automated computer program was used to determine the number of desaturations and the ODI during an overnight oximetry recording. The applied algorithm may differ from established ones implemented in commercially available polygraphy or polysomnography software packages. Most algorithms detect desaturations when SpO2 drops by 3% or more

from the pre-event baseline of SpO2.(18) However, this definition does not implement the requirement of an reoxygenation after a desaturation and can therefore not distinguish between real transient desaturations or random drifts in baseline SpO2.(18) The inclusion of the required reoxygenation after a drop in SpO2 to score a desaturation in our algorithm should increase the specificity to capture real desaturations and likely contributes to its high diagnostic accuracy to detect SDB. T90 and SpO2 did not reliably detect SDB in AF patients, but can provide important additional information about nocturnal hypoxemic burden which is not sufficiently reflected by the diagnosis of SDB severity determined by AHI.(28-30)

Our study may present some methodological limitations. The results have been obtained using oximetry data from PSG recordings, which might have resulted in a better recording quality than simple overnight oximetry recordings in a less standardized setting. Overnight oximetry is unable to distinguish between central or obstructive respiratory events or to detect respiratory events associated with arousals but without desaturation. Nonetheless, the ODI showed an excellent accuracy to detect SDB throughout a cohort of AF patients, which included patients with predominant obstructive and predominant central SDB. Although the prevalence of predominant central sleep apnea was low, all patients with moderate-to-severe and severe predominant central sleep apnea were correctly classified by oximetry derived ODI. In this cohort of patients, the presence of concomitant lung disease remains unknown and detailed information about lung function was not available.

Further prospective studies are warranted to confirm the high diagnostic accuracy shown in this study and to test, whether the proposed novel automated computer algorithm can be implemented in the analysis software package of simple portable

oximetry devices (outpatients setting) or of continuous physiologic patient monitoring units (inpatient setting) to allow broad and low-cost screening for SDB in patients with AF.

4.4.1 Conclusions

In a large AF population, this study demonstrates a high sensitivity and specificity of oximetry derived ODI determined by means of a new computer algorithm for the diagnosis of moderate-to-severe or severe SDB. With a high negative predictive value of above 95%, oximetry derived ODI is particularly effective in ruling out moderate-to-severe and severe SDB. This study suggests that broadly accessible and low-cost overnight oximetry has the potential for routine SDB screening in the standard clinical work-up of patients with AF.

4.5 Tables and Figures

Table 1

Baseline characteristics.

Characteristic	All N= 439	AHI <15/h N= 290	AHI 15–29/h N= 76	AHI ≥30/h N= 73	p-value
General characteristics					
Gender, male (%)	307 (69%)	191 (66%)	57 (75%)	57 (78%)	0.07
Age, years	59.9 ± 11.3	59.2 ± 11.8	60.7 ± 9.8	61.7 ± 11.0	0.21
Sleep-disordered breathing parameters					
ESS	6 ± 4	6 ± 4	6 ± 4	6 ± 4	0.10
AHI, /h	9.5 [3.6-21.0]	4.8 [2.1-9.3]	21.0 [18.0-24.3]	44.0 [36.0-65.0]	<0.001
Mean SpO2, %	93.9 ± 1.7	94.3 ± 1.5	93.5 ± 1.3	92.9 ± 2.3	<0.001
ODI, /h	3.0 [0.8-8.2]	1.4 [0.4-3.2]	8.4 [6.8-12.1]	22.1 [11.2-30.3]	<0.001
T90, min	0.5 [0.0-3.1]	0.1 [0.0-1.3]	1.3 [0.2-3.2]	4.0 [0.5-11.4]	<0.001
AF-specific parameters					
AF-type					0.037
- Paroxysmal, (%) **- Persistent, (%)**	- 274 (62%) - 155 (35%)	- 191 (66%) - 94 (32%) - 5 (2%)	- 38 (50%) - 32 (42%) - 6 (8%)	- 44 (60%) - 26 (36%) - 3 (4%)	

- Longstanding, (%)	- 14 (3.2%)				
AF ablation, (%)	72 (16%)	50 (17%)	11 (15%)	11 (15%)	0.81
Cardioversion, (%)	148 (51%)	98 (52%)	28 (54%)	20 (47%)	0.77
Comorbidities					
Hypertension, (%)	313 (71%)	190 (66%)	57 (75%)	64 (88%)	0.001
Hyperlipidemia, (%)	205 (47%)	126 (44%)	34 (45%)	42 (58%)	0.104
Diabetes, (%)	53 (12%)	22 (7.6%)	12 (16%)	18 (25%)	<0.001
Cerebrovascular disease, (%)	41 (9%)	24 (8%)	4 (5%)	13 (18%)	0.01
CHA2DS2-VASc score	1.8 ± 1.2	1.6 ± 1.4	1.8 ± 1.5	2.2 ± 1.2	0.001
Smoking status, (%)	107 (24%)	63 (21%)	24 (32%)	20 (27%)	0.15
Overweight (BMI 25-30), (%)	205 (47%)	253 (54%)	35 (45%)	18 (25%)	0.004
Obesity (BMI > 30), (%)	191 (44%)	98 (34%)	38 (51%)	54 (74%)	<0.0001

Abbreviations: AHI: Apnea hypopnea index; ESS: Epworth sleepiness score; SpO2: Oxygen saturation; ODI: oxygen desaturation index, T90: time below 90% oxygen saturation; AF: atrial fibrillation, AF; BMI: body mass index.

Table 2

Simple univariate and complex multivariate predictors of moderate-to-severe and severe sleep-disordered breathing using logistic regression.

	Moderate-to-severe SDB			Severe SDB		
Variable	**Odds ratio**	**95% CI**	**p-value**	**Odds ratio**	**95% CI**	**p-value**
Simple model						
ODI	1.682	1.517-1.866	<0.001	1.303	1.227-1.383	<0.001
T90	1.130	1.080-1.182	<0.001	1.144	1.096-1.193	<0.001
Mean SpO2	0.670	0.583-0.770	<0.001	0.688	0.588-0.805	<0.001
Complex forward stepwise prediction model						
ODI	1.691	1.522-1.879	<0.001	1.300	1.224-1.383	<0.001
Gender	2.233	1.021-4.881	0.044	-	-	-
Hypertension	-	-	-	3.310	1.031-10.63	0.044
T90	1.107	1.058-1.159	<0.001	1.134	1.083-1.188	<0.001
Overweight	2.506	0.807-7.906	0.002	-	-	-
Obesity	6.088	1.953-18.98	<0.001	10.97	1.341-89.78	0.026
Diabetes	2.708	1.384-5.297	0.004	2.411	1.108-5.250	0.027
CV disease	4.906	1.790-13.45	0.002	5.380	1.744-16.59	0.003
Gender	2.151	1.272-3.637	0.004	2.110	1.036-4.297	0.040
Mean SpO2	0.734	0.632-0.853	<0.001	0.761	0.641-0.904	0.002
Overweight	2.209	0.691-7.055	0.007	-	-	-
Obesity	5.025	1.567-16.12	0.001	10.03	1.230-81.81	0.031
Hypertension	1.767	1.033-3.025	0.038	2.341	1.065-5.145	0.032
Diabetes	2.781	1.423-5.434	0.003	2.380	1.146-4.939	0.020
CV disease	4.631	1.682-12.75	0.003	4.742	1.616-13.91	0.005
Gender	2.077	1.242-3.475	0.005	1.968	1.014-3.819	0.045

Logistic regression variables (statistical cut-off: p<0.10) modelled in the complex forward stepwise prediction model: BMI-categories (overweight, obesity), cerebrovascular (CV) disease, diabetes, hyperlipidemia, hypertension, gender, atrial

fibrillation type. For the complex model, all significant odds ratios ($p<0.05$) are reported. Oxygen saturation, SpO2; oxygen desaturation index, ODI; time below 90% oxygen saturation, T90; cerebrovascular, CV.

Figure 1

Correlation between the apnea hypopnea index (AHI) and oximetry derived oxygen desaturation index (ODI), time below 90% oxygen saturation (T90) and mean oxygen saturation (Mean SpO2).

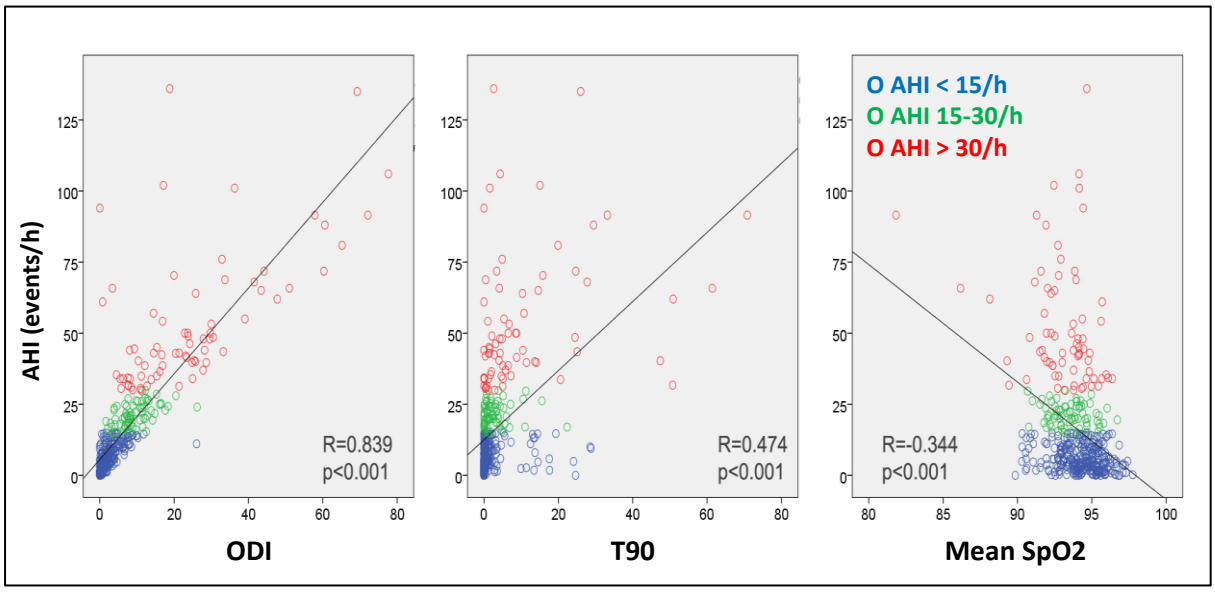


Figure 2

Correlation matrix among ODI, T90 and mean SpO2.

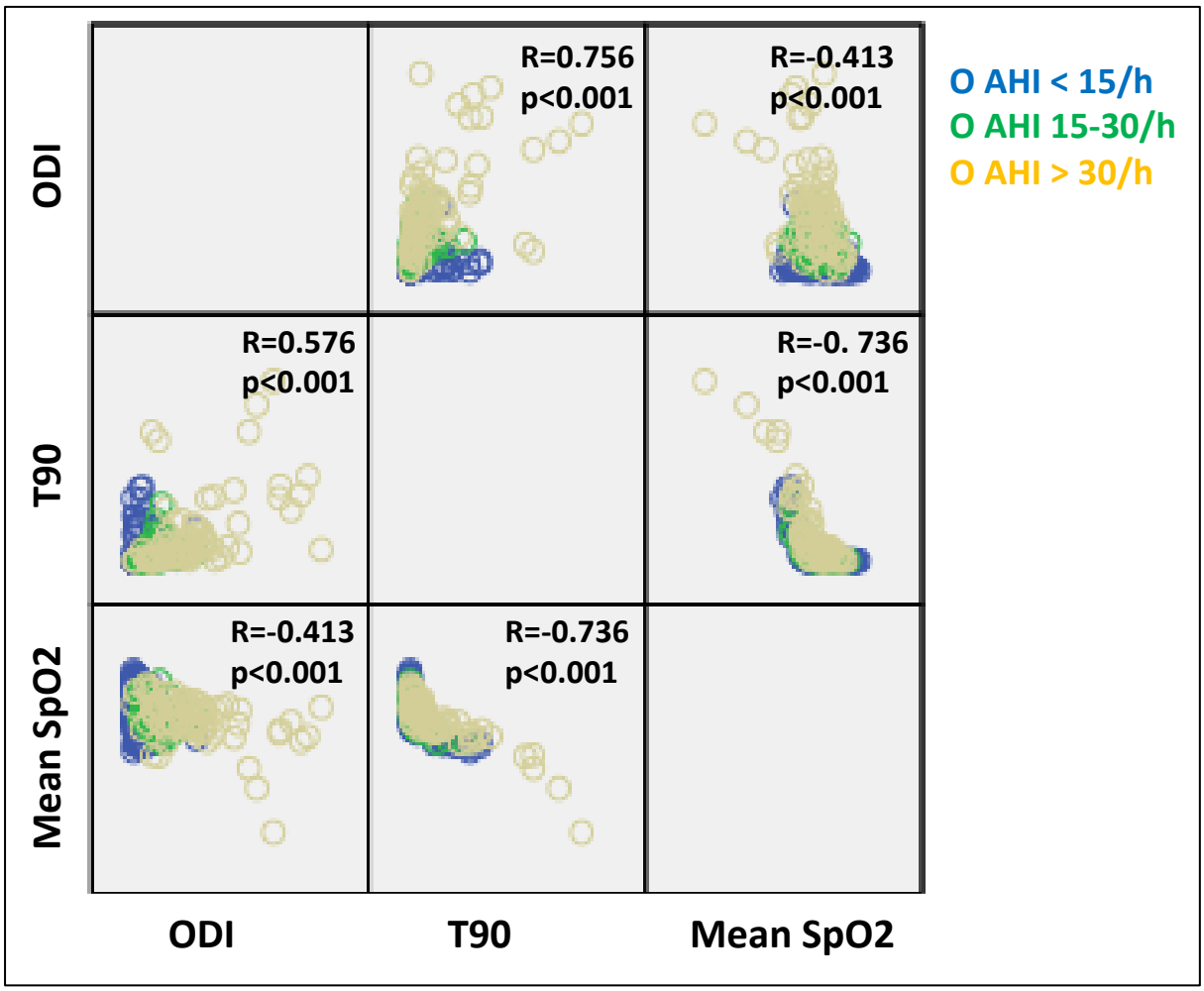
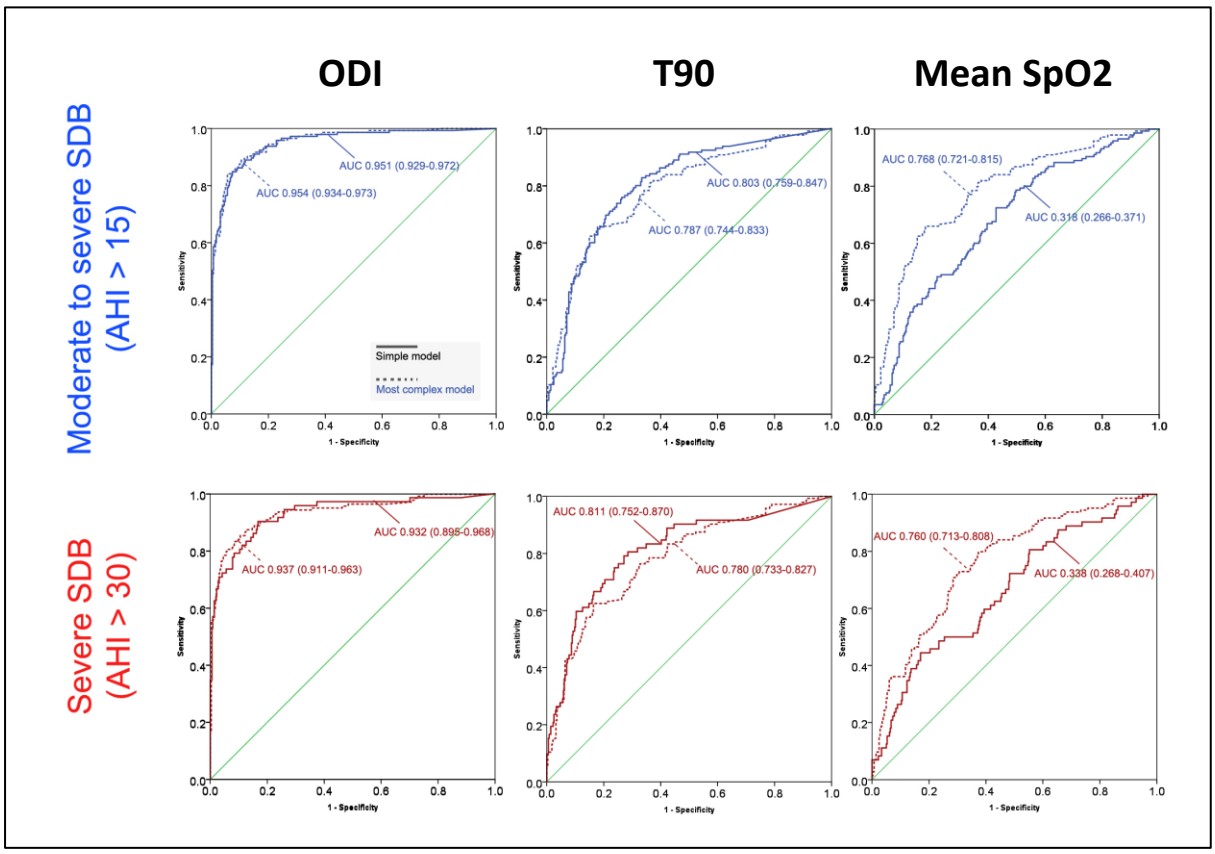


Figure 3

Prediction of moderate-to-severe (blue) or severe (red) sleep disordered breathing (SDB) by oximetry derived oxygen desaturation index (ODI), time below 90% oxygen saturation (T90) and mean oxygen saturation (Mean SpO2). Simple univariate (continuous line) and the most complex multivariable (dotted line) forward stepwise prediction model. Variables included in the model, see main text.



Chapter 5: Development and validation of a Multivariable prediction mOdel to estimate the prObability of significant sleep-Disordered breathing in patientS with Atrial Fibrillation: MOODS-AF

5.1 Introduction

Sleep-disordered breathing (SDB) is a very common comorbidity in patients with atrial fibrillation (AF) affecting ~80%, with moderate-to-severe SDB prevalent in 40% of AF patients[583]. The presence of SDB both increases the likelihood of developing AF[397] and negatively impacts the pursuit of sinus rhythm in AF patients[520]. Evidence from multiple observational studies have demonstrated that treatment of concomitant SDB can reduce AF recurrence post pharmacological or ablation treatment of AF[520]. This has led to the recognition of SDB as a modifiable risk factor in the management of AF patients, with the international AF management guidelines recommending testing for, and treating of, SDB in AF patients[521, 584].

The gold standard for SDB investigation is an overnight sleep study, a time- and resource- intensive test that can be of limited availability[313]. Multiple tools are clinically used in the general population to allow for improved patient selection for SDB testing[585]. The most frequently used tools are questionnaires, which rely either solely or in part on the presence of patient-reported symptoms, particularly excessive daytime sleepiness. However, there is increasing evidence that most AF patients with SDB do not experience excessive daytime sleepiness, regardless of the severity of SDB [528, 567]. Consequently, tools such as the Epworth Sleepiness Scale and the

Berlin Questionnaire, have been demonstrated to have a poor discriminatory performance in AF patients[586]. Hence, AF patients represent a cohort where detection of SDB is clinically relevant but the available tools may not be applicable to guide SDB testing resource allocation.

We therefore undertook our study seeking to develop and validate a multivariable prediction model that allows an accurate estimation of the probabilities of significant SDB in ambulatory AF patients. We further assessed the feasibility of simplifying that prediction model into a clinical score to facilitate clinical application and utilisation as a clinical decision support tool.

5.2 Methods

5.2.1 Study Sample

Data extracted from the multi-centre, prospectively-maintained registry of the Centre for Heart Rhythm Disorders, University of Adelaide were utilised for the derivation cohort. Patients were recruited to the registry from the Cardiovascular Centre, Royal Adelaide Hospital. Consecutive patients with AF who underwent sleep studies as part of their work-up between January 2009 and March 2017 were included. All sleep studies were undertaken as attended polysomnography (PSG) at the Adelaide Institute for Sleep Health (AISH). The external validation cohort comprised consecutive AF patients who had undergone attended PSG from the Royal Melbourne Hospital within the same period, and only the clinical variables relevant to the validation process were collected. The study was approved by the Human Research Ethics Committees of the Central Adelaide Local Health Network (R20180831) and The Melbourne Health (HREC 2004.225) and registered on

Australian New Zealand Clinical Trials Registry (Trial ID. ACTRN12618001859279). The study adheres to the Declarations of Helsinki and the recommendations of the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement[587].

5.2.2 Clinical Evaluation

AF was confirmed by at least one 12-lead electrocardiogram (ECG) documentation and categorised into paroxysmal or non-paroxysmal AF as per guidelines[584]. Data were collected at the time of performing the PSG for all patients and included age, sex, weight, height and body mass index (BMI). Self-reported daytime sleepiness was quantified using the Epworth Sleepiness Scale (ESS), a validated questionnaire that requires subjects to rate their likelihood of falling asleep in several common situations.

Clinical risk factors were actively screened for and included the presence of hypertension, type 2 diabetes mellitus (T2DM), cerebrovascular disease (CVD) (stroke or transient ischaemic attack/TIA), coronary artery disease, dyslipidaemia, vascular disease, smoking status (current, ex-smoker or non-smoker), alcohol intake ≥ 30 grams/week and the CHA_2DS_2-VASc score was calculated accordingly.[138]

5.2.3 Ascertainment of SDB Diagnosis

All patients underwent in-lab overnight polysomnography (PSG; Somte, Compumedics) which included continuous recordings of electroencephalography (EEG), electro-oculography (EOG), and chin electromyography (EMG) for sleep staging. Nasal and oral thermistors were used to measure airflow and inductance plethysmography was used to measure rib cage and abdominal motion. The ECG

and SpO2 were also continuously monitored. A minimum of 4 hours valid recording time was required. PSG data were scored by an experienced sleep technician and reviewed and reported by a registered sleep physician according to methods described in the American Academy of Sleep Medicine manual for the scoring of sleep and associated events.[530]

The apnoea-hypopnea index (AHI) was calculated as the total number of apnoeas plus hypopneas divided by the total sleep time. SDB was considered present if the AHI was ≥5. SDB-severity was determined according to categories AHI: AHI 5-14.9, mild SDB; AHI 15-29.9, moderate SDB; AHI≥30, severe SDB.[530] Moderate-to-severe SDB (AHI≥15) represents the main outcome of interest in our study since those patients are most likely to be considered candidates for continuous positive airway pressure (CPAP) treatment. Hence, identification of SDB in those patients may influence their management. Further, in patients with mild SDB, evidence is hitherto lacking from a rhythm-management perspective to support the routine use of CPAP.[567]

5.2.4 Statistical Analysis

Continuous variables are presented as mean ± standard deviation (SD) if normally distributed or median and inter-quartile range if skewed. Categorical variables are presented as count and proportion. Group differences were tested by two-sided Student t test or one-way analysis of variance test for normally distributed variables, while Mann-Whitney U test and Kruskal-Wallis H test were used for nonparametric variables. Differences in proportions were tested using X^2 or Fisher's exact test where appropriate.

A multivariable logistic regression model was constructed with moderate-to-severe SDB as the binary outcome. Age, gender, hypertension and BMI were selected a priori to be included in the model. Variables different at baseline between patients with or without moderate-to-severe SDB were tested using univariable analysis and entered in the final model with a step-wise backward conditional selection process (α = 0.1). Model fitness was assessed using the Hosmer and Lemeshow X2 test. Discriminatory performance of the model was assessed using the receiver operating characteristic (ROC) curve analysis with the C-statisic equating to the area under the curve (AUC). Internal validation and calibration was performed using 200 bootstrap replicates. The updated model was externally validated using ROC curve analysis.

The calibrated beta-coefficients from the multivariable model were used to derive a clinical point-based scoring system, with the lowest coefficient as a denominator as described by Sullivan et al[588]. The simplified model's performance was assessed using the C-statistic as above. Additionally, sensitivity and specificity were calculated for the simplified model at various cut-offs. Two-sided p values <0.05 were considered statistically significant. Statistical analysis was performed using SPSS statistical software for Windows (Version 26; IBM corp.) and R Version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria).

5.3 Results

5.3.1 Study Population

The derivation cohort included 442 patients, with a mean age of 60±11 years and 69.2% were men. SDB (AHI≥5) was present in 292 (66.1%) of the studied patients, while significant SDB (AHI≥15) was present in 149 patients (33.7%). Patients with

significant SDB were more likely to be men, older and with a higher BMI and higher prevalence of diabetes, CVD and non-paroxysmal AF. The validation cohort consisted of 409 patients with a mean age of 59±10 years and 76% were men. Three-hundred and fifty patients had SDB (AHI≥5) (86%) and significant SDB was present in 220 (54%) patients. Further details on the baseline characteristics of the derivation and validation cohorts can be found in **Tables 1 and 2.**

5.3.2 Model Derivation, Performance and Calibration

Univariable logistic regression analysis demonstrated that type of AF (paroxysmal vs non-paroxysmal) and CVD were predictors of significant SDB. The final model retained 5 variables: age, gender, BMI, type II diabetes and CVD combined as independent predictors of significant SDB ($p<0.05$ for all) as reported in **Table 3**. The model was a good fit for the data as demonstrated by the Hosemer-and-Lemeshow test (X^2=3.255, DF=8, P=0.917).

The model demonstrated a good diagnostic ability for significant SDB, with an internal Harrel's C-statistic of 0.75 (95% confidence interval [CI] = 0.70-0.81, $p<0.0001$) using 200-bootstrap replicates. Model calibration revealed a good predictive accuracy (calibration slope of 0.9427) indicating a mild degree of optimism of 5.73% (**Figure 1 and Table 4)**. The model's correlation coefficients were updated accordingly to account for the overfitting. **Figure 2** displays the calibration plot for the derivation cohort stratified by deciles of predicted probabilities, showing observed, predicted and updated predicted probabilities following calibration.

In the final model, the probability of detecting significant SDB ($\hat{p}$) was calculated using the formula:

$$\hat{p} = \frac{\exp(\text{-7.5419+LP})}{1 + \exp(\text{-7.5419+LP})}$$

Where LP = 0.0219*age + 0.1515*BMI + 0.963*gender (male) + 0.7331*T2DM + 1.395*CVD. A calculator using the above formula can be found online using the link www.MOODS-AF.com.

5.3.3 External Validation and Sensitivity Analysis

The model predicted significant SDB with good discrimination in the external cohort with a C-statistic of 0.750 (95% CI=0.704-0.797, p<0.001) **Figure 2**. Further, we performed sensitivity analysis for model's performance in detecting any SDB (AHI≥5) and severe SDB (AHI≥30) on the derivation, validation and the entire cohort (**Table 5**). The model's discrimination ability remained good throughout (C-statistic of 0.702 to 0.791, p<0.001 for all). There was an apparent stepwise increase in the model's discrimination ability with the increased SDB cut-offs utilised for testing, potentially supporting that the model's variables are positively associated with the underlying SDB disease process.

5.3.4 Point-based model simplification

The calibrated beta coefficients from the updated regression model were used to derive a point-based risk score as described by Sullivan et al[588]. BMI was re-classified using the established categories of normal, overweight and obese and utilised as a categorical variable. Age lost its contribution to the model once binned into a categorical variable and was therefore excluded. The final simplified model included being male (1 point), overweight (BMI 25-29.9, 1 point) or obese (BMI≥30, 3 points), presence of diabetes mellitus (2 points) and stroke/TIA (2 points). The

MOODS score therefore ranges from 0 to 8 **(Figure 3)**. The observed proportions of significant SDB, stratified by categories of MOODS score are displayed in **Figure 4.** The model retained a good diagnostic ability despite attenuation of resolution compared to the continuous model, with a C-statistic of 0.722 (95% CI: 0.674-0.771) in the validation cohort. A MOODS score of 1 had a sensitivity of 100%, while a score of ≥5 had a specificity of 96.3% (**Table 6**).

5.4 Discussion

In this study of ambulatory AF patients, a risk prediction tool identified those with significant SDB with high accuracy and consistency. Combined in a multivariable model, we found that age, male sex, BMI, diabetes and previous stroke/TIA were independently associated with the presence of moderate-to-severe SDB. Further, a simplified point-based scoring tool (MOODS) retained a high accuracy and discrimination ability **Figure 4 (Graphical Abstract)**. Our findings support that the estimation of significant SDB risk in AF patients is feasible from readily ascertainable clinical variables, which has the potential to aid clinical decision making and allow efficient resource allocation.

SDB is increasingly recognised as an important modifiable risk factor for AF[38, 216, 531, 532], implicated both in triggering AF[589] as well as contributing to atrial remodelling and development of the AF substrate[435]. Further, and with the treatment of SDB being associated with improved efficacy of rhythm control strategies in several observational studies[520], international AF guideline recommend testing for, and treatment of, concomitant SDB[521, 584], particularly as part of a comprehensive risk factor modification program. The gold-standard for SDB investigation is a formal in-lab polysomnography – a resource and time intensive test with limited availability[313].

Despite the introduction of ambulatory polygraphy devices[590], universal application of these relatively time consuming and expensive techniques is not practical. This is further complicated by the high prevalence of SDB in AF patients[39]. In our study, two-thirds of patients met the criteria for the diagnosis of SDB and 34% had moderate-to-severe SDB.

Our findings have several potential applications. There is a real clinical need to be able to identify AF patients whose management is likely to be altered by undergoing a sleep study. The MOODS score may be used to effectively rule out SDB among AF patients with low scores with high sensitivity (e.g. 90.5% for MOODS<2), suggest the presence of SDB with reasonably high confidence at higher scores (e.g. specificity of ≥96 for MOODS≥5), and identify patients where additional testing is needed with intermediate scores allowing a personalised approach to patient management, taking into account patients preferences and test accessibility.

The prediction model utilises only a small number of clinical features that are easily determined, which enables the clinician to estimate the probability of significant SDB in an AF patient rather promptly. The calculated SDB probability can be incorporated into electronic health records with individual risks displayed and used clinically or for research purposes, with the potential to prevent unnecessary testing with subsequent resource saving and costs reduction. Further, particularly if utilised as part of an interdisciplinary, integrated care approach, the calculated SDB risk can be utilised to streamline management in an informed and personalised manner[536]. We have provided the formula for the probability estimation calculator and also made it available on www.MOODS-AF.com with the aim of increasing accessibility.

Current AF management guidelines recommend the interrogation for symptoms of SDB in AF patients in order to guide SDB testing[521, 584]. Based on our study and several others[528, 567, 586], it is increasingly clear that self-reported symptoms (e.g. self-reported daytime sleepiness are of limited value in detecting SDB in AF patients, given that the majority of those patients do not report excessive daytime sleepiness. Our findings support that ascertaining objective variables, such as male sex and BMI, are more suitable to identify SDB in patients with AF. This may have implications for future AF guidelines recommends concerning SDB testing and treatment.

5.4.1 Strengths and Limitations

While this study is a retrospective cohort study, the clinical variables included in the prediction and validation models were prospectively collected and maintained, with structured in-lab polysomnography allowing for standardised SDB assessment. It should be noted that the relatively high event-per-variable ratio in our study resulted in minimal optimism and only a small amount of calibration was required. This has reflected in the good discriminatory ability of the model on the external validation cohort.

We did not collect potentially relevant data regarding craniofacial anatomy, neck circumference or ethnicity. While the interaction between obesity and craniofacial anatomy is established, the genetic role of ethnicity is also recognised as a mediator in the development of SDB risk.[591] Lastly, while we tested for daytime sleepiness and fount it of limited utility, potentially other symptoms such as witnessed nocturnal apnoeas could be of value, but this was not collected.

5.4.2 Conclusions

In ambulatory AF patients, the risk of significant SDB can be reliably estimated from a small number of clinical variables that are easily ascertainable. A simplified point-based system (MOODS) can be used as a rule-in or -out the need for SDB testing in a significant proportion of AF patients. For the remainder, individualised risk can be calculated to allow a patient-centred, and informed decision-making process. Potentially, the prediction model can allow efficient resource allocation, timely patient management and may need to be reflected in the future AF management guidelines.

5.5 Tables and Figures

Table 1

A: Baseline clinical characteristics of the derivation cohort

Characteristics	Total population	No or mild SDB (AHI<15)	Moderate-to-severe SDB (AHI≥15)	P
Number of patients	442	293	149	
Male	306 (69.2)	192 (65.5)	114 (76.5)	0.018
Age, years	60±11	59.5 ± 11.3	61.2±10.4	0.15
Weight, kg	91.9±17.2	88.1 ± 14.8	99.4±19.2	<0.001
BMI, kg/m2	30.5±5.2	29.3 ± 4.5	32.9±5.6	<0.001
ESS score (/24)	5.7 ± 4.1	5.5 ± 4.1	6.1 ± 4	0.099
Hypertension	314 (71)	202 (68.9)	112 (75.2)	0.17
Diabetes mellitus	53 (12)	23 (7.8)	30 (20.1)	<0.001
Dyslipidaemia	204 (46.4)	128 (44)	76 (51)	0.16
Coronary artery disease	41 (9.3)	24 (8.2)	17 (11.4)	0.27
Stroke/TIA	21 (4.8)	8 (2.7)	13 (8.7)	0.005
CHA_2DS_2Vasc score	1.8±1.2	1.6 ± 1.2	2±1.2	0.005
Non-paroxysmal AF	169 (38.2)	102 (34.8)	67 (45)	0.04
Previous AF ablation	72 (16.3)	50 (17.1)	22 (14.9)	0.55
Excess alcohol (>30g/week)	93 (21)	67 (22.9)	26 (17.4)	0.18
Smoker: non-smokers	323 (73.1)	219 (74.7)	104 (69.8)	0.04
Ex-smoker	107 (24.2)	63 (21.5)	44 (29.5)	
Current-smoker	12 (2.7)	11 (3.8)	1 (0.7)	
Ejection fraction, %	60.1±10.1	61 ± 8	60.5±10.4	0.056
LVIDd, cm	4.9±0.9	4.9 ± 0.6	5.1 ±0.8	0.001
LA diameter, cm	4.0±0.6	3.9 ± 0.6	4.2±0.6	<0.001

LA volume index, mL/m^2	32.8 ± 11.1	32.0 ± 11.0	34.3 ± 11.3	0.053

B: Clinical characteristics of the validation cohort

Characteristic	**Total population**	**No or mild SDB (AHI<15)**	**Moderate-to-severe SDB (AHI≥15)**	**P**
Number of patients	409	189 (46.2)	220 (53.8)	
Age, years	59±10	56±11	61±9	0.008
Male	310 (75.8)	129 (68.3)	181 (82.3)	0.001
AHI, /hr	22.7 (21)	7.2±3.9	35.9±20.1	<0.001
BMI, Kg/m^2	30.1±5.2	28.3±4.3	31.7±5.4	<0.001
Diabetes	57 (13.9)	6 (3.2)	51 (23.2)	<0.001
Stroke/TIA	22 (5.4)	9 (4.8%)	13 (5.9%)	0.61

Continuous variables are presented as mean ± standard deviation and categorical variables as number (proportion). P values provided are for the differences between the no or mild and moderate-to-severe SDB groups. Abbreviations: BMI= body mass index. ESS=Epworth Sleepiness Scale. LA=left atrium. LVIDd: left ventricular internal diameter in diastole. TIA=transient ischaemic attack.

Table 2

Comparison of baseline characteristics between derivation and validation cohorts.

Variable	Derivation	Validation	P value
Total patients, N	442	409	
Age, years ± SD	60 ± 11	59 ± 12	0.052
Male, N (%)	306 (69.2)	310 (75.8)	0.032
BMI, Kg/m2 ± SD	30.5 ± 5.2	30.1 ± 5.2	0.945
WHO Classification of BMI: Normal, N (%)	41 (9.3)	60 (14.7)	0.015
Overweight, N (%)	207 (46.8)	156 (38.1)	0.01
Obese, N (%)	194 (43.9)	193 (47.2)	0.335
Diabetes, N (%)	53 (12)	57 (13.9)	0.398
Stroke/TIA, N (%)	21 (4.8)	21 (5.1)	0.067
AHI, /hr ± SD	15.8 ± 19.2	22.7 ± 21	<0.001
Any SDB, N (%)	294 (66.5)	350 (85.6)	<0.001
Moderate-severe SDB, N (%)	149 (33.7)	220 (53.8)	<0.001
Severe SDB, N (%)	70 (15.8)	106 (25.9)	<0.001

Table 3

Univariable and multivariable predictors of significant SDB

Characteristic	Univariable		Multivariable		
	OR (95% CI)	P	OR (95% CI)	P	Regression coefficient
Age	1.02 (1.00-1.03)	0.120	1.02 (1.00-1.05)	0.032	0.024
Sex (male)	1.71 (1.09-2.68)	0.019	2.82 (1.65-4.83)	<0.001	1.038
Body mass index	1.15 (1.11-1.21)	<0.001	1.17 (1.12-1.23)	<0.001	0.160
Non-paroxysmal AF	1.53 (1.02-2.29)	0.038	Excluded by model		
Hypertension	1.36 (0.87-2.13)	0.173	Excluded by model		
Type 2 diabetes	2.96 (1.65-5.31)	<0.001	2.11 (1.1-4.04)	0.024	0.747
Stroke/TIA	3.41 (1.38-8.41)	0.008	4.33 (1.62-11.62)	0.004	1.466
				Constant:	-7.965
Hosmer & Lemeshow X2=3.255, DF=8, P=0.917					

Table 4

Original and updated coefficients following internal calibration of the multivariable prediction model.

Characteristic	Original Coefficient	Updated Coefficient
Age	0.024	0.0219
Gender (male)	1.038	0.963
Body mass index	0.16	0.1515
Type 2 diabetes	0.747	0.7331
Stroke/Transient ischaemic attack (TIA)	1.466	1.395
Constant:	-7.9646	-7.5419

Table 5

Sensitivity analysis of C-statistic (area-under-the-curve AUC) for derivation, validation and entire cohorts based on SDB severity.

	Any SDB	Moderate-to-severe SDB	Severe SDB
Derivation	0.702 (0.651 – 0.753)	0.748 (0.700-0.797)	0.791 (0.733 – 0.849)
Validation	0.729 (0.662 – 0.795)	0.750 (0.704-0.797)	0.732 (0.678 – 0.785)
Total	0.702 (0.661 – 0.742)	0.740 (0.706-0.773)	0.752 (0.713 – 0.791)

Table 6

Sensitivity, specificity and frequency of patients per MOODS scores.

MOODS score	Frequency (n)	Sensitivity (%)	Specificity (%)
0	12	100	0
1	66	100	6.3
2	119	90.5	29.6
3	43	66.8	65.1
4	118	59.5	79.4
5	16	20	96.3
6	30	14.1	97.9
7	4	1.8	99.5
8	1	0.5	100

Figure 1

Calibration slope based on 200 bootstrap replicates.

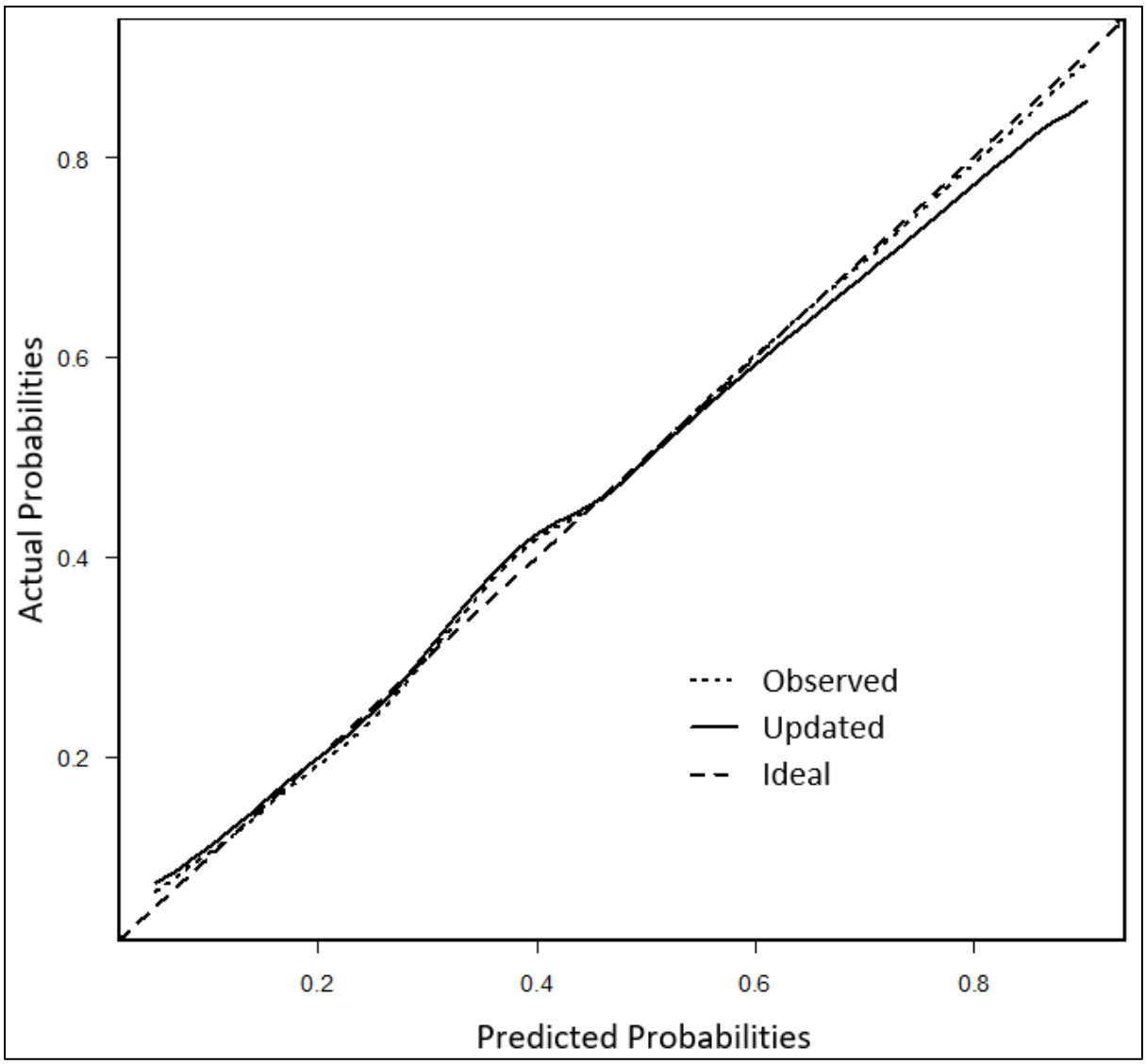


Figure 2

Calibration plot for the derivation cohort stratified by deciles of predicted probabilities showing the observed proportions (blue) and mean model-predicted probabilities (yellow) and updated model-predicted probabilities (green) following calibration.

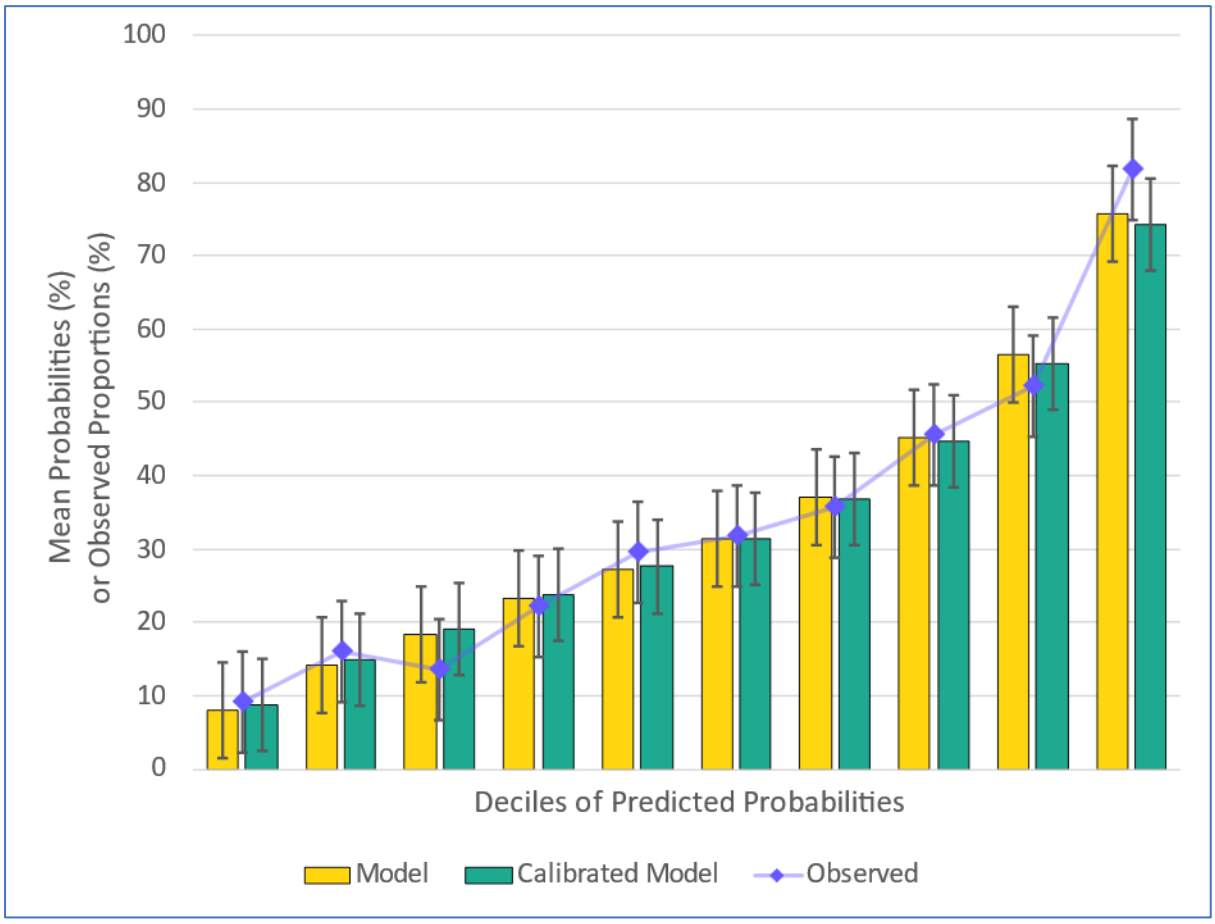


Figure 3

Receiver-operating characteristics (ROC) curve analysis results for the model's diagnostic ability to detect significant SDB on the validation sample. AUC=area under the curve. CI=confidence intervals.

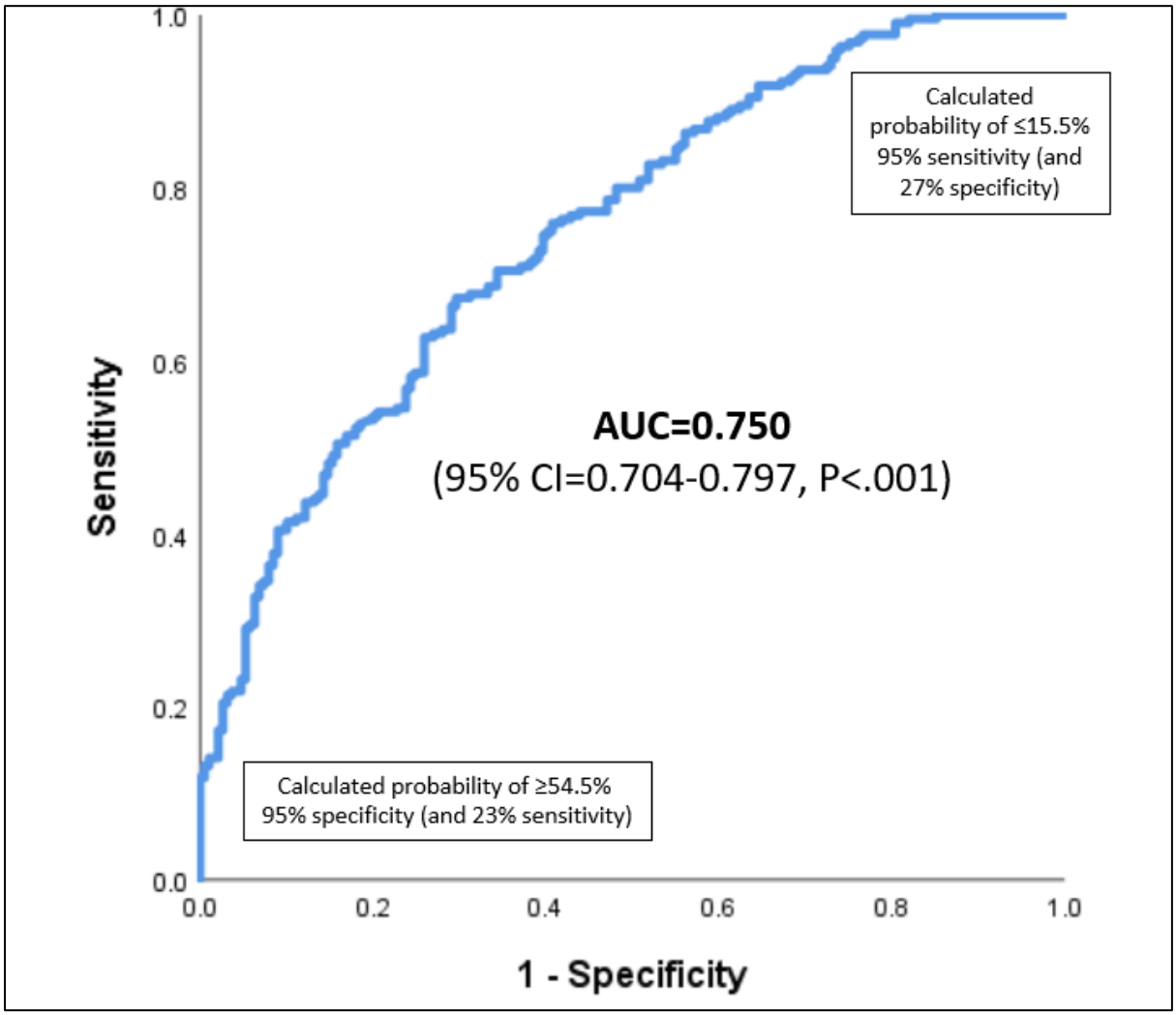


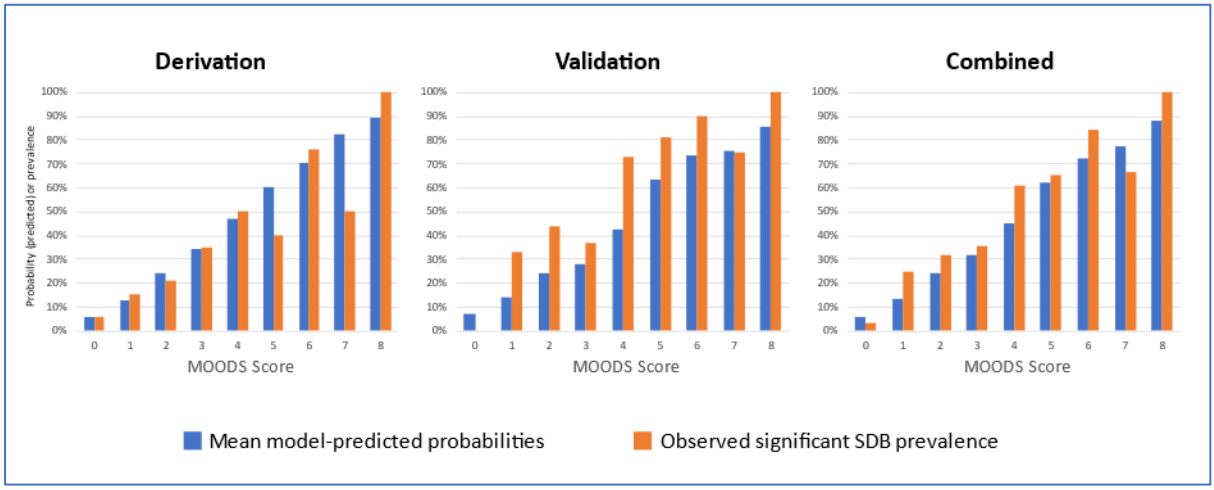
Figure 4

The simplified, point-based prediction tool for the risk of significant SDB. BMI=body mass index. TIA=transient ischaemic attack.

	Clinical Characteristics	Points
M	Male gender	1
O	Overweight (BMI 25-29.9)	1
O	Obesity (BMI ≥30)	3
D	Diabetes	2
S	Stroke/TIA	2
	MOODS score	sum (0-8)

Figure 5

Calibration plot depicting the studied population stratified by MOODS score (X axis). Y axis represents the mean model-derived probabilities of significant SDB, or observed prevalence (%). Hosmer-and-Lemeshow goodness of fit >0.1 for all indicating a good fit.



Chapter 6: Nocturnal Respiratory Events in Atrial Fibrillation Patients: Role of Event Duration in Atrial Remodelling and Disease Progression

6.1 Introduction

SDB, of which OSA is the predominant form[313], affects nearly 80% of patients with AF[583]. The risk of AF development increases with the presence and severity of SDB in a stepwise fashion indicating a dose-response relationship[404]. Treatment of SDB can improve arrhythmia-free survival following pharmacological treatment or catheter ablation of AF[520]. Therefore, international AF management guidelines recommend assessment and treatment of concomitant SDB to improve AF treatment outcomes[3, 592].

The gold-standard test for SDB is polysomnography, during which episodes of apnoea or hypopnea are detected and indexed to the hours of sleep giving rise to the apnoea-hypopnea index (AHI). The AHI is currently the main metric used for the diagnosis of SDB and to assess its severity[313]. However, this approach does not sufficiently reflect the complex pathophysiological processes associated with respiratory events, such as the extent and duration of desaturations, that may be relevant to AF initiation and progression[593]. Furthermore, the AHI does not indicate the total nocturnal hypoxaemic burden, which has recently been shown to be a predictor of mortality[594], adding further evidence to the limitations of AHI.

Preclinical studies showed that negative tracheal pressure promotes AF[595], and that the magnitude and duration of simulated sleep apnoea correlate with the degree of left atrial stretch and associated remodelling[421]. In humans, OSA has been shown to

be associated with increased indexed left atrial volumes in otherwise-healthy obese patients with OSA compared to similarly-obese patients without OSA[422]. Hypoxia is associated with neurohormonal changes and excessive oxidative stress resulting in inflammation and myocardial remodelling pertinent to AF substrate formation[596]. However, in AF patients, the contribution of the various components of the nocturnal respiratory events to atrial remodelling and AF disease progression has not been elucidated.

We therefore undertook this study to describe the respiratory events in a cohort of consecutive ambulatory AF patients. We hypothesised that higher hypoxaemic burden, defined as the total sleep time with oxygen saturations below 90% (T90), and longer duration of respiratory events, are each associated with atrial remodelling and AF progression. The aims of the study were to: 1) describe the components of respiratory events in detail in an AF cohort; 2) test the correlation between AHI and said components; 3) test the correlation between those components and atrial remodelling (defined as indexed left atrial volume dilatation) and AF progression (defined as non-paroxysmal AF subtype).

6.2 Methods

6.2.1 Study design and population

The study included consecutive patients with symptomatic paroxysmal or persistent AF referred from the Centre for Heart Rhythm Disorders at the University of Adelaide to undergo polysomnography (PSG) as part of their AF work-up. Referrals to the Adelaide Institute for Sleep Health from January 2009 to March 2017 were screened and patients without AF or with incomplete PSG data were excluded. The study

protocol was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital (R20180831) and registered on Australian New Zealand Clinical Trials Registry (Trial ID. ACTRN12618001859279).

6.2.2 Patient characteristics

AF was confirmed by at least one 12-lead electrocardiogram (ECG) documentation. Type of AF was defined according to the 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation[584]. Paroxysmal AF was defined as AF that terminated without intervention within 7 days of onset. Persistent AF was defined as continuous AF that is sustained over 7 days, while long-standing persistent AF refers to AF lasting more than 12 months. We use 'non-paroxysmal AF' to refer to persistent and long-standing persistent AF collectively.

Demographic and anthropometric data were collected at the time of performing the PSG for all patients and included age, sex, weight, height and BMI. Clinical risk factors were actively screened for included the presence of hypertension, diabetes mellitus (or impaired glucose tolerance), cerebrovascular disease (stroke or transient ischaemic attack), coronary artery disease, dyslipidaemia, smoking status (current, ex-smoker or non-smoker), alcohol intake ≥ 30 grams/week and the CHA_2DS_2-VASc score was calculated accordingly.[138] In addition, pharmacological therapy at the time of PSG was recorded.

6.2.3 Echocardiogram

Transthoracic echocardiography was performed to assess left atrial and ventricular dimensions and left ventricular systolic function. All measurements were performed

according to the recommended protocols for cardiac chamber quantification by the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[529] In patients with AF during echocardiography, all measurements were averaged over a minimum of 5 cardiac cycles. Left atrial (LA) volume was measured using bi-plane method and indexed to body surface area. The upper limit of normal for LA volume was 34 mL/m2 for both genders as per societal guidelines, and LA structural remodelling was considered present beyond this value.

6.2.4 Assessment of SDB-severity

AF patients underwent standard overnight polysomnography (PSG; Somte, Compumedics) which included continuous recordings of electroencephalography (EEG), electro-oculography (EOG), and chin electromyography (EMG) for sleep staging. Nasal and oral thermistors were used to measure airflow and inductance plethysmography was used to measure rib cage and abdominal motion. The ECG and SpO2 were also continuously monitored. A minimum of 4 hours valid recording time was required. PSG data were scored by an experienced sleep technician and reviewed and reported by a registered sleep physician according to methods described in the American Academy of Sleep Medicine manual for the scoring of sleep and associated events.[530]

Apnoea was defined as a cessation of airflow of more than 10 seconds duration. Hypopnea was defined as a 30% reduction in the airflow signal or thoraco-abdominal movement compared to the baseline value of the immediately preceding breaths lasting more than 10 seconds accompanied by either a fall of ≥3% in saturation or an arousal. A desaturation was therefore not a requisite criterion if an arousal was present with reduction in airflow. The number of central, obstructive or mixed

apnoeas was recorded. If the proportion of central apnoeas over the total number of apnoeas equalled or exceeded 50%, these patients were considered to have predominant central sleep apnoea. The apnoea-hypopnea index (AHI) was calculated as the total number of apnoeas plus hypopneas divided by the total sleep time. SDB was considered present if the AHI was ≥5. SDB-severity was determined according to categories AHI: AHI 5-14.9, mild SDB; AHI 15-29.9, moderate SDB; AHI≥30, severe SDB; AHI≥15, moderate-to-severe SDB).[530]

6.2.5 Scoring of oximetry-derived measures

Digital oximetry signals of the complete recording time were extracted from the PSG for further processing by a novel fully automated and custom made MATLAB® based computer algorithm. Artefacts were excluded by the algorithm. Acute desaturations were defined as episodic, monotonous drops in oxygen saturation levels by at least four percent that were followed by an onset of a resaturation to two-thirds of oxygen saturation level prior to desaturation within a period of 150 seconds. The requirement of a resaturation after a scored desaturation event is not implemented in the current AASM (18) scoring rules but allows the discrimination between episodic desaturation events and transient sustained drifts of baseline oxygen saturation as well as the determination of the onset and end of the desaturation event. The number desaturations per hour recording time was determined and reported as oxygen desaturation index (ODI). Mean nocturnal SpO2, median desaturation duration, nadir, and the total time spent below 90% oxygen saturation (T90) were reported. Further, the respiratory event-associated area under the desaturation curve from pre-event baseline was calculated as the desaturation integral, and represents another metric for hypoxaemic burden[597](**Figure 1**).

6.2.6 Statistical analysis

Continuous variables were tested for normality in distribution using the Shapiro-Wilk test, and are presented as mean ± standard deviation or median and inter-quartile range as appropriate. Categorical variables are presented as count and proportion. Group differences were tested by two-sided Student t test or one-way analysis of variance test for normally distributed variables, while Mann-Whitney U test and Kruskal-Wallis H test were used for nonparametric variables. Differences in proportions were tested using X^2 or Fisher's exact test where appropriate.

The degree and direction of correlation between AHI and the desaturation components was tested using Pearson and Spearman correlation coefficients. Binary logistic regression analyses were used to test the relationship of each of the nocturnal hypoxaemia parameters with atrial remodelling and AF progression as two separate dependant variables. The degree of collinearity with AHI was assessed using Variance Inflation Factor (VIF) statistic for each desaturation component, with an upper limit of 2.5[598]. Once found to be statistically significant in the univariable analysis, a multivariable model correcting for AHI, age, sex, BMI and hypertension was used to test desaturation duration's contribution to atrial remodelling. Further exploratory analysis was performed categorising desaturation duration as high or low based on the cohort's median. Significance was set at $p<0.05$. All statistical analysis was performed using SPSS statistical software for Windows (Version 26; IBM corp.).

6.3 Results

6.3.1 Study population

The study included 435 patients of whom 303 (69.7%) were men. The mean age was 60.1 ± 10.9 years, the mean BMI was 30.41 ± 5.11 kg/m2 and 167 (38.4%) of patients had non-paroxysmal AF. When stratified for the presence and type of SDB, nearly one third of the studied population had no SDB (n=144, 33.1%), one third had mild SDB (n=146, 33.6%) and one third had moderate-to-severe SDB (n=145, 33.3%). Baseline characteristics are reported in **Table 1**.

6.3.2 Sleep Study Parameters

The median AHI for the population was 9.5/hr [IQR 3.6-21.0], with most respiratory events being hypopneas (median hypopnea index 7.6/hr [IQR 3.0-16.3]). The majority of patients with SDB had predominantly-obstructive SDB (212, 73.4%), with a higher proportion of predominantly-obstructive SDB patients in those with moderate-to-severe SDB (79.9%) vs mild SDB (66.9%, P=0.013). **Table 2** provides detailed description of the components of the sleep study parameters for the cohort.

6.3.3 Respiratory events components and AHI

There was a statistically significant correlation between AHI and all the respiratory events tested other than the desaturation integral. A positive (increasing) correlation was found between AHI and each of ODI (strongest overall association, R^2=0.596), desaturation amplitude (R^2=0.260), T90 (R^2=0.216), and desaturation:resaturation time ratio (R^2=0.051). A negative (decreasing) correlation was found between AHI and each of average nocturnal saturation (R^2=0.085), desaturation

duration(R^2=0.106), and desaturation nadir (R^2=0.162). **Figure 2** contains the scatter plots of the tested correlations along with the obtained correlation coefficients.

6.3.4 Respiratory events components and atrial remodelling

Table 3 (A) outlines the results of the binary logistic regression analyses for dilated indexed left atrial volume. Only desaturation duration was found to have a statistically significant univariable correlation with atrial dilatation (OR = 1.013, 95% CI = 1.003-1.023, P=0.014). This remained significant when corrected for AHI (VIF for multicollinearity between desaturation duration and AHI=1.12), age, sex, BMI and hypertension (OR = 1.015, 95% CI = 1.003-1.026, P=0.012).

6.3.5 Respiratory events components and AF progression

Each unit increase in AHI or ODI increased the odds of progression into non-paroxysmal AF by 1.1% and 2.1%, P=0.034 and 0.027, respectively. However, this correlation was only significant in univariable analysis and lost statistical significance when adjusted for potential confounders. None of the other studied parameters predicted AF progression as can be seen in **Table 3 (B).**

6.3.6 Sensitivity analyses: patients with and without moderate-to-severe SDB

The desaturation duration was not statistically associated with atrial remodelling in patients with moderate-to-severe SDB (OR 1.019, 95% CI = 0.987–1.052, P=0.250). However, in patients with no-or-mild SDB, the desaturation duration was independently associated with increased indexed left atrial volume when correcting

for age, sex, BMI, AHI and hypertension (OR 1.018, 95% CI = 1.005 – 1.031, P=0.005).

The role of desaturation duration in predicting atrial remodelling can be graphically appreciated from **Figure 3A**. Patients with higher desaturation duration (above the cohort's median of 48.5 seconds) and no-or-mild SDB had a numerically higher risk of developing atrial dilatation compared to patients with no-or-mild SDB and low median desaturation duration (OR 1.626, 95% CI = 0.868 – 2.733, P=0.066). When moderate-to-severe SDB is present, the duration of desaturation events did not influence the risk of developing atrial dilatation with similar odds for those with low- or high- median desaturation duration (OR 1.927 [95% CI = 1.086-3.420] and 1.975 [95% CI = 0.903-4.316] respectively)

With regards to AF progression, having higher median desaturation duration did not influence the risk of developing non-paroxysmal AF in patient with no-or-mild SDB (OR 1.45, 95% CI = 0.87 – 2.41, P=0.150). In patients with moderate-to-severe SDB, there was an increased risk of developing non-paroxysmal AF, with higher risk in patients with longer desaturation duration (OR 2.11, 95% CI = 1.01-4.44, P=0.049) compared to those with low desaturation duration (OR 1.82, 95% CI = 1.04-3.19, P=0.037) (**Figure 3B)**.

6.4 Discussion

In this cohort of ambulatory AF patients, we found that SDB is common, predominantly obstructive, and is mainly driven by hypopnoeas. The average nocturnal oxygen saturation, total hypoxaemic burden, the amplitude, nadir and desaturation:resaturation ratio all correlated weakly with AHI, and failed to add value

in terms of predicting atrial dilatation or AF disease progression. However, the duration of desaturation episodes, irrespective of the presence or severity of SDB, predicted atrial remodelling, and to a limited degree, AF disease progression, even when potential confounders were considered.

SDB has been repeatedly shown to be prevalent in AF patients with wide variation in reporting owing to the inconsistent assessment methods and definitions used[541]. A recent meta-analysis attempted to address this issue by adopting standardised inclusion and testing criteria. The meta-analysis of >2000 AF patients showed that 78% had SDB of any degree (95% CI: 70-86%), and that 40% have moderate-to-severe SDB (95% CI: 32-48%). In our study, we found that the proportion of AF patients with SDB is not dissimilar at nearly two-thirds, with one third having moderate-to-severe SDB.

Numerous studies report an increasing risk of AF with SDB, including predominantly-central subtype[599]. Tung et al showed double the risk of AF with central sleep apnoea in one analysis of the Sleep Health Heart Study[600]. Leung et al found that patients with idiopathic central sleep apnoea had a higher prevalence of AF compared to those with obstructive sleep apnoea or no sleep apnoea (27%, 1.7%, and 3.3%, respectively, P<.001)[601]. However, within AF patients, the prevalence of SDB subtypes is not well understood. Traaen et al used home polygraphy on nearly 600 paroxysmal AF patients and reported a predominantly-obstructive SDB prevalence of 95.4%[394]. In our study, we observed that predominantly-obstructive SDB subtype was indeed most common with only a quarter of SDB patients having predominantly-central SDB. The proportional differences compared to the study by Traaen and colleagues are likely due to the inclusion of persistent AF patients in our

study as well as the use of the more detailed polysomnography tests. Supporting this are the findings by Albuquerque and colleagues, who used polysomnography and reported a prevalence of central sleep apnoea and mixed sleep apnoea of 17.1% and 13%, respectively in a cohort of 123 persistent AF patients with SDB[528].

Nocturnal hypoxaemic burden is increasingly recognised as an important metric with potential prognostic implications. In the Osteoporotic Fractures in Men (MrOS) study of 2,872 community-dwelling men, severe nocturnal hypoxemia defined by the percentage of sleep time less than 90% oxygen saturation of ≥ 10% was associated with 1.8-fold increased risk of incident stroke[602]. Another report from the MrOS study found that men with time spent below 90% oxygen saturation > 12 minutes were at an elevated risk of cardiovascular mortality (HR 1.59; P = 0.006) and that nocturnal hypoxaemic burden is not merely the consequence of frank desaturations associated with respiratory events, but also reflects non-specific drifts in oxygen saturation[594]. Azarbarzin and colleagues reported on data from both MrOS and the Sleep Heart Health Study studies, which combined included ~8000 participants, and found that increased hypoxaemic burden predicted cardiovascular disease-related mortality independent of AHI[597]. However, nocturnal hypoxaemia parameters are not consistently found to be of prognostic value. In a post-hoc analysis of the Sleep Apnea Cardiovascular Endpoints (SAVE) study, which included 2687 patients with co-occurring moderate or severe OSA and cardiovascular disease, none of the novel hypoxia metrics were associated with increased risk of cardiovascular outcomes.

In preclinical setting, intermittent hypoxia was seen to contribute to alteration in cardiac connexins and gap functions, predisposing to atrial remodelling and AF substrate generation[603]. Increased sympathetic drive due to hypoxaemia has been

shown in healthy adults[430], and the degree of sympathetic overactivity was seen to correlate with the degree of nocturnal hypoxaemia[431]. Rather than hypoxia, Stevenson et al found that hypercapnia, or more precisely, recovery from hypercapnia, was associated with acute alteration in electrical conduction and increased AF vulnerability in a preclinical study. In our study, parameters of hypoxaemic burden were not found to influence atrial structural remodelling or AF disease progression. This gives credence to the notion that the complex pathophysiological associated with respiratory events, and the subsequent cascade of atrial and structural remodelling, are hard to capture using one 'simple' metric[554].

Intrinsically, the AHI as a metric is prone to under-reporting the true burden of respiratory events, with multiple but shorter episodes 'scoring' higher than a single but prolonged respiratory episode of equivalent duration. We confirmed this inverse relationship with AHI in our study and importantly, we found that the duration of the hypoxaemic events to be an independent predictor of atrial remodelling. Substantial intrathoracic pressure swings result from the respiratory events of SDB[407], resulting in increased transmural pressures promoting myocardial stretch particularly in the thin-walled atria[408]. Zhang et al showed that the atrial dimensions begin to increase shortly into simulated OSA experiments (3 hours) in a canine model. Further, they demonstrated gradual enlargement of the left atrium with prolongation of apnoea, along with associated ultrastructural atrial remodelling[421]. In a cross sectional study of 411 71-year old men (The Study of Men Born in 1943), the authors found that left atrial area assessed by echocardiography was independently associated with prevalence and severity of OSA[604]. To the best of our knowledge, ours is the first study to confirm a dose-response relationship of respiratory event duration and atrial dilatation in AF patients.

Our data suggest an increased risk of AF disease progression with increased respiratory events' duration, particularly in patients with no or mild SDB. Atrial remodelling and the development of an AF substrate is integral to disease progression into more persistent forms, and predictors of AF progression include increasing age, higher BMI and increasing blood pressure[605]. It is now well established that atrial substrate formation is a complex process that is mediated by a number of modifiable risk factors, including hypertension, obesity, diabetes, excess alcohol intake and indeed, SDB[38]. The importance of addressing these risk factors collectively has been highlighted in a number of studies. In the REVERSE-AF study, 88% of overweight AF patients who engaged in a comprehensive risk factor management programme and achieved ≥ 10% weight loss managed to reverse the AF subtype from persistent into paroxysmal or no AF[216]. In the ARREST-AF cohort study, aggressive risk factor modification improved the long-term success of AF ablation[312]. SDB assessment and management in AF patients can be challenging and structured testing is rarely adopted[606].

6.4.1 Limitations

An increasing body of evidence points towards SDB being a dynamic condition with significant nightly variation in severity, which has important diagnostic implications(33). The PSGs conducted in our study were performed for one night only and therefore SDB misclassification is possible. Structural assessment was carried out using transthoracic echocardiography only, when cardiac MRI would have been able to provide more detailed assessment of cardiac structure and function, as well as the presence and extent of atrial fibrosis[125]. Further, electroanatomical data for patients who went on to have AF ablation is not available.

While the presence of atrial dilatation can be objectively measured, rather than elucidated indirectly from a sleep study. However, this study provides novel mechanistic insights and casts further doubt on the use of AHI as the main metric for SDB assessment. Finally, our study suggests a link between nocturnal respiratory events and atrial remodelling and disease progression. Whether treatment of SDB would allow reversal of AF substrate and subtype warrants further study.

6.4.2 Conclusions

SDB is common and is predominantly-obstructive in this AF patients cohort. Atrial structural remodelling is independently influenced by the median duration of respiratory events encountered overnight independent of the presence and severity of SDB. In the presence of moderate-to-severe SDB, prolonged respiratory events is associated with increased risk of AF progression into non-paroxysmal forms. Whether treatment of concomitant SDB would result in reversal of AF substrate and subtype warrants further study.

6.5 Tables and Figures

Table 1

Baseline clinical characteristics per sleep-disordered breathing (SDB) category. Continuous variables are presented as mean ± standard deviation or median [25th-75th percentile], while categorical variables are presented as number (proportions).

Characteristic	Total	No SDB	Mild SDB	Mod/Severe SDB	P
Number of patients, N (%)	435	144 (33.1)	146 (33.6)	145 (33.3)	
Age, years, mean ± SD	60.1 ± 10.9	56.8 ± 11.8	61.9 ± 10	61.5 ± 10.2	<.001
Male, N (%)	303 (69.7)	86 (59.7)	107 (73.3)	110 (75.9)	0.006
Non-paroxysmal AF, N (%)	167 (38.4)	38 (26.4)	64 (43.8)	65 (44.8)	0.001
Body mass index, Kg/m2, mean ± SD	30.41 ± 5.11	28.92 ± 4.56	29.59 ± 4.45	32.71 ± 5.49	<.001
Obese, N (%)	189 (43.4)	44 (30.6)	56 (38.4)	89 (61.4)	<.001
Hypertension, N (%)	311 (71.5)	97 (67.4)	104 (71.2)	110 (75.9)	0.277
Heart failure, N (%)	15 (3.4)	4 (2.8)	4 (2.7)	7 (4.8)	0.537
Type 2 diabetes, N (%)	51 (11.7)	8 (5.6)	14 (9.6)	29 (20)	<.001
Left ventricular ejection fraction %, median [range]	62 [56-67]	62 [56-67]	62 [56-66]	61 [55-66]	0.559
Left ventricular internal diameter in diastole, cm, median [range]	5 [4.6-5]	5 [4.6-5.3]	4.95 [4.6-5.3]	5.1 [4.7-5.5]	0.03

Left atrial diameter, cm, median [range]	4 [3.6-4.4]	3.8 [3.4-4.3]	4 [3.6-4.3]	4.2 [3.8-4.5]	<.001
Left atrial volume, mL, median [range]	65 [50-86]	61 [47-86]	64 [49-80]	73 [55-91]	0.009
Left atrial volume indexed to body surface area, mL/m^2, median [range]	31.73 [24.57-39.51]	30.88 [23.73-41.07]	31.38 [24.49-36.52]	32.7 [25.69-40.79]	0.169
Dilated left atrial volume (indexed), N (%)	167 (42.3)	52 (40.3)	51 (38.3)	64 (48.1)	0.234

Table 2

Sleep study parameters stratified by the presence and severity of SDB.

	No SDB	Mild SDB	Moderate-to-severe SDB	Total	P
AHI, /hr	2.05 [1 - 3.6]	9.5 [6.6 - 11.8]	28.5 [20.5 - 43]	9.5 [3.6 - 20.5]	<0.001
ODI, /hr	1.28 [0.57 - 2.15]	4.05 [2.38 - 6.89]	12.89 [8.76 - 22.08]	4.09 [1.49 - 9.78]	<0.001
HI, /hr	1.85 [0.78 - 3.2]	8.17 [6.04 - 10.8]	21.17 [16.32 - 30.56]	7.62 [3.02 - 16.32]	<0.001
AI, /hr	0.15 [0 - 0.38]	0.51 [0.16 - 1.57]	4.68 [1.3 - 12]	0.54 [0.13 - 2.6]	<0.001
Central	0 [0 - 0.18]	0.15 [0 - 0.41]	0.5 [0 - 2.32]	0.17 [0 - 0.55]	<0.001
Obstructive	0 [0 - 0]	0.17 [0 - 0.87]	3.17 [0.42 - 8.74]	0.19 [0 - 1.71]	<0.001
AI as percentage of AHI, %	5.48 [0 - 21.41]	6.56 [1.37 - 15.24]	16.85 [5.1 - 38.44]	9.48 [0.79 - 23.8]	<0.001
Predominantly-central SDB	NA	48 (33.1%)	29 (20.1%)	77 (26.6%)	0.014
Total sleep time, minutes	328 [270.5 - 373]	328.5 [274.5 - 377]	300 [250 - 350]	321 [266 - 366]	0.006
Sleep efficacy	0.76 [0.63 - 0.85]	0.75 [0.62 - 0.83]	0.7 [0.6 - 0.79]	0.74 [0.62 - 0.83]	0.008

Nocturnal SpO2, % (mean ± SD)	94.65 ± 1.74	94.29 ± 1.33	93.59 ± 1.65	94.18 ± 1.64	
T90, minutes	0.09 [0 - 0.9]	2.04 [0.22 - 6.25]	10.57 [3.52 - 24.27]	2 [0.08 - 10.57]	<0.001
Median desaturation duration, seconds	57 [44 - 74]	51 [43 - 60]	44 [38 - 50]	48.5 [41 - 61]	<0.001
Median desaturation nadir, %	92 [90.5 - 93]	91 [90 - 92]	90 [89 - 91]	91 [90 - 92]	<0.001
Median desaturation integral, min%	141.13 [101.25 - 189.99]	138.25 [106.5 - 171]	137 [110.5 - 169]	139 [106.5 - 176]	0.696

Table 3

A: logistic regression analysis for left atrial dilatation

	Univariable Regression				Multivariable Regression			
Variable	Odds Ratio	95% CI lower limit	95% CI upper limit	P	Odds Ratio	95% CI lower limit	95% CI upper limit	P
AHI	0.997	0.986	1.007	0.543				
ODI	0.998	0.979	1.019	0.877				
T90	0.997	0.989	1.006	0.558				
Mean nocturnal O2 saturation	1.027	0.903	1.169	0.683				
Desaturation amplitude	1.067	0.766	1.486	0.702				
Desaturation duration	1.013	1.003	1.023	0.014	1.015	1.003	1.026	0.012
Desaturation integral	1.003	0.999	1.006	0.098				
Desaturation nadir	1.041	0.934	1.162	0.466				
Desaturation : resaturation time ratio	0.877	0.623	1.234	0.45				

B: logistic regression analysis for AF progression into non-paroxysmal AF

	Univariable Regression				Multivariable Regression			
Variable	Odds Ratio	95% CI lower limit	95% CI upper limit	P	Odds Ratio	95% CI lower limit	95% CI upper limit	P
AHI	1.011	1.001	1.021	0.034				
ODI	1.021	1.002	1.04	0.027	0.995	0.965	1.026	0.739
T90	1.003	0.996	1.01	0.348				
Mean nocturnal O2 saturation	1.003	0.891	1.128	0.966				
Desaturation amplitude	1.12	0.852	1.473	0.417				
Desaturation duration	0.997	0.988	1.006	0.522				
Desaturation integral	0.999	0.996	1.002	0.545				
Desaturation nadir	0.995	0.905	1.095	0.925				
Desaturation : resaturation time ratio	1.053	0.759	1.461	0.759				

Figure 1

A: representative example of nocturnal oxygenation trace and the calculated parameters. iSpO2 refers to interpolated saturation time. B: algorithm-detected timepoints of desaturation onset, nadir and end. Desaturation duration=t_{end}-t_{onset}. Desaturation amplitude=iSpO2-t_{nadir}.

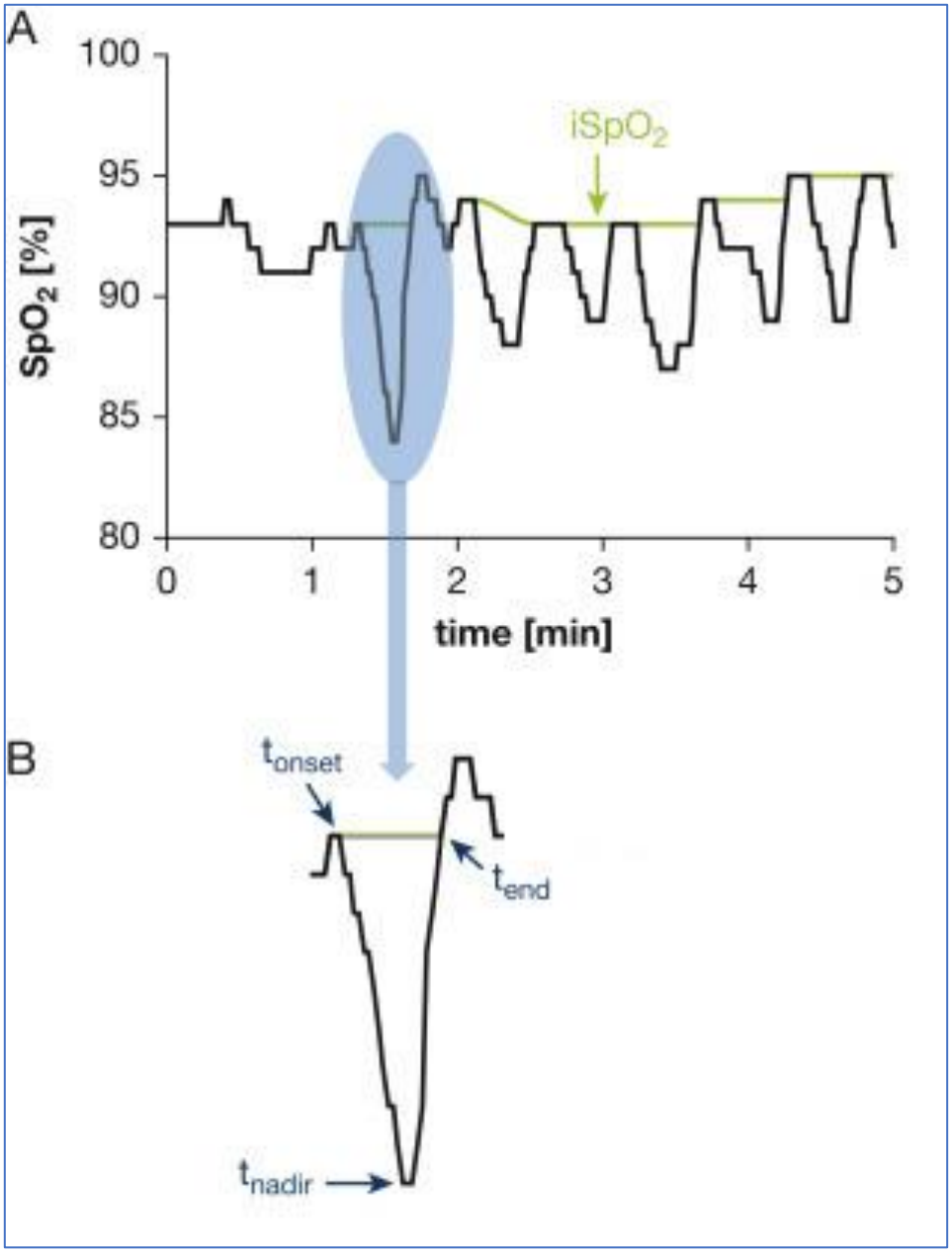


Figure 2

The correlation between AHI and each of the studied parameters of oxygen desaturation index (ODI) (A), hypoxaemic burden defined as total time spent with SpO2<90% (T90) (B), average nocturnal oxygen saturation (C), desaturation amplitude (D), desaturation duration (E), desaturation integral (area below desaturation curve) (F), desaturation:resaturation time ration (G), and desaturation nadir (H).

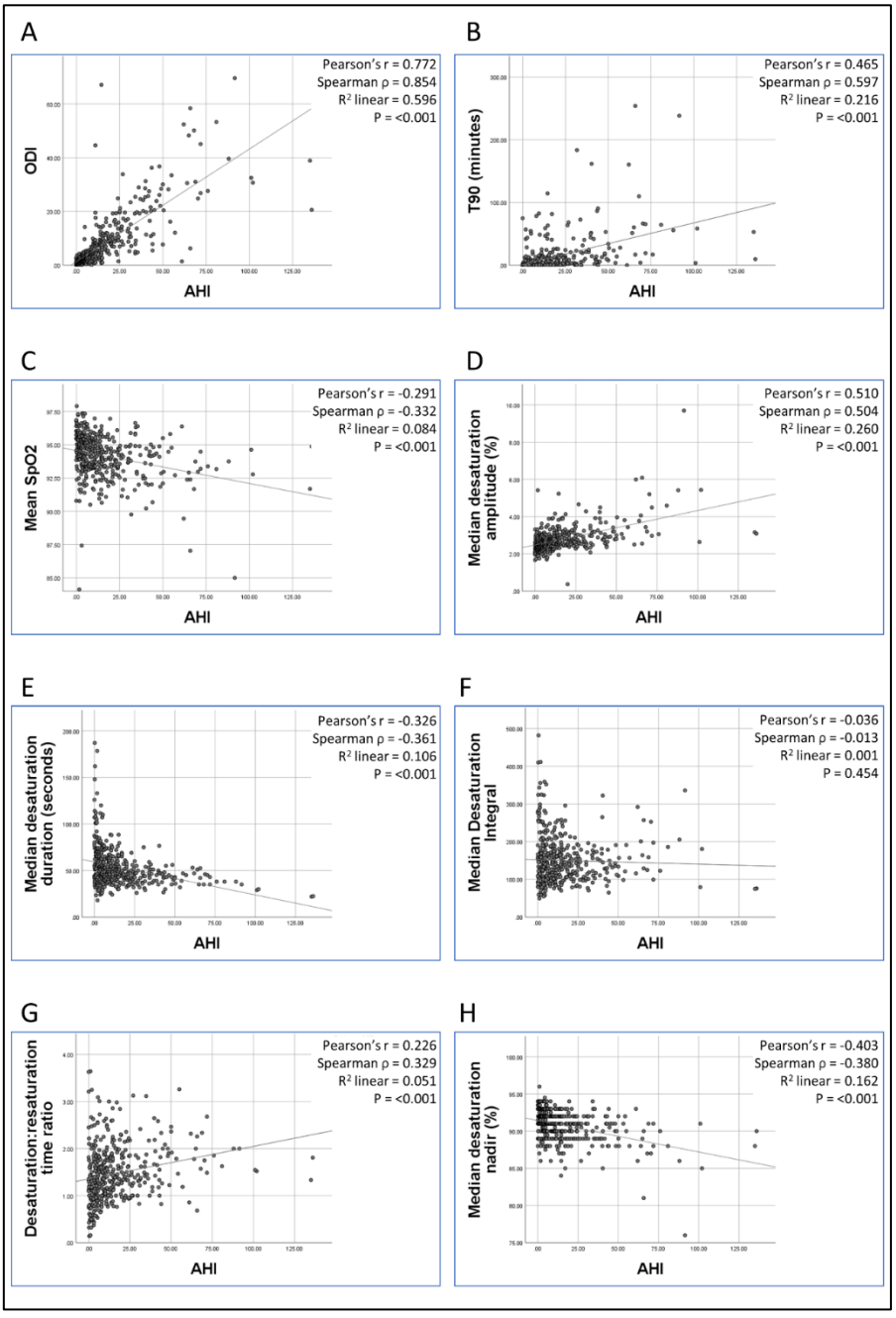
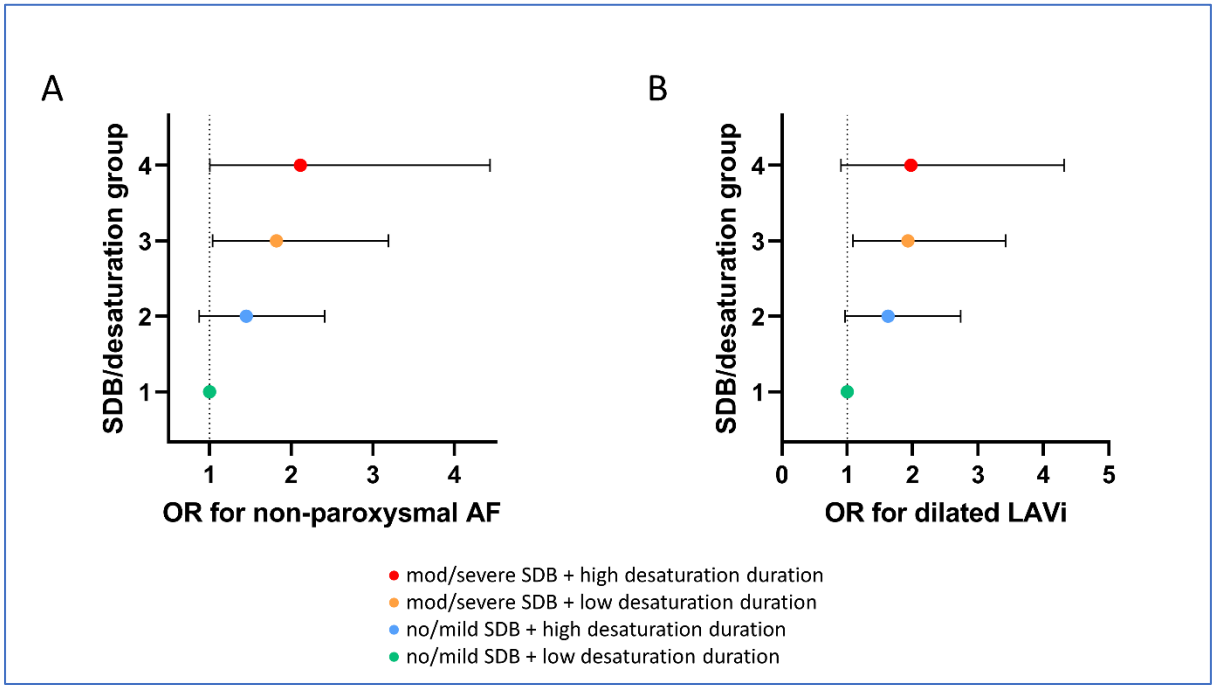


Figure 3

Odds ratio of developing atrial dilatation (A) or AF progression (B) for non-paroxysmal AF (A) and left atrial remodelling (B) based on the having high (>(≥48.5 seconds) or low median desaturation duration, and stratified by the presence or absence of moderate-to-severe SDB.



Chapter 7: Final Discussion

This thesis highlights the importance of detecting SDB as a modifiable risk factor for AF. It provides novel insights into the prevalence of concomitant SDB, the challenges in SDB recognition in AF patients, and delivers potential solutions in simplifying the testing process and optimising patient selection. Further, observations from this thesis advance our understanding of the relationship between SDB and AF and provide potential mechanistic insights into the dose-response relationship between these two conditions.

It is well established that AF is mediated by a number of modifiable risk factors, including excess weight, hypertension, diabetes and alcohol intake. A large body of work produced from this research group and others has shown the importance of controlling these risk factors as part of a comprehensive approach to AF patient care. This is now reflected in international AF management guidelines and the concept of risk factor modification being the ‘Fourth Pillar’, in addition to rate or rhythm control and stroke risk reduction, is now mainstream. However, SDB is a rather important risk factor that is not as well appreciated by clinicians looking after AF patients. This thesis challenges this, and has the potential to disturb the status-quo, both in terms of daily clinical practice and subsequently in AF management guidelines.

Chapter 2 provides evidence that relying on patient-reported symptoms of excessive daytime sleepiness for SDB testing is grossly inadequate. This practice is unfortunately not uncommon, and has the potential for a majority of AF patients with SDB to have their SDB go unnoticed and untreated. Simply put, the lack of excessive daytime sleepiness should not preclude patients from being investigated

for the potential presence of concomitant SDB. The findings of this chapter should allow a significant proportion of AF patients to have a chance of true wholistic approach to their care. It also raises interesting questions that are worthy of future study. Particularly, why does this dissociation between objective measures of SDB severity and subjective symptoms exist in AF patients? We hypothesise that the baseline sympathetic drive of AF patients, which is known to be elevated compared to the general population, is likely counteracting the sleepiness due to the fractured sleep of SDB. This merits further study and may potentially be facilitated by using adjunct measures of sympathetic tone, such as Holter-derived measures of heart rate variability or repolarisation duration.

The thesis then goes on to examine how prevalent SDB is within the AF population, and how SDB is normally tested. Chapter 2 was a systematic review that captured the wide heterogeneity in the assessment and reporting of SDB in the available literature. It then used rigorous criteria and identified the studies where SDB was systematically assessed in consecutive AF patients. This study puts under the spotlight how prevalent SDB is with nearly 8 out of 10 AF patients having some degree of SDB, and how there is a real need for standardisation in the SDB testing and reporting in future research. It would be of interest to assess the AF prevalence within the SDB population, in essence the reverse of this study, to examine any potential bidirectionality in AF and SDB prevalence objectively.

Given the high prevalence of SDB in the AF patients, and the high resource and financial cost associated with formal sleep studies, the thesis went on to examine ways to improve the testing process, either by simplifying it in Chapter 5, or by better patient selection for SDB testing in Chapter 6. In Chapter 5, we utilised a unique

algorithm that examined the overnight oximetry signal recorded routinely as part of formal overnight polysomnography, to detect and index respiratory events. We found that this automated process yielded a metric in the oxygen desaturation index, that had very high accuracy compared to the gold-standard AHI. This is the first time this metric has been assessed and validated in an AF population. Further prospective studies are warranted to confirm the high diagnostic accuracy shown in this study and to test whether the proposed novel automated computer algorithm can be implemented in the analysis software package of simple portable oximetry devices (outpatients setting) or of continuous physiologic patient monitoring units (inpatient setting) to allow broad and low-cost screening for SDB in patients with AF.

In Chapter 5, the focus was to develop and validate a risk prediction model to identify AF patients with moderate-to-severe SDB. This chapter builds on the findings of Chapter 3, and utilises readily-ascertained clinical characteristics to derive a well calibrated risk prediction model. The statistical methods used in this study were rigorous and followed the most strict criteria. The model's performance in an entirely different cohort both in time and location is very encouraging. The results of this study enables accurate and individual calculation of SDB risk, and has the potential to streamline the patient selection process for SDB testing. These individual probabilities can be calculated online using a mobile-friendly website, or a simpler model, MOODS, can help busy clinicians to quickly rule-in or rule-out the need for SDB testing. Future research is required to assess the utility of integration of SDB risk calculation in electronic health records.

The final chapter examined whether novel hypoxaemia parameters, which have gained popularity of late as important independent predictors of 'hard' endpoints,

have any added value to the traditional metric of AHI in SDB assessment in AF patients. Interestingly, the burden of hypoxaemia itself was not found to influence atrial dilatation or be associated with increased prevalence of persistent AF, which we utilised as an indicator of disease progression. However, the median duration of nocturnal hypoxaemic events, a metric inversely proportional to AHI due to AHI's mathematical calculation method, was indeed a predictor of left atrial dilatation, independent of potential confounders. This relationship was found to be particularly strong amongst patients without moderate-to-severe SDB, highlighting the importance of potentially detecting SDB and treating it early to stop the AF substrate reaching a 'point of no return', when SDB is established and the minutiae of the type and duration of respiratory events are lost. These findings invite clinicians to examine the type and duration of respiratory events that affect their patients, regardless of the diagnosis and severity of SDB. Further studies are warranted to examine the impact of the duration of respiratory events on cardiac electroanatomical remodelling assessed in with more detailed cardiac MRI and using 3D mapping.

Chapter 8: Future Directions

Multiple challenges remain in the field of concomitant SDB and AF. First and foremost, the available evidence for SDB treatment in AF is mostly observational and fraught with methodological issues. Future research effort must be directed towards assessing the role of SDB treatment to improve AF-related outcomes in a well-designed, randomised, and controlled trial setting. This is not a simple undertaking and has potential ethical limitations in excluding patients with significant hypoxaemia or excessive daytime sleepiness, where the balance of evidence points towards treatment,

Other challenges related to SDB detection in AF patients include clarification of the appropriate metric, tools, and logistics. The thesis highlights the limitations of AHI as the main metric for SDB assessment, which has long been recognised and debated within the sleep medicine community. Further, the current classification of SDB severity is entirely arbitrary, with potentially significant consequences in terms of treatment options. Categorising a disease spectrum into different entities (mild, moderate and severe) ignores the underlying pathophysiological process that is a continuum rather than separate entities. Research is required to examine whether the current classification is justified in terms of disease progression and outcome from therapy. For example, patients with AF, mild SDB and no excessive daytime sleepiness would not be routinely offered CPAP therapy in most clinical healthcare settings. However, the evidence behind including those patients, or indeed excluding them from therapy, is simply lacking.

The ‘snapshot’ approach to SDB testing with a single overnight test, which is the prevailing practice, runs the risk of misclassifying the severity of SDB. Ample

evidence exists that SDB is a dynamic condition with considerable night-to-night variation. Future research needs to address whether patients with wide variation in the SDB severity represent a unique population within the AF-SDB population. Could these patients derive more benefit from SDB treatment since the SDB phenotype is not fully established? What is the proportion of such patients within the AF-SDB population? Could the longitudinally assessed SDB-severity (e.g. SDB burden), rather than the result of one overnight sleep study, be a better reflection of the exposure to SDB-related AF risk?

Linking with the above is the logistical challenge of SDB testing. While the thesis provides potential solutions by simplifying or streamlining the SDB testing process, future research is required to explore the utility of more readily-available tests that provide longitudinal data. With the advances in technology, the field of non-contact biomotion detectors, sleep tracking devices and smartphone-based applications provide an exciting prospect with the potential to revolutionise patient care in the future. It is already happening that patients present to clinic with a diagnosis and burden of AF established through their well-validated electronic devices. It is therefore not too difficult to imagine a future where in addition to AF, patients present with a comprehensive assessment of their sleep, the burden of sleep-disordered breathing events, and treatment compliance data (which is already possible). The era of large-scale pragmatic data is upon us, and research into upcoming assessment tools is required to establish feasibility and diagnostic accuracy.

While this thesis highlighted the limited role of questionnaire-based tools in the detection of AF patients with SDB, those questionnaires may still have a role in management. For example, are patients with excessive daytime sleepiness (high

ESS score) more likely to adhere to treatment? Could adherence intervention be focused on those who need it most then? (patients with low ESS score)? Additionally, while weight loss and CPAP as SDB interventions have been shown to be associated with ‘reverse remodelling’, it is not clear what the role of other SDB interventions, e.g. mandibular advancement devices, in alleviating obstructive apnoeas and potentially reversing atrial remodelling.

Furthermore, in the age of COVID-19, the long-term consequences of this primarily-respiratory disease, its interaction with the current assessment tools, and its impact on SDB treatment compliance and outcome are all areas that require further study.

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