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Enhancing the Diagnosis and Management of Obstructive Sleep Apnoea in Atrial Fibrillation Patients

A thesis submitted to fulfil requirements for the degree of Doctor of Philosophy

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Table of Contents

Statement of Originality

This is to certify that to the best of my knowledge, the content of this thesis is my own work. This thesis has not been submitted for any degree or other purposes.

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

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Authorship attribution statement

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As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Peter A Cistulli

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Dedication

For Zoe, Ruby and Leo: may you each discover a lifetime love of learning;

and for Pedram, who made this possible.

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Abbreviations

ABPM	Ambulatory Blood Pressure Monitoring
AF	Atrial Fibrillation
AHI	Apnoea Hypopnea Index
AI	Arousal Index
BMI	Body Mass Index
AADSM	American Academy of Dental Sleep Medicine
AASM	American Academy of Sleep Medicine
BQ	Berlin Questionnaire
CABG	Coronary Artery Bypass Grafting
CAI	Central Apnoea Index
CCF	Congestive Cardiac Failure
CPAP	Continuous Positive Airway Pressure
CSA	Central Sleep Apnoea
CTI	Cavo-tricuspid isthmus
DCCV	Direct Current Cardioversion
ECG	Electrocardiogram
EEG	Electro-encephalogram
ESS	Epworth Sleepiness Scale
EOG	Electro-oculogram
EMG	Electromyogram
ENT	Ear Nose Throat
ER	Emergency Room
ESS	Epworth Sleepiness Scale
IHD	Ischemic Heart Disease
MAD	Mandibular Advancement Device
MAI	Mixed Apnoea Index
MAS	Mandibular Advancement Splint
MOODS	Male, Overweight or Obesity, Diabetes mellitus, Stroke
MRA	Mandibular Repositioning Appliance
NoSAS	Neck circumference, Overweight/obesity, Snoring, Age and Sex
NPV	Negative Predictive Value
ODI	Oxygen Desaturation Index

OSA	Obstructive Sleep Apnoea
PAF	Paroxysmal Atrial Fibrillation
pNN50	Percentage of successive NN intervals that differ by > 50ms
PPV	Positive Predictive Value
PSG	Polysomnography
PVAI	Pulmonary vein antrum isolation
PVI	Pulmonary Vein Isolation
QOL	Quality of Life
RCT	Randomised Controlled Trial
REM	Rapid Eye Movement
RMSSD	Square root of mean squared differences of successive NN intervals
ROC	Receiver Operating Characteristic
SACS	Sleep apnoea clinical score
SD	Standard (alcoholic) drinks
SDB	Sleep Disordered Breathing
Sns	Sensitivity
Spc	Specificity
STOP	Snoring, tiredness, observed apnoeas, hypertension
STOP-Bang	Snoring, tiredness, observed apnoeas, hypertension, body mass index, age, neck circumference, gender.
TMJ	Temporomandibular joint
TST	Total Sleep Time

Abstract

Background: Atrial fibrillation (AF), is the most common sustained cardiac arrhythmia, and significantly increases the risk of stroke and cardiovascular mortality. It is strongly associated with obstructive sleep apnoea (OSA), another common chronic disorder characterised by recurrent airway obstruction, oxygen desaturation and cardio-metabolic perturbations during sleep. Mechanistic pathways for the association between these two important conditions are incompletely understood, but may involve atrial stretch and remodelling, intermittent hypoxia, inflammation and autonomic dysregulation. OSA is acknowledged as a treatable risk factor for AF, however the optimal clinical pathways for the diagnosis and management of OSA in AF patients are not well described.

Aims: This thesis manuscript contributes to our knowledge of both the diagnostic and management pathways for OSA in AF patients via the following aims: 1. To examine the epidemiology of OSA in a hospital cohort with AF. 2. To compare the diagnostic accuracy of potential clinical screening tools for OSA in patients with AF. 3. To compare cardiac autonomic function in AF patients with and without OSA. 4. To conduct a pilot study of mandibular advancement splint (MAS) therapy for OSA in AF patients.

Methods: Study 1 involved recruitment of AF patients from two pathways (N=107): emergency department admissions and pulmonary vein isolation waitlists. Epidemiological and demographic data were collected. The diagnostic accuracy of a number of screening tools including a level 3 (portable) sleep study device as compared to the gold standard, polysomnography, in AF patients was assessed (chapter 2). Study 2 focussed on cardiac autonomic function as a potential

mechanistic link between OSA and AF. This was assessed using Heart Rate Variability (HRV) (chapter 3). Study 3 was a pilot study of OSA treatment in AF patients using MAS therapy (chapter 4).

Results: 62.6% of patients were newly diagnosed with OSA: 31.8% mild, 18.7% moderate, 12.1% severe. Patients with moderate to severe OSA (AHI ≥ 15/hr) showed an increased BMI, neck circumference and Mallampati score, but were not significantly different in terms of daytime somnolence (Epworth sleepiness scale 5.7 ± 3.3 vs 6.9 ± 3.4, p =0.079). Oxygen desaturation index (ODI) derived from a Level 3 portable sleep study device performed best for the diagnosis of moderate to severe and severe OSA, with excellent diagnostic accuracy (AUC 0.899, 95% CI 0.838 – 0.960 and AUC 0.925, 95% CI 0.859 – 0.991 respectively). Although limited differences in HRV were found between OSA and non-OSA groups, we found a chronic increase in parasympathetic nervous activity in paroxysmal AF patients with OSA. MAS therapy showed high rates of acceptance, compliance and efficacy in AF patients.

Conclusions: This PhD thesis contributes to our understanding of the association between AF and OSA across a spectrum of epidemiology, diagnosis, mechanistic pathways and treatment.

1.0 Literature Review:

1.1 Introduction

A strong epidemiological link between Obstructive Sleep Apnoea (OSA) and Atrial Fibrillation (AF) has long been established. What is less clear is the nature of this association, and whether or not OSA plays a causative role in the generation and perpetuation of AF, at least in some patients. Certainly, numerous studies provide pathophysiological plausibility to support the idea of OSA as a promoter of atrial remodelling, and a trigger for acute AF episodes (1-3). Further, observational studies have consistently demonstrated that effective treatment of OSA, particularly following rhythm control strategies, may improve outcomes in AF patients (4-7). The accumulated evidence so far has prompted writers of international guidelines to recommend that best practice management of AF should include diagnosis and treatment of underlying OSA (8-11). However, optimal clinical pathways by which to achieve this are poorly studied and remain unarticulated.

Despite the above-mentioned evidence, there is a lack of high quality, randomised controlled data to show the impact of effective OSA treatment on AF outcomes. Indeed, randomised trials of Continuous Positive Airway Pressure (CPAP) therapy for other cardiovascular outcomes have been disappointing (12-14), perhaps in part due to low CPAP compliance in cardiovascular populations. The usual second line therapy for OSA, Mandibular Advancement Splint (MAS) therapy, while less effective at lowering the AHI, may be better tolerated in cardiovascular populations. It may therefore be more effective at lowering the overall burden of sleep disordered

breathing, if it is worn for a greater proportion of the night. The role of MAS in AF populations has not been reported.

This literature review is presented in several parts in order to contextualise and support the clinical studies of this thesis. **Section 1.2, "Sleep Disordered Breathing"**, introduces the common condition of obstructive sleep apnoea and summarises its diagnosis and management. Several management options are reviewed, including Continuous Positive Airway Pressure (CPAP) therapy and Mandibular Advancement Splint (MAS) therapy. MAS is an oral appliance treatment for OSA, and is of particular relevance since Study 3 of this thesis (Chapter 4) comprises a pilot study of MAS therapy for AF patients. The section on OSA and Cardiovascular Risk also highlights the association between OSA and AF, the central theme of this thesis.

Section 1.3 "Clinical Approaches to the Diagnosis of OSA" provides a more in-depth review of the various screening tools and tests which are used for the diagnosis of OSA. Importantly, it describes a Level 3 portable sleep study device and compares this to the gold standard investigation for OSA, in-laboratory polysomnography. The diagnostic accuracy a portable sleep study device in an atrial fibrillation population is reported in Study 1 (Chapter 2).

Section 1.4 "Mandibular Advancement Splint Therapy" describes in detail Mandibular Advancement Splint (MAS) therapy, the leading treatment alternative to CPAP for the treatment of OSA. It discusses the mechanism of action, efficacy and adherence, neuro-behavioural and cardiovascular outcomes and side effects. Areas

for future research are identified, including the need to quantify the impact of MAS therapy on cardiovascular outcomes. A pilot study of MAS therapy in an AF cohort is reported in Study 3 (Chapter 4).

Section 1.5 "The Relationship between Obstructive Sleep Apnoea and Atrial Fibrillation" examines the state of the published literature to date addressing the relationship between these two chronic conditions. This includes studies of pathophysiology, epidemiology, screening and treatment studies. The section on mechanistic pathways and particularly of autonomic perturbations is relevant to Study 2 (Chapter 3) which examines changes in cardiac autonomic modulation in AF patients with and without OSA.

In summary, this literature review provides an overview of OSA, its diagnosis and treatment, particularly with MAS therapy, and the relationship between OSA and AF.

1.2 Sleep Disordered Breathing

A slightly modified version of this chapter was published as:

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1.2.1 Introduction

The term Sleep Disordered Breathing (SDB) encompasses a spectrum of abnormalities including snoring, obstructive sleep apnoea (OSA), central sleep apnoea (CSA), respiratory related arousals and hypoventilation. This chapter focuses on OSA, and to a lesser extent CSA. It provides a clinical update of recent advances in the diagnosis, management and prognosis of these two conditions. An increasing array of treatment modalities, particularly for OSA, broadens the opportunity for personalised therapy tailored to the individual patient.

1.2.2 Definition of Obstructive Sleep Apnoea

OSA is characterised by repetitive upper airway collapse during sleep, accompanied by recurrent oxygen desaturations, nocturnal arousal and fragmented sleep. Patients may present with classic symptoms including snoring, unrefreshing sleep, choking arousals, poor sleep quality, reduced neurocognitive functioning or even motor vehicle accidents sustained due to “micro-sleeps” whilst driving. A growing number of asymptomatic patients are presenting for assessment as recognition of the disorder increases, particularly among patients with cardio-metabolic disorders (eg. atrial fibrillation, hypertension, coronary artery disease, type 2 diabetes) in whom there is a high prevalence of OSA.

1.2.3 Diagnosis of Obstructive Sleep Apnoea

In-laboratory polysomnography (PSG) remains the gold-standard for diagnosis of sleep apnoea (both obstructive and central) although the use of full or limited channel

sleep studies which may be performed at home is rapidly increasing. These limited channel home devices have a good sensitivity and specificity for moderate to severe OSA, however they are less reliable in patients with co-morbidities and complex forms of sleep disordered breathing (15).

1.2.4 Obstructive Sleep Apnoea Phenotypes

In the era of personalised medicine, individual phenotypic characteristics provide an opportunity for targeted therapy. The aetiology of OSA is complex and is influenced by a number of factors including craniofacial structure, obesity, upper airway collapsibility, muscle tone during sleep, arousal threshold and ventilatory control (16). The relative contributions of these factors vary between individuals and provide research targets for the ongoing development of personalised treatment. In the clinical setting there are a number of phenotypic factors which already provide the opportunity for a targeted management approach. Obesity is the most obvious of these, and weight loss is a critical component of therapy. Supine-dependent OSA, when present, lends itself to positional therapy, either alone or in combination. Specific upper airway factors may warrant surgical assessment (see surgical treatment, below).

1.2.5 Obstructive Sleep Apnoea Management

Therapy for OSA continues to evolve as no treatment has yet combined the ideals of optimal efficacy and universal tolerability. Treatment goals for OSA include improvement in daytime symptoms and quality of life, improved sleep quality, reduction in cardio-metabolic risk, as well as normalisation of the Apnoea Hypopnoea Index (AHI) and nocturnal oxygen desaturations. Individuals may also have specific

treatment goals, such as the hypertensive patient who wishes to optimise blood pressure control, a professional driver who wishes to maintain their driving license, or the patient with atrial fibrillation who wishes to improve their risk of post-ablative recurrence. Hence therapy choice should focus on individual treatment goals, as well as on specific OSA characteristics. As patient engagement is critical to successful therapy, elucidating the patient's treatment preferences and addressing concerns is an important aspect of management. A burgeoning number of treatment modalities exist, all with relative advantages and disadvantages.

1.2.5.1 Positive Pressure Therapies

In the early 1980s, nocturnal continuous positive airway pressure (CPAP) applied via the nares was first described as a highly effective therapy for OSA (17). Positive airway pressure (PAP) interfaces have undergone significant development and today a diverse range of machines and masks exist. PAP persists as the most effective therapy for lowering parameters of OSA severity including AHI, Oxygen desaturation Index (ODI) and oxygen saturation (SaO_2) nadir (18). Advances to PAP therapy include features such as expiratory pressure relief to improve patient comfort, and the development of other modalities including automatic and bilevel positive airway pressure machines (APAP and BPAP respectively). APAP removes the need for in-laboratory titration and ongoing treatment maintenance associated with changing pressure requirements, though it is more expensive.

Adherence remains the most significant obstacle to the real world effectiveness of PAP therapy (19). Adherence is influenced by numerous factors including tolerability, patient and partner expectations and symptom control. There is a dose-response relationship between hours of usage and improvement in daytime symptoms (20-22), with PAP most effective when worn on most nights for the duration of sleep time. A minimum nightly usage of four hours is now embedded in government funding access schemes.

When commencing patients on PAP, clinicians may choose to order a CPAP titration study to determine the patient's optimum treatment pressure in an overnight laboratory setting. Alternatively, APAP may be used in an outpatient setting for an "at-home" pressure titration. Close follow-up is critical to address problems and optimise adherence. New technology in the form of remote monitoring, machine displays and web-based applications facilitate patient engagement in monitoring their own usage data and response to therapy. Perhaps more than any other field in medicine, sleep medicine is situated at the forefront of objective monitoring of patient adherence with therapy. Cloud-based software allows physicians and patients to monitor adherence and response to therapy on a nightly basis, and to make therapeutic adjustments accordingly.

The clinician can also monitor for the development of Treatment Emergent Central Sleep Apnoea (TECSA), also known as Complex Sleep Apnoea Syndrome, reported to occur in 8% of cases (23). This is the development of central apneas and hypopneas with the alleviation of obstructive events in response to PAP therapy, and

can negatively impact treatment tolerance and adherence. Treatment options for TECSA include permissive airflow limitation – reducing CPAP pressures to allow some minor upper airway obstruction, judicious application of oxygen, or Adaptive Servo Ventilation (see ASV, below).

1.2.5.2 Mandibular Advancement Splint Therapy

Mandibular Advancement Splint (MAS) therapy is the leading treatment alternative which may be considered following intolerance to PAP or on the basis of patient preference (24). Although not as efficacious in lowering the AHI, this reduced efficacy may be balanced by increased adherence and patient tolerance. In the short term, this may result in overall similar outcomes, including similar improvement in daytime somnolence and blood pressure (25-28), although more studies are needed to assess long term outcomes, particularly for severe OSA. Additionally, MAS has the advantages of being highly portable, silent, and often preferred by users to CPAP treatment. Like PAP devices, MAS now has the capability to document patient adherence via a compliance recorder in the form of an embedded intra-oral temperature sensor.

It should be noted that therapeutic response to MAS is much more variable than PAP. Some patients may have an excellent response, even in the presence of severe OSA, whereas others may derive little benefit. Around 70% of the OSA population will receive clinical benefit from MAS therapy (>50% reduction in OSA) with one third showing complete resolution of OSA. Normalisation of the AHI is more common in

mild or moderate OSA, as compared with severe OSA. Reliable predictive factors for treatment response remain elusive, and are the topic of ongoing research. A number of patient factors have been associated with treatment response such as lower AHI, younger age, female gender, and less obesity (by BMI and neck circumference measures). However such patient factors alone are insufficient for reliable prediction and objective tests are likely needed to determine response (29, 30). A recent review summarises various prediction tests proposed to determine MAS treatment outcome (e.g. craniofacial and nasophayngoscopic assessments, optimal CPAP pressure, spirometry, nasal resistance, site of pharyngeal collapse) (31). These have variable diagnostic accuracy and clinical applicability and many have not been validated in subsequent samples. A single night titration approach, analogous to CPAP titration, appears promising for clinical applications (32). It is recommended that patients be fitted with a MAS by a qualified dentist and should undergo a repeat diagnostic sleep study with the device in situ once the MAS has been optimised, to assess its efficacy. MAS therapy is addressed in detail in section 1.4.

1.2.5.3 Positional Therapy

Position-dependent OSA is that in which obstructive events occur exclusively or predominantly in one sleeping position, most commonly the supine position (~50% of patients (33)). Targeted therapy to prevent supine sleep may be an effective treatment in this subgroup of patients. Various techniques have been employed to prevent supine sleep, ranging from the crude “tennis-ball in the back” technique, where a tennis ball or similar object is sewn into the back of sleepwear, to new-generation devices which have a neck or thoracic band that vibrates in increasing intensity when

the patient lies in the supine position. Positional therapy has been tested only in small studies, and is not as effective as CPAP in lowering the AHI, though it may be better tolerated. Positional therapy lends itself to combination treatment approaches and may be used in conjunction with other modalities, such as MAS or weight loss, to reduce OSA in non-supine positions for an additive effect

1.2.5.4 Surgical Treatments for Obstructive Sleep Apnoea

A number of surgical approaches have been used in the treatment of OSA, targeting a range of anatomical structures including the nose, soft palate, tongue, tonsils, and jaw position. For example, radio-assisted uvulopalatoplasty combined with tonsillectomy has success rates reported between 60 and 70%, albeit with a liberal definition of success (post-operative AHI <20/hr and a reduction of at least 50% in the pre-surgical AHI) (34). Assessment of factors including tonsillar size and palate position can predict response to surgery (35). Other surgical procedures which target jaw structure include maxillomandibular advancement (MMA). Whilst a highly invasive surgery, MMA has a surgical success rate of 85% using the same liberal definition of success. An AHI less than 5/hr was achieved in approximately 40% of patients (36). Therefore, surgical approaches, while not as effective as CPAP in lowering the AHI, may have a role in select patients who are intolerant or non-compliant with CPAP or MAS and who have suitable anatomical characteristics.

Implantable hypoglossal-nerve stimulation devices have been shown in a multi-centre cohort study to significantly improve the AHI, ODI and patient symptoms in a select

group of patients with moderate to severe OSA who failed CPAP (37). The technique has only recently been implemented into clinical practice. Its clinical role is likely to be limited due to its invasive nature and cost. At this point in time it is not clinically available in Australia.

Bariatric surgery should be considered as part of the overall management of morbid obesity in patients with concomitant OSA (see Weight Loss, below).

1.2.5.6 Weight Loss

Non-surgical weight loss is well-demonstrated to reduce parameters of OSA such as AHI. However, normalisation of the AHI is achieved in only a minority of cases (38). Similarly, bariatric surgery substantially reduces the AHI, although the response is variable and a degree of residual OSA is likely to persist post-operatively (39). One RCT found no statistical difference in AHI between surgical and non-surgical approaches to weight reduction, despite substantial differences in the amount of weight lost. (40). For either approach, a repeat diagnostic sleep study is recommended following weight stabilisation to reassess baseline OSA and inform the need for ongoing OSA management. Weight loss should be routinely recommended in the management of OSA, and lends itself to multi-disciplinary collaboration with dieticians, physiotherapists and endocrinologists or engagement with a healthy weight clinic if available.

1.2.5.7 Other treatments

Nasal Expiratory Positive Airway Pressure (EPAP) devices (Provent) are small valvular devices worn in the patient's nostrils which provide resistance on expiration. The self-generated increase in EPAP provides a pneumatic splint to prevent upper airway collapse, in a similar manner to CPAP. Nasal EPAP devices are effective in reducing the AHI, ODI and SaO2 nadir, though not to the same extent as nasal CPAP (41). Tolerance is highly variable.

Supervised cardiovascular exercise has been demonstrated in a recent meta-analysis to effectively lower the AHI, independently of weight loss (42). This effect was surprisingly not significantly different from CPAP, though the analysis included a relatively small number of studies examining the effects of exercise. Cardiovascular exercise should be routinely recommended in all ambulant patients with OSA as an adjunct to other therapy.

Pharmacological agents including SSRIs (eg Mirtazapine, Paroxetine), Theophylline and Aminophylline, nasal decongestants (eg Xylometazoline), steroids (eg Fluticasone), anti-reflux agents (eg Pantoprazole), the carbonic anhydrase inhibitor Acetazolamide, and the sedative Eszopiclone have been examined in the treatment of OSA, each targeting different aspects of OSA pathophysiology. For example, SSRIs may stablise the upper airway and increase hypoglossal tone (43). Eszopiclone has been shown to reduce the AHI in patients with a low arousal threshold (44). While some of these agents are promising, evidence of their efficacy is thus far insufficient to recommend their clinical use (24) and further trials are awaited.

1.2.6 Symptom Control for Obstructive Sleep Apnoea

Occasionally daytime symptoms such as hypersomnolence may persist, despite adequate control of the AHI on treatment. This should flag the possibility of co-morbid disorders for exclusion, which may be sleep-related (e.g. insomnia, narcolepsy, idiopathic hypersomnolence, periodic limb movement disorder), or secondary to other aetiologies (e.g. iron deficiency, thyroid disease, drug-related). If other causes are excluded, the clinical focus may shift to symptom control. Non-pharmacological measures include scheduled naps, increased sleep time or improved sleep hygiene. Pharmacological options include vigilance promoting agents (e.g. Modafinil), which has been shown to improve wakefulness in CPAP-treated OSA patients (45), or a stimulating anti-depressant such as the SNRI Venlafaxine.

1.2.7 Obstructive Sleep Apnoea and Cardiovascular Risk

A common question encountered by patients and physicians is whether the relatively asymptomatic individual should persist with OSA therapy solely in order to lower their cardiovascular risk. In the case of hypertension, there is convincing evidence, including meta-analysis of RCTs, that both CPAP and MAS therapy reduce blood pressure, albeit to a small degree (~2.5mmHg) (25, 46). Blood pressure reduction may be greater in specific patient groups, such as those with baseline hypertension, especially resistant hypertension (47) and in severe OSA (48). Hypertension has been linked specifically to REM-OSA, independent of overall OSA severity (49). The highest proportion of REM sleep occurs in the latter half of the night, which has implications for treatment effectiveness. For example, the patient who removes PAP after three hours may still experience significant REM-OSA, although this effect has yet to be

examined in clinical treatment trials. One meta-analysis showed that for minimally symptomatic OSA patients, CPAP is only effective in lowering blood pressure when worn for > 4 hours per night (50).

To date there is a paucity of randomised control trial evidence addressing the impact of OSA treatment on cardio-vascular endpoints including mortality. The SAVE trial (51) found that CPAP did not prevent cardiovascular deaths in patients with established cardiovascular disease and moderate to severe OSA. However, average CPAP usage was in the sub-optimal range at 3.3 hours per night. No large RCTs have examined CPAP for primary prevention of cardiovascular endpoints. This is despite strong epidemiological data identifying OSA as a risk factor for stroke, cardiac events and death (52, 53).

In atrial fibrillation (AF), small to medium observational treatment studies suggest that patients undergoing Pulmonary Vein Isolation (PVI) or electrical cardioversion for AF have a higher risk of recurrence if they have untreated OSA, a risk which is mitigated by treatment with CPAP. These studies are examined in detail in section 1.5. Once again, there is a paucity of randomised control data to assess the impact of OSA treatment on AF burden, or beyond that to assess impact on cardiovascular outcomes such as stroke. Nonetheless, mounting expert opinion suggests that risk factor assessment for AF should include assessment and treatment for OSA (5, 54-56).

1.2.8 Definition of Central Sleep Apnoea

Central Sleep Apnoea (CSA) is much less common than OSA, and is characterized by apnoeic events in the absence of respiratory effort. The pathophysiology is complex and can involve hyperventilation or hypoventilation states. In most cases encountered in clinical practice it is associated with left ventricular failure or neurological pathology including opioid use; in the former it may manifest as Cheyne-Stokes respiration. Management therefore should include a multi-disciplinary strategy to address the underlying cause, including optimisation of heart failure and minimisation of opioids or sedative medications, as applicable.

1.2.9 Continuous Positive Airway Pressure (CPAP) for Central Sleep Apnoea

Randomised control trial data from the CANPAP study demonstrates that CPAP reduces the AHI, improves nocturnal desaturation and also improves Left Ventricular Ejection Fraction (LVEF) in patients with a LVEF < 40% and moderate to severe CSA. These benefits did not translate into extended survival in this study (57), although a post-hoc analysis suggested survival benefit and improved LVEF in patients with the greatest reduction in AHI (58). Nonetheless, CPAP may be considered as the initial therapy of choice in patients with CSA and reduced ejection fraction.

1.2.10 Adaptive Servo Ventilation for Central Sleep Apnoea

Adaptive Servo Ventilation (ASV) is a sophisticated variation on bilevel ventilation which responds to the cyclical nature of Cheyne Stokes Respiration (CSR), by detecting the apnoeic and hyperpnoeic phases and varying pressure support accordingly in real time. Although effective in normalising CSR, this technology has come under increased scrutiny following the publication of the SERVE-HF trial (59).

This trial showed increased cardiovascular and all-cause mortality for patients with reduced LVEF (<45%) and predominantly central sleep apnoea treated with ASV as compared to best medical care, though neither of these outcomes was the primary end point. Reasons for the findings remain unclear. In general, ASV is now considered contra-indicated in patients with CSA and reduced LVEF (<45%) as the results of further trials are awaited. Ongoing indications for ASV may include CSA (especially with CSR) and preserved ejection fraction, CPAP emergent CSA, and opioid induced CSA. From a practical standpoint, ASV should be reserved for indications where a trial of a less costly therapy like CPAP has failed.

1.2.11 Other Therapies for Central Sleep Apnoea

Transvenous stimulation of the phrenic nerve can be achieved by an implantable device which provides nocturnal stimulation of the phrenic nerve in order to alleviate central apnoeas. Recently published data shows improvement in the AHI and CAI (central apnoea index) sustained at 12 months in patients with moderate to severe CSA, as well as improved symptoms and quality of life (60) . Acetazolamide, a carbonic anhydrase inhibitor, has been demonstrated to lower the AHI in both primary CSA and CSA associated with heart failure, although there are relatively few studies demonstrating this. Its mechanism is to induce a metabolic acidosis and thereby increase central respiratory drive. In practice it may be a useful adjunct to PAP therapies or as an alternative when PAP is not tolerated. Similarly, supplementary nocturnal oxygen may be used judiciously as a second line in a select group of patients who are intolerant of PAP with significant nocturnal oxygen desaturations.

1.2.12 Sleep Disordered Breathing: Models of Care

As a chronic, multi-system disease, OSA (and CSA) requires a multi-disciplinary approach to management. The primary care physician plays a critical role and is often the first practitioner to be alerted to patient symptoms, with a high index of suspicion required to consider the diagnosis. This is especially true when patient symptoms are subtle or atypical. Specialists in other areas such as cardiology or endocrinology must similarly maintain a high index of suspicion, as patients with other cardio-metabolic co-morbidities may have limited daytime symptoms, despite having a very high prevalence of OSA (61).

Like other chronic diseases, sleep apnoea presents the challenge of frequently required reviews in order to assess therapy adherence, control of symptoms (particularly with regards to sleepiness and accident risk) and efficacy of treatment including data from PAP machines. This provides an opportunity for a stratified, team-based model of care including nurse practitioners, sleep technicians, general practitioners and sleep physicians.

1.2.13 Future Directions: P4 medicine

P4 medicine is a proactive approach to chronic disease management, incorporating the concepts of disease prevention, personalized precision medicine, the use of technology and advances in “omics” (eg genomics, proteomics, metabolomics). The concept of P4 medicine was originally developed by Leroy Hood, and has been articulated specifically as it relates to OSA by Allan Pack (61). The four Ps are: predictive, preventive, personalized and participatory, with an emphasis identifying

phenotypic characteristics of relevance to the individual and using these to prevent disease and optimise clinical care.

The large variation in response amongst OSA patients to the various treatment modalities highlights the importance of tailoring treatment to the individual. Certainly with regards to the final P, participatory, sleep apnoea lends itself to this approach arguably more than any other field in medicine. Patients can now use apps and other tools to monitor their own PAP compliance data and control of respiratory events. Likewise, their clinicians can follow this data in real time and make treatment modifications accordingly.

There is an evolving future ahead in the management of SDB, as the one-size-fits-all approach is gradually falling away to be replaced by a tailored, focused and informed approach which involves patients more than ever in their own medical care.

1.3 Clinical Approaches to the Diagnosis of OSA

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1.3.1 Introduction

The diagnosis of Obstructive Sleep Apnoea (OSA) involves a comprehensive clinical assessment of patient symptoms, physical signs, co-morbidities and objective investigation using an appropriate diagnostic test. Ideally, this occurs within a multi-disciplinary framework, and may require input from a Family Physician, Sleep Physician, Ear-Nose-Throat Surgeon, Dentist and Sleep Technologist.

1.3.2 Symptoms of OSA

Hallmark symptoms of OSA include snoring, witnessed apnoeas and daytime fatigue, which are described in further detail below. Importantly however, there is a substantial group of patients who may report few, or atypical, symptoms.

1.3.2.1 Symptoms during Sleep

Sleep related symptoms of OSA may arise directly from the repetitive upper airway obstruction that is characteristic of OSA. Snoring is highly prevalent in OSA (62, 63). It is produced by vibrating soft tissues of the upper airway in the context of turbulent airflow caused by partial upper airway obstruction. Snoring is commonly reported by the patient's bed-partner rather than the patient themself, and may cause significant social disruption. Although very common in OSA, snoring is also highly prevalent in the general population, and is therefore is not a specific diagnostic feature. Similarly, the absence of snoring does not exclude the presence of OSA.

The presence of witnessed apnoeas is a highly specific feature of OSA, although with

a lower sensitivity (present in only around 77% of patients) (63). Witnessed apnoeas are the directly observed cessation of nocturnal airflow, usually by the patient's bed-partner.

Other nocturnal symptoms include frequent nocturnal arousals, nocturia, nocturnal choking, sleep fragmentation, insomnia and poor sleep quality and diaphoresis (see Table 1).

1.3.2.2 Symptoms during Wakefulness

Symptoms of OSA during wakefulness reflect the impact of OSA-related sleep fragmentation and intermittent hypoxia. The most prominent symptom is daytime fatigue and/or hypersomnolence, often with a propensity to fall asleep in passive situations. Other daytime symptoms include reduced cognition (manifesting as poor memory or concentration), altered mood, and an increase in the risk and severity of motor vehicle accidents (64). The presentation of OSA is highly variable, and recent cluster analysis work has highlighted the existence of distinct and heterogeneous symptom phenotypes, including a sleepy group, a relatively asymptomatic group, and a group with comorbid insomnia (63).

1.3.3 Physical Examination

Physical examination may reveal anatomical risk factors and/or co-morbidities of OSA. In addition, anatomical characteristics may aid in understanding the underlying

pathophysiological causes, and thereby may play a role in predicting response to particular therapies (see chapters 6, 12, 13 and 19).

Age and gender specific considerations should also inform the examination.

1.3.3.1 Craniofacial and Airway Features

Specific craniofacial features increase the risk of airway collapsibility and therefore OSA. Mandibular retrusion, maxillary deficiency and/or constriction, inferior displacement of the hyoid bone, and cranial base abnormalities are among the most commonly reported findings on cephalometry of patients with OSA (65, 66). Clinical examination should include an assessment for these craniofacial factors (see Table 2).

Tonsillar (palatal and lingual) hypertrophy, macroglossia, oropharyngeal narrowing, oedema and erythema of the soft palate are soft tissues abnormalities that can relate to OSA and snoring. The level of obstruction of the oropharynx can also be assessed with the modified Mallampati classification, performed with the patient sitting upright with the tongue fully protruded (67). Nasal obstruction should also be assessed because it is often an initiating or exacerbating factor, and may warrant referral to an ENT surgeon for assessment and management (see chapter 15).

1.3.3.2 Obesity

The association between obesity or increased body mass index (BMI) and OSA is well established. In a sleep clinic population, 28% of patients were obese (BMI

greater than 30 kg/m^2) and 47% were overweight (BMI between 26 and 30 kg/m^2)(68). Specifically, distribution of fat around the neck and waist, known as *central obesity*, is particularly important. Both neck and abdominal circumference are strong predictors for OSA (68, 69). The metrics of obesity generally have a linear association with the likelihood and severity of OSA, and there is no single threshold value of neck or abdominal circumference above which OSA occurs. The role of obesity in the pathogenesis of OSA is likely to differ between ethnic groups. For example, Asian patient may demonstrate OSA at lower levels of obesity when compared to Caucasians, due to increased craniofacial restriction (70, 71).

1.3.4 Co-morbidities

OSA is associated with many other comorbidities. These include hypertension (especially resistant hypertension), cardiovascular diseases including arrhythmia, stroke, diabetes, thyroid disease, as well as rare genetic conditions such as Marfan's syndrome. Features of these should be elicited during the clinical history and examination. In certain high risk groups, screening for OSA may be warranted despite the absence of symptoms. As an example, in patients with atrial fibrillation (a common cardiac arrhythmia), the diagnosis and treatment of OSA has been recommended as part of routine management (9, 72) .

1.3.5 Questionnaires

Several questionnaires including the Berlin Questionnaire, Stop-Bang and OSA50 have been developed to identify patients at high risk of OSA. Many questionnaires have a high sensitivity for the presence of moderate to severe OSA, though this may be offset by a low specificity (see table 3). In dental practice, these questionnaires

should be considered as screening tools and they should be interpreted with caution in light of their low specificity. Hence, questionnaires are generally inadequate for the diagnosis of OSA but may be clinically useful as a means to detect high risk patients who should be referred for further diagnostic testing.

The Epworth Sleepiness Scale (ESS) is commonly used to assess daytime sleepiness but was not developed as a diagnostic screening tool for OSA. The ESS assesses the propensity of an individual to fall asleep in passive situations (such as when watching TV or whilst a passenger in a motor vehicle). A score of ≥ 11 out of a possible 24 indicates excessive daytime somnolence (EDS), whilst a score ≥ 16 indicates severe EDS. Changes in the ESS can be monitored to evaluate response to OSA treatment.

Fatigue is distinct from sleepiness, and may have a higher sensitivity and specificity for the diagnosis of OSA (73). The impact of fatigue as a symptom of OSA requires further evaluation, and may be particularly relevant for patients who are commercial drivers, (74, 75) or those with co-morbidities (76). Fatigue can be assessed using the Fatigue Severity Scale (FSS) (see Table 4).

1.3.6 Diagnostic Tests

There are a number of diagnostic tests for OSA available, each with particular advantages and disadvantages (see Table 3). The choice of investigation depends upon several factors including accessibility to specialist laboratory facilities, patient mobility, local resources, and the pre-test probability of OSA.

1.3.6.1 Polysomnography

Polysomnography (PSG) is considered the gold-standard investigation for the diagnosis of OSA. It is comprised of a collection of non-invasive biological signals which are recorded during sleep and interpreted together in a diagnostic montage. These signals include: 1) Electro-encephalogram (EEG) which records brain wave patterns for sleep staging, 2) Electro-oculogram (EOG) which records eye movements, 3) Electromyogram (EMG) which records muscular activation of certain muscle groups including the mandible, diaphragm, anterior tibialis (other muscle groups can be added for specific purposes, such as the addition of temporalis and masseter EMG in the diagnosis of bruxism), 4) naso-oral airflow via a thermistor, 5) nasal air pressure via prongs, 6) snore sensor 7) haemoglobin-oxygen saturation probe, 8) thoracic and abdominal movement bands for the measurement of respiratory effort, 9) body position sensor, 10) Electrocardiogram (ECG) to record the electrical activity of the heart (see Figure 1). Taken together these signals provide a rich, multi-layered tool for the diagnosis of numerous sleep-related conditions including OSA, central sleep apnea (CSA), parasomnias, nocturnal cardiac arrhythmias, bruxism, nocturnal epilepsy, sleep fragmentation and others.

Recordings gathered by the PSG are manually scored by trained sleep technologists and interpreted by sleep physicians, taking into account the clinical context. The data is examined for the occurrence of apnoeas (complete cessation of airflow for 10 seconds or more) and hypopneas (reduction in amplitude of airflow or thoraco-abdominal wall movement for 10 seconds or more with an accompanying oxygen desaturation of at least 3% and/or associated arousals). Notably, variations exist in

scoring definitions, especially for hypopneas.

The severity of sleep apnoea is assessed with the apnoea-hypopnea index (AHI), which is the number of apnoeas and hypopneas that occur per hour of recorded sleep time. An AHI of 5 to <15/hr is considered mild, 15 to < 30/hr is moderate and ≥30/hr is severe OSA. The value of the AHI in diagnosis, classification of severity, and treatment decisions has been called into question, and current efforts are aimed at identifying novel PSG biomarkers that have clinical relevance beyond the AHI. For example, additional factors including the degree of oxygen desaturation and the extent of sleep fragmentation are important for the clinical interpretation of OSA severity. Other notable features of OSA may be identified including the presence of REM-related OSA, positional OSA or the presence of concomitant central apnoeic events. Artificial intelligence is anticipated to change the way such information is analysed in the future.

Generally, a diagnosis of OSA can be based on a single night of testing, although night-to-night variability in results should be considered, especially if test results are negative for a patient with high clinical risk of OSA. Apparent variability in the severity of OSA may result from multiple factors, including variability in sleeping position, alcohol use, prior sleep debt, sleep efficiency, and sleep stage distribution. Further, variation in the definitions and scoring of the respiratory events can also significantly alter the AHI. The major limitations of PSG are that it is costly, labour-intensive and may be difficult to access for certain patient groups. Hence it is best reserved for more complex cases, with comorbid sleep disorders or other medical comorbidities.

1.3.6.2 Limited Channel Sleep studies

Although not as information-rich as full PSG, limited channel sleep studies have the advantage of being potentially more accessible and less costly than in-laboratory PSG. While they may fail to elicit some of the subtleties of sleep disordered breathing described above, they generally perform well in the detection of simple sleep apnoea, particularly in uncomplicated patients with a high pre-test probability on the basis of symptoms or other risk factors. A level 2 sleep study refers to a full PSG which is performed at home, without the direct observation of a sleep technician, and therefore with a slightly higher risk of a technically inadequate study. A level 3 sleep study comprises only 4 signals, which generally includes thoraco-abdominal excursion, nasal air pressure, haemoglobin-oxygen saturation, and heart rate. Thus the sleep stage is not captured due to the absence of EEG, and the presence of sleep must be inferred. Overnight oximetry (a level 4 device) is a single channel sleep study device which provides information only about the timing and severity of oxygen desaturation events, and may also record heart rate. Importantly, oximetry alone is unreliable for distinguishing obstructive vs central sleep apnoea. These limitations should be considered when using oximetry to screen for sleep apnoea and for follow-up assessments.

1.3.7 Conclusion

In summary, the diagnosis of OSA is made following a comprehensive clinical assessment and an appropriate diagnostic test under medical supervision. Familiarity with the chosen diagnostic test characteristics is critical to an effective diagnostic pathway. Clinicians need to be cognisant of the pitfalls associated with diagnostic

testing, and a multidisciplinary approach to diagnosis and management is highly recommended.

Table 1: Prevalence of Symptoms in a large country-specific cohort (Iceland) with moderate to severe OSA

Symptom	Reported Prevalence
Snoring	92%
Daytime sleepiness / fatigue	88%
Witnessed apnoeas	77%
Frequent nocturnal arousals	73%
Restless sleep	60%
Nocturnal diaphoresis	50%
Nasal congestion	48%
Daytime nap	45%
Insomnia	29%
Morning headaches	24%
Micro-sleeps whilst driving	18%
Choking arousals	18%
Other symptoms include: Sexual dysfunction, impaired concentration, impaired memory, oesophageal reflux	

Data from Ye et al 2014 (63)

Table 2: Signs of OSA

Signs of OSA
• Obesity
• Increased neck circumference
• Increased waist circumference
• Retrognathia
• Maxillary constriction
• Overjet
• Overbite
• Tonsillar hypertrophy
• Macroglossia
• Oropharyngeal narrowing (assessed by Mallampati class)
• Soft palate erythema and edema
• Nasal obstruction
• Hypertension

Table 3: Comparison of diagnostic tests available for OSA and test characteristics for the detection of an AHI ≥ 15/hr (moderate to severe OSA), as compared to the gold standard of PSG.

Test	Channels	Sensitivity	Specificity	PPV	NPV
Level 1: In-laboratory PSG	EEG, EOG, EMG, ECG, airflow, air pressure, respiratory and abdominal effort, SaO2, HR, limb movement, snore probe, position sensor	100% (gold standard)	100% (gold standard)	100% (gold standard)	100% (gold standard)
Level 2: Portable PSG	EEG, EOG, EMG, ECG, airflow, air pressure, respiratory and abdominal effort, SaO2, HR, limb movement, +/- snore probe, position sensor	83 – 86% (77)	92 – 97% (77)	89 – 97% (77)	86 – 88% (77)
Level 3: Portable limited channel devices	4 – 7 channels, usually airflow, respiratory effort, HR, SaO2.	64–100% (15, 78)	41 – 100% (15, 78)	94% (79)	88% (79)
Level 4: Overnight Oximetry	SaO2, HR	90-93% (80-82)	75 - 83% (80-82)	73.6% (80)	95.5% (80)
Questionnaires					
Berlin		77%- 87 % (83, 84)	39 - 44% (83, 84)	72% (84)	62% (84)
Stop-Bang		93% (84)	39% (84)	74% (84)	76% (84)
OSA-50		91% (84)	46% (84)	76% (84)	74% (84)

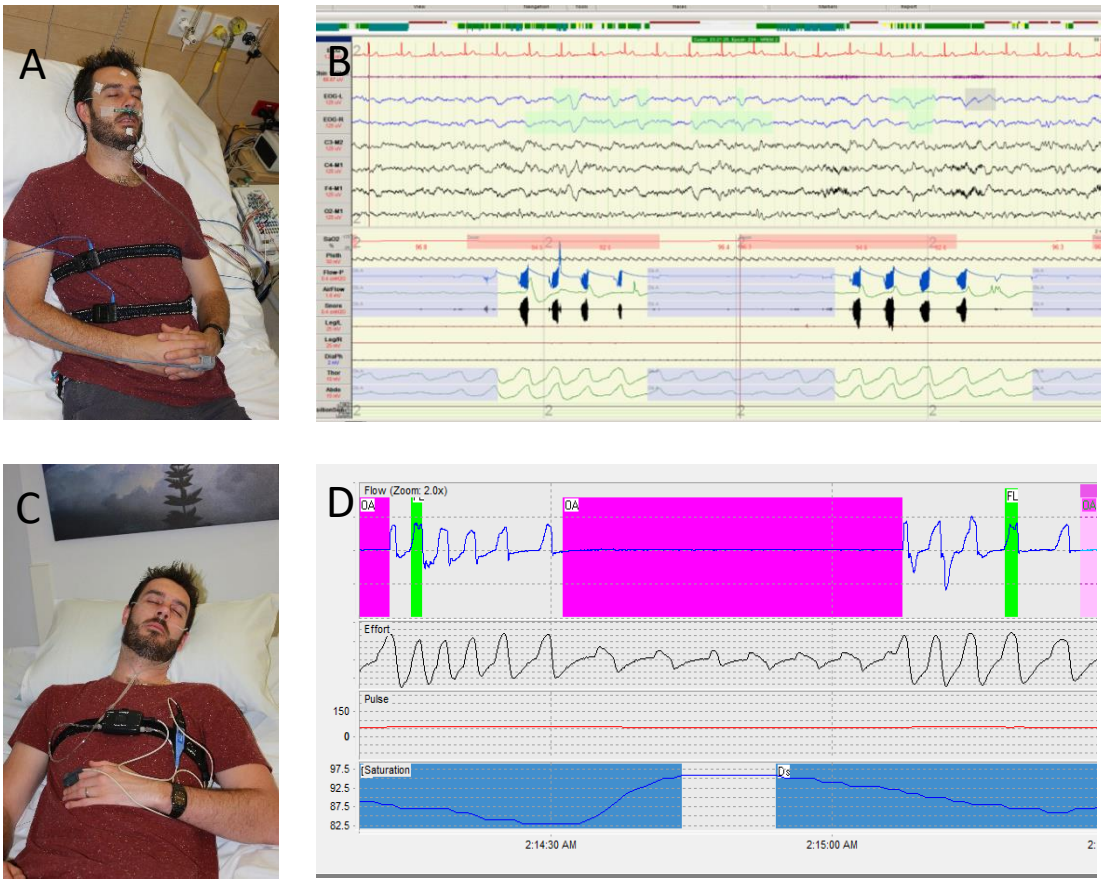
PSG: polysomnography, EEG: Electro-encephalogram, EOG: Electro-oculogram, EMG: Electromyogram, ECG: Electrocardiogram

Table 4: Fatigue Severity Scale (FSS)

NB: Patients are instructed to choose a number from 1 to 7 that indicates their degree of agreement with each statement. 1 indicates strongly disagree and 7 indicates strongly agree.

STATEMENT:
1. My motivation is lower when I am fatigued.
2. Exercise brings on my fatigue.
3. I am easily fatigued.
4. Fatigue interferes with my physical functioning.
5. Fatigue causes frequent problems for me.
6. My fatigue prevents sustained physical functioning.
7. Fatigue interferes with carrying out certain duties and responsibilities.
8. Fatigue is among my three most disabling symptoms.
9. Fatigue interferes with my work, family, or social life.

Figure 1: A Level 3 Portable Sleep Study Device as compared with full in-Laboratory Polysomnography



Full channel polysomnography performed in a sleep laboratory (a) provides a montage of biological channels (b), usually from 12 or more signals. A level 3 portable sleep study device (c) can be performed in the patient's own home and provides an abbreviated montage of 4 channels (d). See text.

1.4 Mandibular Advancement Splint Therapy for the Treatment of Obstructive Sleep Apnoea

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1.4.1 ABSTRACT

Mandibular Advancement Splint (MAS) therapy is the leading alternative to continuous positive airway pressure (CPAP) therapy for the treatment of obstructive sleep apnoea. A MAS is an oral appliance which advances the mandible in relation to the maxilla, thus increasing airway calibre and reducing collapsibility. Although it is less effective than CPAP in reducing the apnoea-hypopnoea index (AHI), it has demonstrated equivalence to CPAP in a number of key neurobehavioural and cardiovascular health outcomes, perhaps due to increased tolerability and patient adherence when compared to CPAP. However, response to MAS is variable, and reliable prediction tools for patients who respond best to MAS therapy have thus far been elusive; this is one of the key clinical barriers to wider uptake of MAS therapy. In addition, the most effective MAS devices are custom-made by a dentist specialising in the treatment of sleep disorders, which may present financial or accessibility barriers for some patients. MAS devices are generally well tolerated but may have side effects including temporomandibular joint (TMJ) dysfunction, hyper-salivation, tooth pain and migration as well as occlusal changes. A patient-centred approach to treatment from a multi-disciplinary team perspective is recommended. Evidence-based clinical practice points and areas of future research are summarised at the conclusion of the chapter.

Keywords

Mandibular Advancement, OSA therapy, MAS titration, MAS customisation, Apnoea hypopnoea index

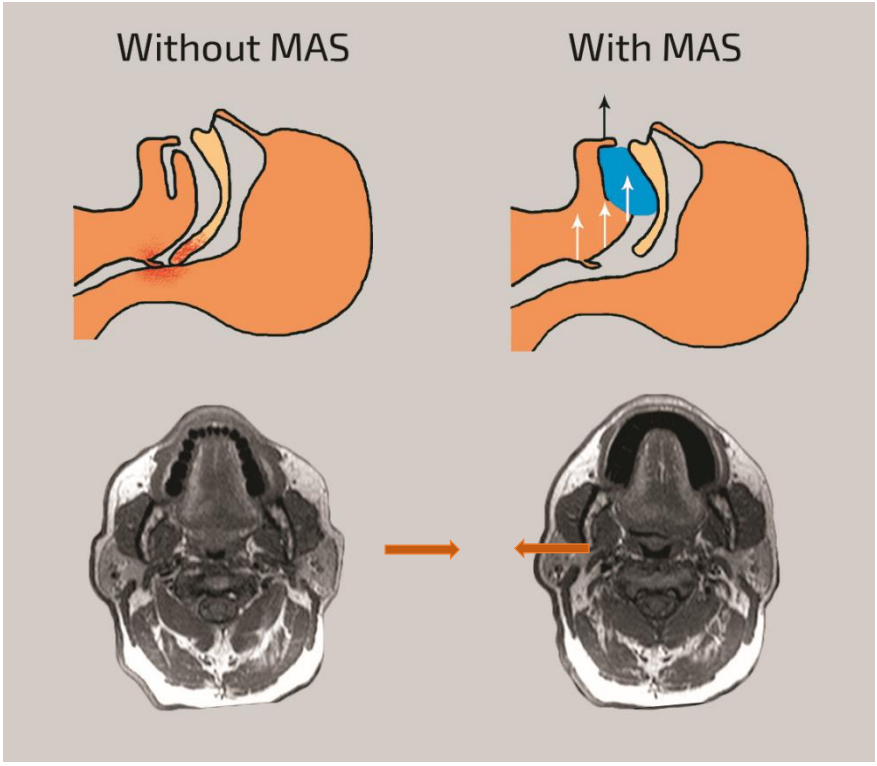
1.4.2 Introduction

A mandibular advancement splint (MAS), also referred to as a mandibular advancement device (MAD) or mandibular repositioning appliance (MRA) is an oral appliance for the treatment of sleep apnoea and snoring. It is recognised as the lead alternative to continuous positive airway pressure (CPAP) therapy for the treatment of obstructive sleep apnoea (OSA). Guidelines of the American Academy of Sleep Medicine (AASM) and American Academy of Dental Sleep Medicine (AADSM) recommend MAS therapy for the treatment of OSA where CPAP is not tolerated, or if there is a patient preference for an alternative device (85). A MAS advances the mandible in relation to the maxilla, increasing the calibre of the upper airway and reducing upper airway collapsibility. Several iterations of the device exist, and may differ substantially in terms of design and customisation.

1.4.3 Mechanism of Action

Imaging studies provide insights into anatomical changes in the upper airway which occur with a MAS device *in situ*. MAS functions via two principal mechanisms to increase airway size: 1. anterior movement of the tongue and 2. lateral expansion of the airway walls, especially in the velopharynx (86, 87). Although intuitively one might expect a MAS to increase the calibre of the airway in an anterior-posterior dimension, it is the lateral dimension which is increased to the greatest degree. This may be due to the MAS increasing airway wall tension through direct connections between the lateral airway walls and the ramus of the mandible (86). A schematic of MAS airway changes and MRI with and without MAS *in situ* are depicted in figure 2.

Figure 2: The effect of MAS on upper airway calibre



Schematic diagram (above) showing upper airway obstruction during sleep in a patient with OSA (without MAS) and mandibular advancement maintaining patency of the upper airway (with MAS). Axial MRI (below) shows baseline airway calibre in an awake patient with OSA (without MAS) and mandibular advancement producing an increase in the calibre of the upper airway (with MAS). Note the particular increase in airway calibre in the lateral dimension (arrows).

Structural changes with the MAS *in situ* cause a reduction in airway collapsibility (88) and therefore an improvement in the AHI. This has been demonstrated in studies of passive pharyngeal collapsibility with MAS *in situ* (89). Further, when used in conjunction with CPAP therapy, MAS reduces the requirement for CPAP pressure in a dose-response relationship with increasing mandibular advancement. This indicates

progressive reduction in airway collapsibility with increasing mandibular protrusion (90).

1.4.4 Efficacy and Adherence: MAS Vs CPAP

MAS therapy is often compared to CPAP therapy as the accepted “gold-standard” for the treatment of OSA. Although CPAP is known to provide superior control of OSA (measured by the AHI) whilst it is in use (26, 91, 92), adherence and patient tolerance are generally higher with MAS therapy (92). Therefore the reduced efficacy of MAS may be offset by its superior adherence, thus leading to the equivalence in neuro-behavioural and cardiovascular outcomes which has been observed in many comparative studies (see below).

Unlike that of CPAP, however, MAS response is variable, with the mean proportion of patients who respond completely to MAS (residual AHI < 5/hr) reported between 29 and 71% (93). One study suggested that around two thirds of patients have either a complete (37%) or partial (64%) response to MAS, with a partial response defined as a reduction in AHI of at least 50% (30). This highlights one of the significant barriers to MAS therapy, which is the selection of patients who are most likely to derive benefit.

For the severe OSA group (AHI ≥ 30/h), titratable MAS therapy is less effective at reducing the AHI and the oxygen desaturation index (ODI) compared with CPAP; however, this is offset by increased adherence and patient preference in favour of MAS (94). Further, MAS is equivalent to CPAP in terms of improvement in sleep architecture, with equivalent increases in slow wave and rapid eye movement (REM)

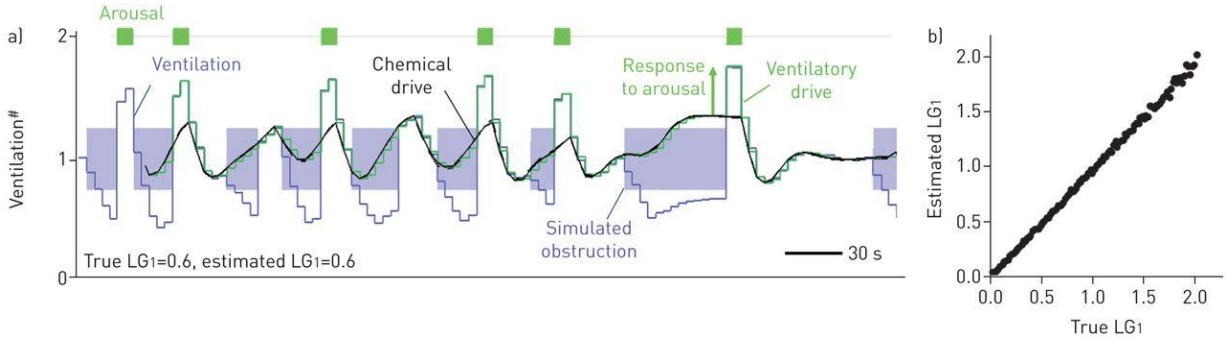
sleep (94). A MAS is therefore recognised as a viable alternative to CPAP therapy even in the treatment of severe OSA.

1.4.5 Patient Selection and Prediction of Response: Endotypes and Phenotypes

MAS therapy is highly efficacious in selected patients, including those with severe OSA. However, reliable prediction tools for treatment success remain elusive. An ideal prediction tool would be readily available from simple anatomical or routine polysomnographic data, and would predict MAS treatment response with a high degree of accuracy. Studies looking at predictors of MAS response have investigated endotypic and phenotypic traits.

An endotype refers to a subtype of a condition with a distinct functional or pathobiological mechanism (95). Examples of OSA characteristics which may be used to define endotypes include arousal threshold (defined as the degree of ventilatory drive required to trigger an arousal from sleep), loop gain (defined as instability in ventilatory control in response to a disturbance) and airway collapsibility. Traditionally, these parameters have only been available from physiological studies performed in a highly-controlled research setting (96, 97), however more recently endotypic data has been extracted from routine clinical polysomnography. For example, in the case of loop gain, Terril et al have developed a mathematical algorithm to reliably impute loop gain from the rise in ventilatory drive that follows an obstructive respiratory event (98). The mathematical basis of this method is depicted in figure 3.

Figure 3: Mathematical model for the imputation of loop gain from polysomnographic data



a) Schematic of the feedback loop controlling ventilation showing the influence of arousal and airflow obstruction. Ventilatory drive is the sum of chemical drive and the response to arousal (γ). Airflow obstruction provides a disturbance that reduces ventilation from the intended level (*i.e.* ventilatory drive). In response, chemical drive rises as determined by the chemical control system (loop gain). b) Time course of chemical drive during a step reduction in ventilation (*e.g.* obstructive hypopnoea). The rise in chemical drive is governed by and the parameters that determine its gain (LG_0), time constant (τ) and delay (δ); these system characteristics are revealed in the time course of ventilation when the airway is reopened.

In a group of 93 patients with, on average, moderate OSA, greater MAS efficacy was associated with 5 endotypic traits derived using algorithms applied to clinical polysomnographic data: lower loop gain, higher arousal threshold, lower ventilatory response to arousal, moderate pharyngeal collapsibility and weaker muscle

compensation. The association of lower loop gain and MAS response has been confirmed in another smaller study (99).

Similarly, characteristics which act as direct or surrogate markers for the site of airway collapse have been studied as predictors of response to MAS therapy. For example, the level and specific type of airway collapse observed on drug-induced sleep endoscopy (DISE) has been associated with response to MAS. Tongue-base collapse indicates a favourable outcome, whereas complete concentric collapse or complete latero-lateral oropharyngeal collapse are seen in those less likely to respond (100), as is complete antero-posterior epiglottic collapse (101). Further, certain “airflow shapes” derived from routine polysomnography have been used to predict the site of airway collapse and thereby response to MAS. Increased drop in airflow during respiratory events as well as a “pinched” expiratory flow shape (indicative of palatal prolapse) are associated with the least response to MAS therapy (102). Research is ongoing in order to translate these endotypic characteristics into reliable clinical predictive tools.

Phenotype refers to “observable” anatomical features or consequences of the disease. Small individual studies as well as meta-analyses have identified certain phenotypic characteristics associated with increased response to MAS therapy. These include younger age, female gender, lower body mass index (BMI), shorter neck circumference, milder and supine-dependent OSA (30, 103) and the absence of a tendinous pterygomandibular raphe (104), the latter of which may allow increased mandibular advancement. Craniofacial characteristics associated with a positive MAS

response include a retracted maxilla and mandible, a narrower airway and shorter soft palate (103). However, the predictive ability of these individual characteristics is relatively low. Research is ongoing to find more accurate predictors of clinical response to MAS therapy. In clinical practice, many patients undergo a repeat diagnostic sleep study with the MAS device in situ to assess clinical response and guide decisions about ongoing therapy. This strategy is recommended in the guidelines of the AASM/AADSM (85).

MAS relies on dental retention for its efficacy and therefore candidates for this therapy should be selected only after careful dental review. Patients are likely to be ineligible if they suffer from significant periodontal disease, insufficient native teeth to ensure device retention, severe TMJ disease or a severe gag reflex (105).

1.4.6 Health Outcomes

A number of health outcomes are derived from effective OSA treatment; some of which may have more ascribed importance than others for each individual patient. Health outcomes can be discussed in terms of neuro-behavioural outcomes, quality of life and cardiovascular outcomes.

1.4.6.1 Neuro-behavioural outcomes

MAS has been shown to improve daytime sleepiness as measured by the Epworth Sleepiness Scale (ESS) when compared to conservative management, though the average effect is modest (106). Nonetheless, a meta-analysis found that the

improvement in ESS was not significantly different to that of CPAP (91). Not all studies of MAS effects on ESS are consistent, however, with one randomised control trial showing that MAS did not improve the ESS when compared to a placebo device for mild to moderate OSA (107).

Small and medium sized studies indicate that MAS improves driving simulator performance to the same degree as CPAP (26, 108). One trial compared the performance of patients treated with a titratable, bi-bloc, fully customised MAS device with CPAP therapy on a monotonous driving simulator task. After eight weeks of therapy, performance in terms of lapses of attention improved to the same degree with both therapies (108). In a 1-month crossover trial of a titratable bi-bloc MAS vs CPAP, speed deviation and reaction times to divided attention tasks during driving simulation improved to the same extent with both treatments (26).

A meta-analysis found that there was no difference between MAS and CPAP for functional outcomes and neurocognitive tasks (92). Despite the superiority of CPAP in improving the AHI, it was hypothesised that the similarity in neurocognitive outcomes was due to the increased nightly adherence that was seen with MAS.

Taken together, these studies suggest non-inferiority of MAS to CPAP therapy for neuro-behavioural outcomes, though sample sizes have been modest and many studies were not blinded and/or did not include placebo control groups.

1.4.6.2 Quality of Life

MAS improves quality of life to at least the same degree as CPAP (26, 92). This is true for both the mental component score and the physical component score of the SF-36, a validated quality of life questionnaire (109). Similarly, when considering severe OSA only, a meta-analysis of RCTs comparing MAS to CPAP shows a similar impact on both the SF-36 and FOSQ questionnaires, two validated tools for the assessment of quality of life (94).

1.4.6.3 Cardiovascular outcomes

There is a paucity of data examining the effect of MAS therapy on cardiovascular outcomes, though some short-term studies exist. For example, in a sub-group of hypertensive patients, MAS improved blood pressure by 2-4mmHg and was non-inferior to CPAP (25, 26). MAS also improves markers of oxidative stress and cardiac autonomic activity when compared with placebo (110). To date there are no large, randomised control trials looking at the effect of MAS therapy on cardiovascular endpoints. In contrast, a few moderately sized randomised control trials have examined the effect of CPAP therapy on cardiovascular endpoints including stroke, myocardial infarction and revascularisation of coronary artery disease, but have failed to demonstrate a benefit (13, 14, 51). However, these trials have all been characterised by very poor CPAP adherence (less than four hours per night), which may have contributed to the negative result. In addition, subgroup analysis in groups with higher adherence have shown some significant cardiovascular benefits (111). As

MAS therapy has increased adherence when compared to CPAP, further research is required to examine the impact of MAS therapy on cardiovascular outcomes.

1.4.7 Design and Customisation

MAS design falls generally into one of two categories: i. a single piece (mono-bloc) design or ii. an upper and lower component with a coupling mechanism (bi-bloc/duo-bloc design). Bi-bloc designs have the advantage of facilitating some lateral and vertical jaw movement, to varying degrees, and may improve patient comfort and tolerance.

MAS may be pre-fabricated from thermoplastic material (the “boil-and-bite” model) or can be formally customised to the patient’s own dentition. The “boil-and-bite” model, in which thermo-plastic trays are heated by immersion in hot water and then moulded directly to the patient’s mandibular and maxillary dental arches, foregoes the need for specialist dentist impressions and is therefore less costly and more accessible. However, boil-and-bite designs have a higher failure rate due to reduced dental retention, and are less effective at lowering the AHI than a fully customised device (112, 113). In contrast, customised designs provide superior fit and dental retention, and are better tolerated (114). For these reasons, fully customised, titratable devices are recommended in MAS guideline statements from the AASM and AADSM (85).

For a fully-customised device, dental impressions and measurements of occlusal relationships are taken by a specialist dentist. More recently, dental scan technology

has been introduced, allowing for a digitalised model of the teeth and intra-oral tissues (115). Full-arch digital impressions have been shown to be more accurate than traditional impressions (116), and also allow a more streamlined digital workflow production process.

Devices also differ significantly in terms of fabrication materials and construction. Materials include hard acrylics, thermal acrylics, laminates, biocompatible polymers and alloys (88). Devices may be manufactured by 3D milling or 3D printing. There is little data available to allow comparisons between the various models or brands of fully customised MAS devices in the treatment of OSA (117), hence data from individual studies should be extrapolated with caution. An example of a customised MAS device is shown in figure 4.

Figure 4: An example of a bi-bloc, fully customised MAS device.

This model (Avant device, SomnoMed Australia) uses a series of straps, incrementally shorter in length, to titrate the mandible forward and articulate the upper and lower components. The strap is also designed to limit jaw opening.

1.4.8 Adherence

An additional design feature for some models is an in-built adherence recorder which allows collection and storage of patient adherence data using a thermal-sensor chip. These devices, about the size of a button cell battery, can be embedded into the MAS during the manufacturing process, see figure 5. When the temperature lies within a certain range (generally 31.5–33℃ to 38.5–39.2℃), it is inferred that the device is *in situ* within the oral cavity, and therefore in use (118). This information can be downloaded and read in a research or clinical setting and may assist with clinical management. An example of downloaded data from an inbuilt compliance recorder is shown in figure 6. Previous studies of CPAP adherence have shown that subjective patient recollection tends to under-estimate objectively recorded adherence data (119). However, few studies have assessed whether MAS subjectively reported adherence is consistent with objective adherence data. One small study showed that there was no difference between objective and self-reported MAS adherence at 3 months (120). At 12 months, close correlation between subjective and objective measures of adherence continued, with an over-estimation of 30 minutes by subjective (self-reported) adherence compared with objective data collected by an in-built thermal sensor chip (121).

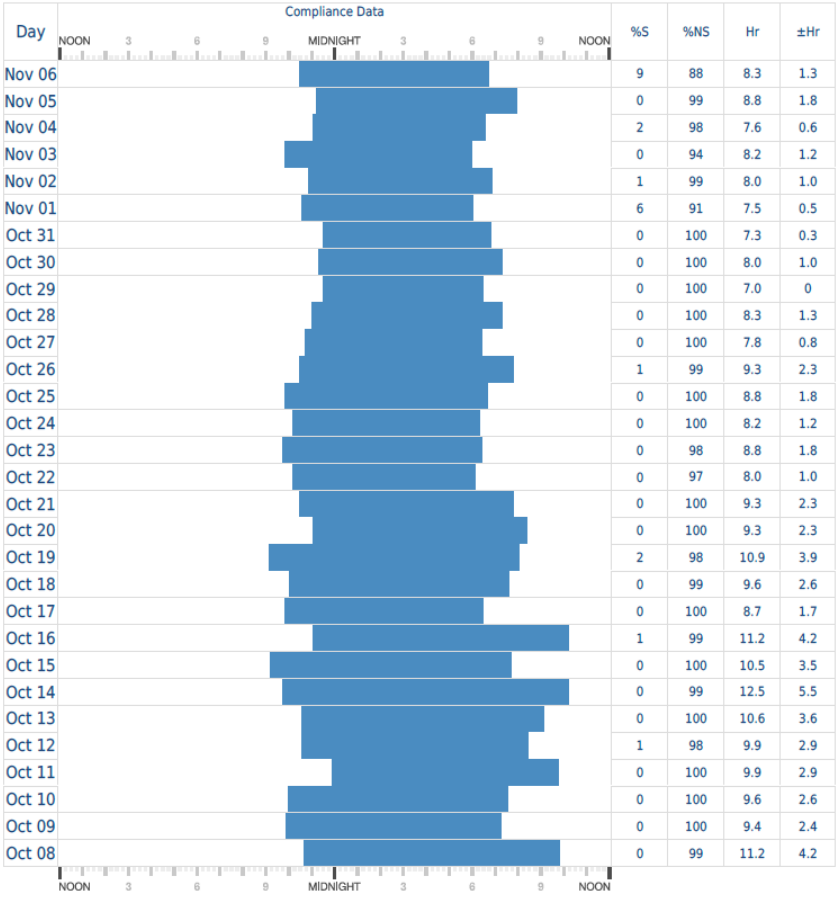
Disadvantages of the in-built adherence monitors include a small increase in bulk added to the device, although this is usually well tolerated, as well as an increased manufacturing cost. In future, in-built monitors may also collect other clinically relevant data including cardiorespiratory parameters. One prototype device captures intra-oral

photoplethysmography (PPG) signals, and correlates highly to PPG signals obtained from the more traditional and commonly used finger probe (122). PPG has numerous applications including the acquisition of heart rate, respiratory rate and percent of oxygen-saturated haemoglobin (SpO2).

As with CPAP, adherence to MAS can be variable, though in general MAS adherence is superior to that of CPAP (92). Cluster analysis over 60 days of MAS usage identified three adherence subtypes: 48.3% were “consistent users” who used MAS most of the time (daily usage 7.3 ± 0.8 hours), 32.8% were “inconsistent users” with variable usage (daily usage 4.6 ± 0.8 hours) and 19.0% were “non-users” (daily usage 1.0 ± 0.6 hours)(123). Patients could be identified into these subtypes within the first 20 days of therapy, suggesting that the early period of MAS therapy is a critical time for close clinical monitoring and support.

Figure 5: An example of an in-built adherence recorder (DentiTrac, Braebon Medical) embedded within a MAS device.

Figure 6: An example of downloaded data from an in-built MAS adherence recorder in a highly adherent patient.



Day	%S	%NS	Hr	±Hr
Nov 06	9	88	8.3	1.3
Nov 05	0	99	8.8	1.8
Nov 04	2	98	7.6	0.6
Nov 03	0	94	8.2	1.2
Nov 02	1	99	8.0	1.0
Nov 01	6	91	7.5	0.5
Oct 31	0	100	7.3	0.3
Oct 30	0	100	8.0	1.0
Oct 29	0	100	7.0	0
Oct 28	0	100	8.3	1.3
Oct 27	0	100	7.8	0.8
Oct 26	1	99	9.3	2.3
Oct 25	0	100	8.8	1.8
Oct 24	0	100	8.2	1.2
Oct 23	0	98	8.8	1.8
Oct 22	0	97	8.0	1.0
Oct 21	0	100	9.3	2.3
Oct 20	0	100	9.3	2.3
Oct 19	2	98	10.9	3.9
Oct 18	0	99	9.6	2.6
Oct 17	0	100	8.7	1.7
Oct 16	1	99	11.2	4.2
Oct 15	0	100	10.5	3.5
Oct 14	0	99	12.5	5.5
Oct 13	0	100	10.6	3.6
Oct 12	1	98	9.9	2.9
Oct 11	0	100	9.9	2.9
Oct 10	0	100	9.6	2.6
Oct 09	0	100	9.4	2.4
Oct 08	0	99	11.2	4.2

This particular device (DentiTrac, Braebon Medical) also records sleep position: supine (S) vs non-supine (NS), number of hours used per night (Hr) and the difference between the physician-set “goal” adherence time, in this case 7 hours, and the actual time worn each night (±Hr).

1.4.9 MAS titration

Titration refers to the incremental advancement of the mandible towards the level of protrusion which provides maximal clinical efficacy. This is an important practice point since increased MAS efficacy has been demonstrated with increasing mandibular protrusion, in a dose-dependent relationship (124). Some specialist research centres have used remotely controlled titratable MAS devices in the sleep laboratory, allowing

real-time assessment of MAS efficacy at progressive levels of protrusion (125-127). A commercially available remotely controlled mandibular protrusion device (MATRx, Zephyr Sleep Technologies Inc, Calgary, Canada) has been used both to predict clinical response to MAS, as well as to determine the optimal level of mandibular protrusion. This device consists of upper and lower dental trays which are fitted to the patient's teeth with an impression material. A small motor which sits just outside the patient's mouth titrates the mandible forward in small increments during sleep, under the control of a remote operator. With the use of this device, one study demonstrated a positive predictive value of 87% for therapeutic success, defined as an AHI < 10/h and ≥ 50% reduction from baseline at the determined effective target protrusive position (128). In addition, a portable version of this device has been used in an at-home setting, consisting of the titratable mandibular protrusion device, nasal cannula to detect flow and pulse oximetry, together with a portable laptop computer for signal processing. Using this system, unattended mandibular titrations were performed at home using real-time feedback from the nasal cannulae and oximetry to guide the titration. Overnight titrations in the patient's home using this device yielded a positive predictive value of 97% and negative predictive value 72% to predict a residual oxygen desaturation index (ODI) ≤10/h (129).

Other researchers have used overnight oximetry devices alone to assess hypoxic burden at various levels of protrusion, and titrate accordingly. In the absence of these research tools, for practical clinical purposes, the titration goal may be the maximal level of protrusion that is well tolerated by the patient. Symptoms, such as snoring or daytime somnolence can also be used as titration guides by the patient at home.

Titration mechanisms will depend upon the individual design of the device and its coupling mechanism. Coupling mechanisms are variable and may include elastic or plastic connectors, metal pin and tube connectors, hook connectors, acrylic extensions or magnets. All titration mechanisms will incrementally advance the mandible forward in relation to the maxilla.

1.4.10 Side Effects

Patients should be warned of the possibility of both short and long term side effects prior to commencement of MAS therapy. Short term side effects are common and often temporary. They include hyper-salivation, temporomandibular joint (TMJ) pain and discomfort, a dry mouth and pain or irritation of the intra-oral tissues. Many of these side effects, if not temporary, can be addressed by minor device adjustments.

Long term side effects include progressive changes in dental occlusion; and have been observed out as far as 11 years (130). The prominent changes are a reduction in overbite (-2.3 ± 1.6mm) and overjet (-1.9 ± 1.9mm), as well as an expansion of the mandibular arch with reduction in mandibular dental crowding (130). Of note, some of these dental changes may be favourable, depending upon baseline dentition.

MAS devices have a finite life span, and are commonly reported by providers to last approximately five years, though evidence on the lifespan of MAS devices is limited. One study followed 15 patients out to five years of MAS therapy and found that the most commonly encountered technical problems requiring review by a dental

technician were acrylic breakage at the point of articulation attachment, poor retention and other required adjustments to improve comfort (131).

1.4.11 Patient-centred approach

One of the key indications for MAS therapy is patient preference when compared to CPAP (85) and, as with management of any chronic condition, a patient-centred approach is central to treatment success. Patient preferences around treatment must be elucidated after the diagnosis of OSA, incorporating a discussion around the advantages and disadvantages of available suitable therapeutic options. Qualitative analysis has identified MAS convenience and transportability as factors which influence patient choice in favour of MAS therapy, while alterations in bite and concerns about durability are identified as important disadvantages (132). In addition, the cost of MAS therapy will be an insurmountable barrier to some patients, particularly in jurisdictions where CPAP, but not MAS, may attract a government subsidy. Therefore the choice to proceed with a trial of MAS therapy must be tailored to the individual patient's treatment goals.

When commencing CPAP therapy, patients may undergo a therapeutic trial of a rental or loan device, before making a decision about progression to permanent therapy. With MAS therapy however, this approach is more challenging, since the device is manufactured specifically for the individual patient and normally requires an initial financial investment before the therapy can be trialled. Some patients may choose to undergo an initial trial with a commercially available "boil and bite" MAS, to see whether the sensation of mandibular advancement is tolerable for them, and whether

they experience any improvement in symptoms. If this approach is undertaken, the patient should be informed that boil-and-bite devices are more likely to cause soft tissue discomfort, may be less adherent and less effective than custom-made devices.

1.4.12 Multi-disciplinary Management

As MAS treatment of OSA lies at the intersection of dentistry and sleep medicine, it is recommended that both of these specialists play an ongoing role in the care of MAS patients (85). Other specialists such as Ear Nose Throat (ENT) surgeons and general practitioners may also play an active role. An initial clinical review will be required to confirm the diagnosis of OSA, to quantify the severity of OSA with a baseline nocturnal sleep study, and to confirm patient suitability and preference for MAS therapy. Once the device is fabricated, follow-up is important to ensure ongoing efficacy of the MAS (for example using overnight polysomnography with the MAS *in situ*), to monitor patient satisfaction with the device and to screen for and treat short and long term side effects.

1.4.13 Future Directions

Recognition of OSA as a heterogenous disorder is increasing. As with other areas of medicine, a “one-size-fits-all” approach to the treatment of OSA is being abandoned, in favour of a more personalised approach, which takes into account specific clinical features and the disease subtype of the individual patient. For example, there is now recognition that some OSA is driven by “pharyngeal” endotypes (e.g., high airway collapsibility), while other OSA is driven by non-pharyngeal traits including high loop gain and reduced arousal threshold (133). Future research will focus on further

differentiating OSA as a whole into clinically relevant subgroups, some of which may be more responsive to MAS therapy than others (95). At the time of writing there is little personalisation in the choice of MAS therapy for an individual patient in the clinic, other than a failed trial of CPAP, or on the basis of patient preference. Future research will focus on the development of reliable endotypic and phenotypic prediction tools for MAS treatment success, and translation of these into a clinical setting.

Another advancement in the field of sleep medicine as a whole is the increasing trend towards automated and remote (at-home) diagnosis and management of sleep apnoea (134). This includes the explosion of wearable devices and “apps” which collect physiological data relating to sleep, including sleep times and staging, snoring, oximetry and ECG data. In future we may anticipate that MAS therapy will also progress in this regard. For example, the technology for remote (at-home) MAS titration studies already exists (129), and may expand to a clinical setting, thus reducing the need for in-laboratory titration studies which are resource intensive. In addition, in-built MAS adherence data recorders described above raise the possibility of remote monitoring and assessments via telemedicine, a technology which is already in common usage with CPAP.

1.4.14 Clinical Practice Points: Evidence-based Summary

- There is a variable clinical response to MAS, with approximately one third achieving a complete response and a further one third achieving a partial response (reduction in the AHI of ≥50%).

- Increasing MAS efficacy is observed with increasing mandibular protrusion. In practice, patients may be advised to titrate their MAS to the maximal comfortable limit of protrusion to optimise OSA control.

- Although CPAP is more effective than MAS at lowering the AHI, this may be offset by improved patient tolerance and adherence with MAS therapy, leading to equivalence in key neuro-behavioural and cardiovascular outcomes.

- MAS improves key outcomes including daytime somnolence, driving risk and quality of life to the same extent as CPAP. Further research is needed to examine the impact of MAS on cardiovascular endpoints.

- MAS is generally well tolerated. Short term side effects include hypersalivation, TMJ dysfunction and pain or irritation of the intra-oral tissues. Long term side effects include tooth migration and dental occlusal changes.

1.4.15 Areas of Future Research

- Moderately sized CPAP trials have failed to demonstrate a benefit when looking at cardiovascular endpoints, however these have all been characterised by poor compliance. Since MAS compliance is generally higher than that of CPAP, further research is required to examine the impact of MAS therapy on cardiovascular outcomes.
- A number of phenotypic and endotypic traits have been associated with MAS response, but accurate and reliable clinical predictive tools remain lacking. Further research is required into the development and refinement of reliable prediction tools for MAS treatment success, and translation of these into a clinical setting.
- A major barrier to more widespread MAS usage is the expense of the device and the need to have the device custom-made by a specialist dentist, which also increases patient cost and reduces accessibility. Future research should focus on reducing production cost and improving the quality of affordable “boil and bite” or other preliminary models to allow for effective MAS trial phases.
- Remote monitoring of adherence and other data is already commonplace for CPAP therapy. Future research will focus on the development of MAS in-built adherence recorders including the availability of remote access, as well as the collection of other relevant data to assess nightly efficacy, including haem-oxygen saturation, heart rate, position sensors, snore microphones, respiratory events and even sleep staging.

1.5 The Relationship between Obstructive Sleep Apnoea and Atrial Fibrillation

1.5.1 Introduction

Atrial Fibrillation (AF) is a costly public health problem, increasing a patient's risk of heart failure, stroke, and all-cause mortality (135). It is the most common sustained cardiac arrhythmia, with an overall prevalence of approximately 1% (136, 137). This prevalence increases to 5% in those aged 55 years and over (137, 138). Beyond its risk of significant morbidity and mortality, AF places a huge strain on healthcare expenses with an estimated direct medical annual cost variably estimated at AUD$1.25 billion in Australia (136), USD$6.65 billion in the United States (139), and €655 million in the United Kingdom (137). The most significant single contribution towards these expenses is from hospital admissions with a primary diagnosis of AF (137, 139). These costs are exclusive of lost productivity from patient disability and mortality. Hence the treatment of AF and its underlying risk factors is potentially hugely impactful towards the preservation of global healthcare resources.

AF is commonly associated with another chronic condition, obstructive sleep apnoea (OSA). This association appears to be independent of shared risk factors including age, sex and BMI (140, 141). Physiological studies suggest that sleep apnoea may trigger and perpetuate AF via a number of mechanisms discussed in detail below. Numerous observational studies suggest that treatment of OSA can reduce the AF burden, particularly following therapeutic interventions for AF such as cardiac ablation or pulmonary vein isolation (PVI) procedures. However, there is a paucity of randomised controlled trial data to assess the impact of OSA treatment on AF burden, or to assess impact on cardiovascular outcomes such as stroke or cardiac events. Nonetheless, international AF management guidelines

recommend aggressive holistic risk factor management, including the diagnosis and treatment of OSA (8-11)

This narrative review chapter examines the published literature addressing the relationship between OSA and AF. This includes studies of epidemiology, pathophysiology and treatment. There is a particular emphasis on the literature involving screening for OSA in AF patients.

1.5.2 Epidemiology

1.5.2.1 Prevalence of OSA in AF patients

The finding of a high prevalence of OSA among AF patients has been replicated in a number of studies (140, 142-149). The first study to report this association, published in 2004, was a prospective cohort study demonstrating that a high risk of OSA was present in 49% of AF patients referred for electrical cardioversion, as compared with 32% of cardiology outpatients without AF ($p < 0.0004$) (150). Of note, OSA was diagnosed via the Berlin Questionnaire in this study, and not by in-laboratory polysomnography (PSG), which is the accepted gold-standard investigation. A large retrospective cohort study by the same group showed that the oxygen desaturation index (ODI), a measure of OSA hypoxic burden, was associated with incident AF over 4.7 years of follow up, and that this association was independent of obesity (151).

In an Australian population, the prevalence of moderate or severe OSA amongst cardiology clinic outpatients with AF has been reported at 65% (142), though this

study excluded those with abnormal left ventricular ejection fraction. This was compared to a prevalence of 38% in a control group of other cardiology clinic patients ($p < 0.01$). In addition, OSA was more prevalent amongst patients with permanent and high frequency paroxysmal AF, compared with low frequency paroxysmal AF. This finding becomes important when considering a later large treatment registry which showed that the application of CPAP reduces the risk of progression to more permanent forms of AF (152) (see Treatment Studies, below). In a group of 52 Brazillian patients with chronic persistent AF, the prevalence of OSA (AHI > 10/hr) was determined by PSG to be 81.6% vs 60.0% in matched community controls ($p = 0.03$). This result was found despite no differences in age, gender, body mass index (BMI), cardiovascular risk factors, and sleepiness scores between groups. There was a larger neck circumference identified in the OSA group despite no difference in BMI (140).

A randomised controlled trial which screened 579 AF outpatients diagnosed moderate to severe OSA (AHI ≥15/hr) in 42% on a portable level 3 sleep study (144), though there was no control group for comparison. Similarly in a group of 289 consecutive patients hospitalised in a Polish centre for AF, 45.5% were diagnosed with OSA on PSG (145), and an Australian study of 442 consecutive ambulatory rhythm control candidates reported a high prevalence of OSA at 66% overall, with 32% being mild, 17% moderate and 17% severe (146). Not all studies have been consistent however; one case control study of patients with lone AF (defined as AF with no associated cardiac or other significant comorbidities) did not find an increased prevalence of underlying OSA compared with matched community controls, though study numbers were small (153).

A recent prevalence meta-analysis (154) examined 13 studies and found a pooled prevalence of 40% (95% CI 32%-48%; $p < 0.001$) for moderate to severe sleep disordered breathing in AF patients. However, few included studies used level 1 PSG for diagnosis. Hence, though there are numerous studies examining the prevalence of OSA among AF patients, very few (140, 145-147) have prospectively screened consecutive AF patients for OSA with level 1 (in-laboratory) PSG, the gold standard investigation. Of these, one (140) was a small study looking at community-based patients with chronic AF and three (145-147) used level 1 PSG as part of the diagnostic pathway in the workup of rhythm control candidates referred for pulmonary vein isolation (PVI) or cardioversion. Between them, these studies estimate the prevalence of OSA in AF patients between 45.5 and 81.6%. These studies have looked at specific AF populations and must be extrapolated to other AF groups with caution. To date there are no studies screening sequential patients presenting to hospital emergency departments with paroxysmal AF with level 1 PSG. In chapter 2 of this manuscript we report on the prevalence of OSA in a hospital-based AF cohort. We use the gold standard investigation (level 1 PSG) to screen sequential AF patients from two pathways, in order to represent a number of AF phenotypes: including those presenting to hospital emergency departments with a diagnosis of AF and those referred for PVI for the treatment of AF. Studies evaluating the Epidemiology OSA in AF patients are summarised in Table 5.

1.5.2.2 Prevalence of AF in OSA patients

A high prevalence of AF amongst patients with OSA has also been well demonstrated. The Sleep Heart Health Study examined PSG data from over five hundred individuals recruited from the community. Those with severe OSA had four times the prevalence of nocturnal atrial fibrillation on the study night when compared to those without significant sleep disordered breathing (OR 4.02; 95% CI, 1.03–15.74) after adjusting for age, sex, BMI, and prevalent congestive heart disease (155). Further, in a large, multi-ethnic American cohort, the prevalence of AF increased in relation to sleep apnoea severity, as measured by the apnoea hypopnoea index (AHI) and ODI: AF prevalence was 4.0% in patients with mild OSA, 6.0% with moderate OSA and 7.5% in subjects with severe OSA (linear trend: p = 0.04). However this relationship did not persist when controlling for mutual risk factors including comorbid cardiovascular disease (156). In a Japanese study of 1456 patients who underwent PSG for suspected OSA, patients with OSA were 6.44 (1.53–27.08, p = 0.011) times more likely to have paroxysmal AF demonstrated on the ECG component of their sleep study (157). In this study there was a non-significant trend towards increasing incidence of PAF with increasing OSA severity: 1.0% prevalence in mild OSA, 3.3% prevalence in moderate OSA and 3.4% prevalence in severe OSA (p=0.051). In a large Australian retrospective longitudinal study, a PSG-confirmed diagnosis of OSA was associated with increased rates of incident hospitalisation for AF over 12 years, independent of obesity and other established AF risk factors (141).

OSA has also been consistently identified as a strong predictor of AF in the early post-operative period following coronary artery bypass grafting (CABG) (158-162). For example, Zhao et al showed that the presence of OSA, as diagnosed pre-

operatively via a portable tonometry device (WatchPat), increased the risk of early post-operative AF by over four times, independent of other risk factors (160). It was noted that left atrial diameter was higher in the sleep apnoea group, supporting a proposed mechanistic pathway of atrial stretch and remodelling (see Mechanistic pathways, below). Mooe et al showed that a pre-operative ODI > 5/hr, but not AHI > 5/hr, increased the chance of post-operative AF by 2.8 times (CI 1.2 – 6.8, $p < 0.05$) following CABG (161). Of note, central sleep apnoea (CSA) and Cheyne-Stokes respiration have also been shown to predict the incidence of AF in older men (163), though a detailed discussion of CSA and AF is beyond the scope of this review. Studies evaluating the epidemiology of AF in OSA patients are summarised in Table 6.

1.5.3 Screening for OSA in patients with Atrial Fibrillation

As outlined above, OSA is highly prevalent amongst AF patients. In addition, the presence of OSA increases the risk of adverse outcomes. As mentioned above, numerous national and international guidelines for the management of AF now incorporate recommendations for the screening and subsequent management of OSA in AF patients. However, there are several challenges involved in a universal screening approach.

Firstly PSG, considered the gold standard investigation for the diagnosis of OSA, is a resource-intensive investigation and only accessible in specialist centres. Additionally, many AF patients with underlying OSA are not symptomatic of their disease, thus making detection on history or questionnaire unreliable (143, 147, 164). As an example, only 52% of patients with moderate to severe OSA in a large

cohort of patients undergoing PCI were identified as “high risk” on the Berlin questionnaire, and in the same study only 24% of OSA patients were identified as having excessive daytime somnolence (EDS) as defined as an Epworth Sleepiness score > 10 (165).

1.5.3.1 Questionnaires

A number of validated questionnaires exist for the diagnosis of obstructive sleep apnoea including the Berlin Questionnaire, STOP-BANG questionnaire and the OSA-50 questionnaire. Many of these questionnaires have been applied to AF populations, with most proving inadequate for the effective diagnosis of OSA in an AF population (164, 166).

The Epworth sleepiness scale (ESS) was not developed as a diagnostic tool specifically for OSA but rather to assess the symptom of daytime sleepiness in patients with various sleep disorders (167). In fact, most patients with AF and OSA do not demonstrate excessive daytime sleepiness (168). Perhaps unsurprisingly then, the application of the ESS as a diagnostic tool for OSA has demonstrated a poor level of accuracy in AF patients (146, 147, 164, 166). Similarly, the Berlin Questionnaire which relies on questions in three categories: snoring, daytime symptoms and hypertension, has demonstrated poor diagnostic accuracy (ROC AUC < 0.7) for the diagnosis of OSA in AF patients (164). For the diagnosis of severe OSA (AHI ≥ 30/hr), a panel of seven commonly used screening questionnaires: ESS, Berlin, SACS, NoSAS, OSA50, STOP-Bang and MOODS all demonstrated poor diagnostic accuracy in AF patients (AUC < 0.7) (166). Of all

the questionnaires, STOP-BANG appears to perform best in an AF population, with fair diagnostic accuracy (ROC AUC between 0.7 and 0.8) on two studies (164, 169), though this is usually considered insufficient for clinical population screening. Overall, questionnaires remain inadequate for the diagnosis of OSA in AF patients, and a lack of symptoms should not preclude investigation for OSA in this population.

1.5.3.2 Overnight Oximetry (Level 4 portable sleep study)

Overnight oximetry is used in clinical practice as a screening tool for OSA. Compared with in-hospital PSG, it is inexpensive and more widely available as well as portable. Overnight oximetry has been shown to have a high positive predictive value for moderate to severe OSA in a population referred for sleep studies at a veteran's hospital on suspicion of sleep disordered breathing (ODI ≥ 7/hr gave a PPV of 92% (95% CI 86% - 96%, Kunisaki et al 2015). The utility of overnight oximetry as a screening tool in an AF cohort has been reported by Linz, who found a high sensitivity (91%) and specificity (83%) using an ODI cut-off of 4.1/hr. However, it must be noted that overnight oximetry for this study was derived from the PSG result, therefore performed under strict laboratory conditions, and not from a home-based study (80). The diagnostic accuracy of portable (at-home) overnight oximetry in an AF population has not been reported.

1.5.3.3 Level 3 portable sleep studies

A level 3 sleep study device is a limited-channel portable sleep apnoea test which comprises 3 or 4 channels; including at least two respiratory variables such as respiratory effort and/or airflow as well as oxygen saturation, and at least one cardiac variable such as heart rate and/or electrocardiogram. At the time of writing, there are no diagnostic accuracy studies comparing a level 3 portable home sleep study device with in-laboratory PSG in AF patients. Diagnostic accuracy studies in sleep clinic populations have reported sensitivities between 64 – 100% and specificities between 41 – 100% (170) for these devices. In chapter 2 of this manuscript, we report the first diagnostic accuracy study of a level 3 portable sleep study device compared with the gold standard PSG for the diagnosis of OSA in an AF cohort. This study allowed us to compare the diagnostic accuracy of both apnoea hypopnoea index (AHI) and ODI derived from a level 3 device.

Screening tools for OSA in AF patients and their diagnostic accuracy are summarised in tables 7 and 8 respectively.

1.5.4 Mechanistic Pathways

Though the exact nature of the association between OSA and AF remains unclear, several studies have suggested that OSA may play a causative role in the generation and perpetuation of AF (1, 5, 6, 171). This has pathophysiological plausibility via a number of mechanisms, discussed in further detail below. These mechanisms may be acute, with individual obstructive respiratory events triggering arrhythmia: this has been demonstrated in the case of obstructive respiratory events triggering premature atrial contractions (PACs) after cardioversion (1). Alternatively, long term exposure to sleep apnoea events may contribute to the

vulnerability of the atrial substrate by fibrosis and structural remodelling, thus lowering the threshold for atrial arrhythmic events and contributing to chronic and progressive AF (172).

1.5.4.1 Atrial Stretch and Remodelling

During obstructive airway events, persistent inspiratory effort against an occluded upper airway results in surges of negative intra-thoracic pressure. These repetitive pressure changes increase myocardial trans-mural pressure gradients and thereby atrial stretch (173, 174). Simulated obstructive sleep apnoea events in the form of the Muller Manoeuvre in young, healthy adults shows via real-time echocardiography that increased negative intra-thoracic pressure has a profound effect on cardiac chambers. During an obstructive event, left ventricular end systolic volume increases, cardiac output falls and left atrial volume falls, with a reciprocal increase in right atrial volume (175). Left atrial volume increases above baseline with the cessation of the Muller Manoeuvre (176). Animal studies have shown that application of negative intra-thoracic pressure shortens the atrial effective refractory period (ERP), and increases susceptibility to inducible AF, when compared to upper airway occlusion without the application of negative intra-thoracic pressure (177).

A biomarker of atrial stretch is Atrial Naturetic Peptide (ANP). ANP is a powerful diuretic, natriuretic and vasodilator. It is released from atrial myocytes in response to atrial stretch (178). It is elevated in patients with OSA (179), and normalises with CPAP therapy (180). Increased ANP in OSA patients is likely to explain, at

least in part, the symptom of nocturia which is increased in OSA patients (181). There are no detailed studies looking at ANP levels or nocturia in AF patients with OSA.

Echocardiographic studies have determined that left atrial volume is significantly increased in OSA patients, and that severe OSA correlates independently with left atrial volume after adjusting for age, sex, systolic blood pressure, body mass index, and measurements of LV diastolic function (182). Left atrial volume improves with up to 12 months of CPAP therapy (183). Cardiac MRI studies have similarly demonstrated that OSA patients have increased left atrial size when compared with controls, and that treatment with CPAP is associated with a reduction in atrial size (184). A detailed study of atrial mapping in OSA and non-OSA patients with AF shows that OSA patients with AF have a higher degree of atrial remodelling and atrial conduction abnormalities (2). A subsequent high-density atrial mapping study (3) showed that increasing AHI was associated in a dose-response relationship with markers of a more diseased atrial substrate, including: lower bipolar voltage, greater voltage/conduction heterogeneity, and higher proportions of low voltage and complex points. Further, a small randomised study showed that markers of atrial remodelling improved after six months of CPAP therapy in patients with moderate to severe OSA (AHI > 15/hr) (185) Overall these studies demonstrate that OSA is associated with a more diseased atrial substrate, which may contribute to both the development and perpetuation of AF, and that this process may be reversed with OSA treatment.

1.5.4.2 Intermittent Hypoxaemia

The impact of the intermittent hypoxaemia that characterises OSA on the cardiovascular system is complex and not yet fully elucidated. Nocturnal hypoxaemia increases myocardial demand under conditions of reduced myocardial oxygen supply, thus predisposing to ischaemia and arrhythmogenesis. Hypoxia stimulates the sympathetic nervous system to induce vasoconstriction, which in turn increases blood pressure (174). Additionally, hypoxia induces free-radical formation and stimulates a cascade of inflammatory pathways that impair vascular endothelial function (174, 186).

The relationship between hypoxic burden and AF is supported by a large cross-sectional prevalence study, showing an association between increasing AHI and prevalence of AF, which was replicated in the association between oxygen desaturation index (ODI) and AF (156). Further, another large longitudinal study found that ODI but not AHI was associated with AF following coronary artery bypass grafting (161).

1.5.4.3 Autonomic nervous system perturbations

Mounting evidence implicates derangements in the cardiac autonomic axis in arrythmogenesis (187). The role of the pulmonary vein ostia in the initiation and maintenance of AF is well described, and forms the basis of the interventional treatment for AF known as PVI (pulmonary vein isolation). This invasive procedure electrically isolates the pulmonary vein ostia from the remainder of the left atrium and prevents the propagation of arrythmogenic impulses from this area of the heart. The pulmonary vein ostia are densely populated with both sympathetic and

parasympathetic nerve fibres, with input from both these arms of the autonomic nervous system playing a complex, inter-related a role in AF generation (188).

The obstructive respiratory events that characterise obstructive sleep apnoea are accompanied by marked perturbations in autonomic tone. For example, the initial apnoeic period is characterised by vagally-driven bradycardia, followed by a sympathetically-driven surge in heart rate and blood pressure with an accompanying arousal at the termination of the apnoeic event (189). Increased sympathetic tone persists into the awake state in sleep apnoea patients when compared to controls (190, 191). Further, the blood pressure surges which accompany this increased SNS activity have also been observed to persist into the awake state (192). CPAP does reduce heart rate and blood pressure in patients with OSA on CPAP when compared with no CPAP, likely due to a reduction in sympathetic activity (193).

Premature atrial contractions (PACs) can act as a trigger for AF episodes. In a pig model, obstructive respiratory events were found to induce PACs. Further, inducible PACs following obstructive respiratory events were ameliorated by renal surgical denervation which reduces sympathetic output. This suggests that the mechanism by which obstructive events lead to PACs relies on sympathetic activation (1). Additionally, shortening of the atrial effective refractory period (ERP) and increased AF inducibility that accompanied upper airway occlusion with increased negative intrathoracic pressure did not occur in the presence of vagotomy or atropine (177). The implication here is that vagal activity mediates the interaction between negative intrathoracic pressure and predisposition to AF.

There is a paucity of literature examining the role of the autonomic nervous system as a possible mediator between obstructive sleep apnoea and atrial fibrillation; and this requires further study. In chapter 3 of this manuscript we report the first study of Heart Rate Variability, a measure of cardiac autonomic function, in paroxysmal AF patients with and without OSA.

1.5.5 Outcome Studies

OSA is associated with worse outcomes in AF patients. OSA has been identified as an independent risk factor for stroke in patients with atrial fibrillation, in a retrospective cohort study (Yaranov 2015). In a large prospective registry of AF patients, those with a prior diagnosis of OSA had worse symptoms and more hospitalisations over 2 years (Holmqvist 2015). Nonetheless, there was no difference in all-cause mortality, cardiovascular death, hospitalisation or major bleeding in AF patients with or without OSA. This registry did not screen patients for OSA but rather relied on a history of prior diagnosis, hence it is likely that the control group contained many patients with undiagnosed OSA.

1.5.6 AF recurrence following Pulmonary Vein Isolation (PVI) and mechanical Cardioversion

Numerous non-randomised studies, including several meta-analyses, report that OSA increases the risk of AF recurrence following cardioversion and ablative procedures for AF (194-199), a risk which appears to be mitigated by effective OSA treatment (4-6, 196, 200, 201). Table 9 summarises 6 observational studies of

moderate to large size and one meta-analysis looking at the recurrence of AF following ablative procedures in OSA compared with control groups without OSA. Apart from one study which used only the Berlin Questionnaire for diagnosis (202), they all suggest that OSA significantly increases the risk of AF recurrence following ablation procedures. However, few of these studies diagnosed OSA via PSG, the gold standard investigation for OSA on all patients. In fact, many relied upon questionnaires which have a significantly reduced sensitivity and specificity for the diagnosis of OSA. This suggests that OSA may have been significantly underdiagnosed in several of these studies. One study did perform an abbreviated (level 3) sleep study on all patients (196), and another used a stepwise combination of the Berlin Questionnaire plus laboratory PSG (194); these two are most likely to have adequately diagnosed OSA. Of these, Szymanski et al found AF recurrence occurred more often in OSA patients up to 30 months following an ablation procedure (65.2% vs. 45.6 %; p=0.003) (196). Similarly, Matiello et al reported the arrhythmia-free probability at one year post PVI was 48.5% in patients without OSA (low BQ score or AHI < 10/h), 30.4% in the non-severe OSA group (AHI 10 - 30/hr) and 14.3% in the severe OSA group (AHI ≥ 30/hr) (194).

Further studies have also looked at the recurrence of AF following cardioversion or ablation in treated vs non-treated OSA groups (see Treatment Studies, below).

1.5.7 Treatment Studies

Whether or not treatment of OSA can reduce the burden of AF is yet to be demonstrated in large randomised controlled trials. Treatment studies to date have been mostly observational, though the majority are consistent with a positive

treatment effect. At the time of writing, only two small randomised controlled trials have assessed the impact of OSA treatment in isolation on AF burden. Caples et al looked at a small group of OSA patients randomised to CPAP (n=12) vs usual care (n=13) following cardioversion for AF, and found no difference in AF recurrence between groups (203). Similarly, Traaen et al treated 55 AF patients with moderate to severe OSA with CPAP and found no difference in AF burden over a five month period measured by implantable loop recorder when compared to the control group (n = 54) (144). In both these studies CPAP compliance exceeded 4 hours per night, however these preliminary studies are small and likely to be underpowered. Therefore larger RCTs looking at the effect of OSA treatment on AF outcomes are required. Another small randomised control trial by Craig et al looked at the effect of CPAP vs sham CPAP on various arrhythmias in a group of OSA patients and found no difference, though they did report a reduction in mean heart rate on CPAP therapy. This study did not specifically report on AF which was included in the broader category of supraventricular arrhythmia (193)

There are several prospective observational cohort studies looking at AF recurrence following treatment procedures (PVI or cardioversion) for OSA patients, both with and without CPAP. In 2003, Kanagala et al followed a cohort of 120 AF patients undergoing cardioversion, with and without a previous PSG diagnosis of OSA. Recurrence of AF at 12 months in untreated OSA patients was 82%, significantly higher than the 42% recurrence in the OSA group treated with CPAP (n = 12, p=0.013) and the 53% recurrence (n = 79, p=0.009) in the 79 control patients who did not undergo a background PSG (5). This finding was replicated in a retrospective analysis of an AF population undergoing PVI, which found that for patients with a previous PSG-confirmed diagnosis of OSA, adherence with

CPAP therapy was associated with a higher AF-free survival rate at 12 months (71.9% vs. 36.7%; p = 0.01) (6). Similarly, there have been at least five meta-analysis studies of AF recurrence following PVI and/or cardioversion in OSA patients treated with CPAP compared to those on no treatment, all of which demonstrate an improved rate of AF recurrence with CPAP compared to no CPAP (200, 201, 204-206). One retrospective study showed no benefit with CPAP (207). See table 10.

Taken together these studies suggest that patients undergoing PVI or cardioversion for AF have a higher risk of recurrence if they have a known diagnosis of OSA, a risk which appears to be mitigated by treatment with CPAP. The limitations of these data are that the vast majority of studies are observational, and have not always screened the control groups for OSA. In addition, these studies are subject to bias such as the “healthy-user” effect, a demonstrated association between CPAP adherence and compliance with treatment medications (208), which may include anti-arrhythmic medications. Further, there is heterogeneity in the diagnostic strategies and definitions of OSA. As such, they should be interpreted cautiously pending the results of ongoing randomised controlled trials.

There is a relative paucity of evidence examining the effect of OSA treatment on AF outcomes outside the setting of cardioversion or PVI. In a retrospective study of 316 Japanese patients who underwent both a diagnostic PSG and subsequent CPAP titration study, there was a significant improvement in the number of patients experiencing incident paroxysmal AF on the CPAP night compared with the original PSG (16 patients vs 1 patient, p < 0.001) (157). In a very large registry of AF

patients, Patients with OSA on CPAP treatment were less likely to progress to more permanent forms of AF compared with patients without CPAP (HR, 0.66; 95% CI, 0.46-0.94; P = .021) (152). One published case study documents an apparent resolution of AF with effective CPAP therapy (209). Overall, the evidence for the impact of effective OSA treatment on AF burden outside the setting of PVI or cardiac ablation is scarce, and further studies are needed.

1.5.8 Continuous Positive Airway Pressure (CPAP) for Atrial Fibrillation Patients

Observational studies very strongly support an association between CPAP therapy and improved AF outcomes. However, as discussed above, there are no large randomised studies looking at the impact of CPAP therapy on AF incidence or burden.

A small number of moderately sized randomised control trials have examined the effect of CPAP therapy on other cardiovascular outcomes including stroke, myocardial infarction and revascularisation of coronary artery disease, but have failed to demonstrate a benefit in terms of the primary end point (12-14, 51). However, these trials have all been characterised by very poor CPAP adherence (less than four hours per night), which may have contributed to the negative result. In addition, subgroup analysis in groups with higher CPAP adherence have shown some significant cardiovascular benefits (111). For example, in the SAVE study which looked at CPAP therapy for secondary prevention of cardiovascular end-points, there was a significant improvement in the incidence of stroke in CPAP adherent versus usual care patients, with a hazard ratio 0.56 (0.32 to 1.00, p =

0.05) (12). The mechanism behind this result is unknown, but one could postulate that better control of AF may have contributed.

Although it is considered first line OSA therapy, CPAP is often poorly tolerated, and has demonstrated suboptimal compliance rates in cardiovascular populations (12, 210). This may be in part due to the relative paucity of OSA symptoms in cardiovascular patients. No randomised studies have yet looked at the impact of therapies other than CPAP on AF outcomes. As mandibular advancement splint (MAS) therapy has increased adherence when compared to CPAP, further research is required to examine the impact of MAS therapy on cardiovascular outcomes, including atrial fibrillation. In chapter 4 of this manuscript, we seek to address this gap in the literature with a pilot study for the treatment of OSA with MAS therapy. This study will inform a future randomised control trial.

1.5.9 Conclusion

In summary, the literature demonstrates a strong epidemiological relationship between OSA and AF, as well as plausible mechanistic links between these two highly prevalent and chronic conditions. While many treatment studies do suggest a benefit from CPAP therapy on AF recurrence following cardioversion or PVI, the vast majority of these are observational and further, they are heterogenous in terms of OSA diagnosis and severity. To date, there is no randomised controlled study evidence that treatment of OSA can improve outcomes in AF. There is an urgent need for high quality, randomised studies examining the impact of effective OSA therapy on AF burden and outcomes, including non-CPAP therapies. In the meantime, best practice management of AF includes aggressive treatment of underlying risk factors, including atrial fibrillation. Therefore accessible and accurate OSA screening strategies are required for the clinical management of AF patients. In addition, there is a need for research on alternative treatment options for this clinical context.

Table 5: Epidemiology OSA in AF patients

Ref	Study population	Control	Study Type	Follow-up	OSA Dx	AF Dx	Result	Limitations
Gami et al, 2004 (150)	N = 151 consecutive patients undergoing cardioversion for AF	N = 312 referred to a general cardiology practice	Prospective case control study	Nil	BQ	Cardioversion referral	OSA was more common in the AF group compared with controls (49% versus 32%, P<0.0004). Adjusted odds ratio for the association between AF and OSA 2.19 (95% CI 1.40 - 3.42, P<0.0006).	OSA was diagnosed on BQ (although the BQ was validated against PSG in a subgroup of 44 patients)
Gami et al, 2007 (151)	N= 133 with incidental AF detected on PSG	N = 3409 patients undergoing PSG without incidental AF	Retrospective case control	Mean 4.7 years	Level 1 PSG	Medical record database	OSA predicted incident AF on univariate analysis (HR 2.18, 95% CI 1.34 to 3.54). ODI but not AHI ≥ 5/hr predicted OSA in patients < 65years old.	Patients were recruited from sleep study referrals and hence may not extrapolate to the general population
Stevenson et al, 2008 (142)	N = 90. AF outpatients EF > 50%, no IHD.	N = 45 age and sex matched general cardiology patients	Prospective case control	Nil	Level 2 (domiciliary) PSG	Diagnosis of AF via outpatient cardiology service.	Mod to severe OSA (AHI > 15) was more prevalent in AF patients vs general cardiology patients (62% vs 38%, p = 0.01).	AF burden was assessed subjectively by patient recall.
Braga et al, 2009 (140)	N = 52 chronic persistent and permanent AF patients	N = 32 age matched community based sample	Prospective case control	Nil	Level 1 PSG	AF excluded in controls on Holter and clinical exam.	AF group had a higher frequency of OSA (AHI > 10) compared to the control group (81.6% versus 60%, p = 0.03)	Atypical definition of OSA (AHI ≥ 10/hr) is not explained
Porthan et al, 2004 (153)	N = 59 patients with “lone” AF (ie AF without an identified risk factor.	N = 56 matched community controls	Prospective case control	Nil	Level 3 device	Hospital database.	11.9% of patients in the AF group had mod-severe OSA, compared with 5.4% in the control group, though this was not statistically significant (p = 0.22). Neck circumference highlighted as a RF for AF.	OSA diagnosed without full PSG.

Szymanski et al, 2014 (145)	N = 289 consecutive AF patients hospitalised for catheter ablation	Nil	Cross-sectional prevalence study	Nil	Prior Level 1 PSG	Primary hospital admission diagnosis of AF	45.5% of patients were diagnosed with OSA (27.8% mild, 13.2% moderate, 4.5% severe)	No control group for comparison
Kadhim et al, 2019 (146)	N = 442 rhythm control candidates who underwent PSG	Nil	Diagnostic accuracy study	Nil	Level 1 PSG	12 lead ECG	66% of patients had OSA (AHI ≥ 5/hr), with 32% diagnosed with mild OSA, 17% moderate and 17% severe.	No control group for comparison
Albuquerque et al, 2012 (147)	N = 151 AF patients referred for DC cardioversion who also underwent PSG	Nil	Diagnostic accuracy study	Nil	Level 1 PSG	DC cardioversion referrals	57% of patients were diagnosed with OSA (AHI ≥ 5/hr), 52.3% had moderate to severe OSA (AHI ≥ 15/hr). An additional 10.6% were defined as mixed obstructive/Central sleep apnoea.	No control group for comparison
Bazan et al, 2021 (148)	N = 73 patients with new onset AF and no previous diagnosis of OSA	Nil	Cross-sectional prevalence study	Nil	Level 3 device	12 lead ECG	82% were newly diagnosed with OSA: 19 (26%) had mild OSA, 19 (26%) moderate OSA and 22 (30%) severe OSA	No control group for comparison
Marti-Almor et al, 2020 (149)	N = 553 unselected pacemaker patients with AF	Nil	Cross-sectional prevalence study	18 months	Transthoracic impedance algorithm from implantable pacemaker device	Continuous monitoring: Pacemaker device	"Significant AF" was higher in the severe SA group (25.0% vs 13.9%; difference 11.1%; 95% confidence interval 3.7%-18.4%; P = .002). Persistent AF was higher in severe SA group at 12 months (16.9% vs 7.3%).	Diagnosis using a pacemaker algorithm is not the gold standard but has been previously validated in a non-AF group (211).
Kadhim et al, 2021 (154)	N= 2660 AF patients in 13 studies	Nil	Meta-analysis	Nil	Various	Various	For moderate-to-severe SDB (AHI ≥ 15/hr), the pooled SDB prevalence was 40% (95% CI 32%-48%; *P* < 0.001).	Heterogenous diagnostic threshholds and diagnostic tools used to identify SDB. Only 14% of studies used a level 1 PSG.

AF: Atrial fibrillation, AHI: Apnoea hypopnea Index, BQ: Berlin questionnaire, ECG: Electrocardiogram, ODI: Oxygen desaturation index, OSA: Obstructive sleep apnoea, PSG: Polysomnography, SDB: Sleep disordered breathing, SA: Sleep apnoea

Table 6: Epidemiology AF in OSA patients

Ref	Study Population	Control	Study Type	Follow-up	OSA Dx	AF Dx	Result	Limitations
Mehra et al, 2006 (155)	N = 228 subjects with severe OSA (RDI≥ 30)	N = 338 subjects without sleep-disordered breathing (RDI < 5/hr)	Prospective community-based cohort study	Nil	Level 1 PSG	PSG ECG	After adjusting for age, sex, BMI, and CHD, patients with AHI > 30/hr had 4 x the odds of nocturnal AF on PSG ECG (OR 4.02; 95% CI, 1.03–15.74).	Some significant cardiovascular differences between the groups were noted: hypertension was more prevalent in the SDB group (58.6 vs 39.7%, p < 0.0001).
Kwon et al, 2015 (156)	N = 2048	Nil	Cross-sectional prevalence study	Nil	Level 1 PSG	Diagnostic codes, ECG, PSG.	Increasing AHI and ODI was associated with a higher prevalence of AF, though not when adjusted for variables including CVD.	AF diagnosis derived from hospital codes and not matched to PSG
Cadby et al, 2015 (141)	N = 6,841 sleep clinic referrals	Nil	Retrospective longitudinal cohort study	Median 11.9 years	Level 1 PSG	hospital admission with a primary or secondary diagnosis of AF/flutter	After multivariable adjustment, AHI >5/hr predicted incident AF (HR 1.55; 95% CI, 1.21-2.00).	Patients were all sleep clinic referrals, reducing generalisability. AF was diagnosed on the basis of hospitalisation only.
Mooe et al, 1996 (161)	N = 121 consecutive patients undergoing CABG, 49 with ODI >5/hr	N = 72 patients with ODI < 5/h4	Prospective cohort	Immediate post-operative period	Level 3 device	AF episode requiring anti-arrhythmic medication or intervention	ODI ≥ 5/hr but not AHI ≥ 5/hr increased the risk of post-operative AF (RR 2.8, 95% CI 1.2 – 6.8).	Level 3 device may underestimate OSA. Some confounders eg obesity were not considered.
Guilleminault et al, 1983 (212)	N = 400 with OSA, screened for nocturnal arrhythmia on Holter	Nil	Prospective cohort	Nil	Level 1 PSG	Holter monitor	3 % of patients demonstrated AF on Holter. In 8 patients with nocturnal AF and OSA, tracheostomy resolved AF in all 8.	Statistical significance of results (p values) not reported.
Zhao et al, 2015 (160)	N = 160 elective CABG patients,	N = 32 CABG patients without OSA	Prospective cohort	Immediate post-operative period	Level 3 device (Watch-pat)	Continuous telemetry for 3	New-onset post-CABG AF was increased in the sleep apnoea	Level 3 device may underestimate OSA. BMI differed between groups but was not included in the multi-variate analysis.

	128 (80%) with OSA (AHI ≥ 5/hr)					days then daily Holter thereafter	group (24.8% vs 9.7%; P = .07).	
Hendrikx et al, 2017 (213)	N = 201 patients referred for PSG for suspected OSA	Nil	Prospective cohort	14 days	Level 1 PSG	12 lead ECG in hospital and intermittent portable ECG recordings at home	AF occurred in 6.5% of subjects, and in 20% of subjects > 60 years. Prevalence increased with OSA severity (p = 0.038).	Sleep clinic referrals only, no control group.
Guo et al, 2021 (214)	N = 187,933 screened for both OSA and AF using portable photo-plethysmographic devices	Groups were stratified into high risk, moderate risk and low risk for both OSA and AF	Cross sectional cohort study	Nil	Level 3 (photo-plethysmography) High risk sleep apnoea	Photo-plethysmography	High risk sleep apnoea increased the risk of AF by 5.36 (95% CI 3.43 – 8.37) independent of age, sex, BMI, hypertension, diabetes mellitus, CAD, heart failure and hyperthyroidism.	Diagnosis of both OSA and AF was via home-based photo-plethysmography which is not the gold standard for either condition. Multiple types of devices were used, neither concordance between devices nor validation with a gold standard was discussed.

AF: Atrial fibrillation, AHI: Apnoea hypopnea index, BMI: Body mass Index, CABG: Coronary artery bypass grafting, CAD: Coronary artery disease, CVD: Cardiovascular disease, ODI: Oxygen desaturation index, RDI: Respiratory disturbance index

Table 7: Screening tools for OSA in Patients with Atrial Fibrillation as compared with PSG

Ref	N	Study Type	Study Population	OSA Screening Tool(s)	OSA gold standard Dx	Result	Limitations
Delesie et al, 2021 (166)	100	Diagnostic accuracy	AF patients referred for PSG	ESS, Berlin, SACS, NoSAS, OSA50, STOP-Bang, MOODS	PSG	None of the seven screening tools demonstrated an AUC > 0.7 in the detection of severe OSA	AF patients were not sequential but recruited from those referred for PSG
Kadhim et al, 2019 (146)	442	Retrospective analysis of prospectively collected data	Consecutive AF rhythm control candidates	ESS	Level 2 (ambulatory) PSG	ESS poorly predicted SDB at all levels of severity AUC: 0.48-0.56	Symptomatic AF rhythm control candidates only, results may not apply to other AF populations.
Albuquerque et al, 2012 (147)	151	Prospective diagnostic accuracy	Sequential AF patients referred for cardioversion	ESS	PSG	ESS demonstrated a low sensitivity (32.2%) and specificity (54.5%) for SDB	Specific population: direct current cardioversion patients.
May et al, 2020 (164)	300,	Prospective, case control Diagnostic accuracy	Cardiology outpatients: 150 with PAF, 150 matched controls	ESS, Berlin, OSA50, STOP-Bang, STOP, NoSAS	PSG	For AHI > 15/hr, the best performing of the assessed screening tools was STOP-Bang with an AUC of 0.75 (0.66–0.86)	All study group patients had PAF, results may not apply to other AF populations
Linz et al, 2018 (80)	439	Retrospective analysis of prospectively collected data	Consecutive AF rhythm control candidates	Overnight oximetry derived from PSG	PSG	An ODI cut-off of 4.1/hr gave a sensitivity of 91%, specificity of 83% for moderate to severe OSA (AHI ≥ 15/hr).	Overnight oximetry was derived from PSG, not performed at home.
Abumuamar et al, 2018 (169)	95	Prospective cohort diagnostic accuracy	Arrhythmia clinic outpatients with a documented history of paroxysmal or chronic AF	STOP-Bang	Level 2 (ambulatory) PSG	STOP-Bang ≥3 gave a Sensitivity of 89%, Specificity of 36% for a diagnosis of OSA (AHI ≥ 5/hr), AUC 0.74, (p = .004, 95% CI 0.6–0.8).	Diagnostic accuracy for moderate to severe OSA (AHI ≥ 15/hr) was not reported.
Wyckmans et al, 2021 (215)	132	Meta-analysis of 4 studies	AF patients with a pre-existing cardiac	Cardiac Implantable Electronic device: transthoracic	PSG	AUC was 0.8689 (0.6872; 0.9456) for the detection of severe OSA (AHI ≥ 30/hr).	Screening method only applicable to patients with an implantable cardiac device, low generalizability.

	implantable electronic device.	impedance measurement

AHI: Apnoea hypopnoea index, AUC: area under the curve, BQ: Berlin questionnaire, ESS: Epworth sleepiness scale, MOODS: Male, Overweight or Obesity, Diabetes mellitus and history of Stroke, NoSAS: Neck circumference, Overweight/obesity, Snoring, Age and Sex, OSA: obstructive sleep apnoea, SACS: Sleep apnoea clinical score, PAF: Paroxysmal atrial fibrillation, SDB: Sleep disordered breathing, STOP = 4 point scale on snoring; tiredness; observed apnoeas; and arterial hypertension (pressure), STOP-Bang; Snoring, Tiredness, observed apnoeas, arterial hypertension (Pressure), Body mass index, Age, Neck circumference and Gender.

Table 8: Diagnostic Tests for OSA in AF patients: test characteristics for the detection of an AHI ≥ 15/hr (moderate to severe OSA), as compared to level 1 PSG.

Test	Channels	Reference	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	ROC AUC
Level 1: In-laboratory PSG	EEG, EOG, EMG, ECG, airflow, air pressure, respiratory and abdominal effort, SaO2, HR, limb movement, snore probe, position sensor	n/a	100% (gold standard)	100% (gold standard)	100% (gold standard)	100% (gold standard)	
Level 2: Portable PSG	EEG, EOG, EMG, ECG, airflow, air pressure, respiratory and abdominal effort, SaO2, HR, limb movement, +/- snore probe, position sensor	**No published studies**					
Level 3: Portable limited channel devices	4 – 7 channels, usually airflow, respiratory effort, HR, SaO2.	**No published studies**					
Level 4: Overnight Oximetry	SaO2, HR	Linz et al (80) ODI 4.1/hr	91	83	73.6	95.5	0.951 (0.929–0.972)
Questionnaires	**Cut-off value**	**Reference**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**ROC AUC**
Berlin		Delesie et al (166)	76.8 (64.8—85.8)	48.4 (30.6—66.6)	76.8 (64.8—85.8)	48.4 (30.6—66.6)	Not reported
		May et al (164)	72 (60–83)	58 (46–68)	57 (45–67)	73 (61–83)	0.64 (0.52–0.75)
Stop-Bang	≥ 5 “high risk”	Delesie et al (166)	59.4 (46.9—70.9)	61.3 (42.3—77.6)	77.4 (63.5—87.3)	40.4 (26.7—55.7)	0.673 (0.553—0.794)
	≥3 “intermediate to high risk”	May et al (164)	89 (79–96)	42 (32–54)	54 (44–64)	84 (69–93)	0.75 (0.66–0.86)

	≥3 “intermediate to high risk”						
OSA-50	>5	Delesie et al (166)	89.9 (79.6—95.5)	12.9 (4.2—30.8)	69.7 (58.9—78.7)	36.4 (12.4—68.4)	0.686 (0.576—0.795)
ESS		Kadhim et al, 2019 (146)	14.8	90.1	67.5	43.1	0.56 (95% CI: 0.5-0.62)
		Albuquerque et al, 2012 (168)	29.1 (20.3-39.9)	58.3 (46.8-69.0)	43.4 (31.0-56.7)	42.9 (33.5-52.7)	Not reported
	>11	Delesie et al (166)	30.4 (20.2—42.8)	74.2 (55.1—87.5)	72.4 (52.5—86.6)	32.4 (22.0—44.7)	0.532 (0.411—0.654)
		May et al (164)	25 (15–37)	74 (63–83)	42 (26–59)	56 (47–66)	0.50 (0.42–0.60)

EEG: Electro-encephalogram, EOG: Electro-oculogram, EMG: Electromyogram, ECG: Electrocardiogram, ESS: Epworth sleepiness scale, PSG: polysomnography,

Table 9: AF recurrence following Ablation therapies or cardioversion in OSA patients

Ref	Study Population	Control	Study Type	Follow-up	OSA Dx	AF recurrence Dx	Result	Limitations
Szymanski et al, 2015 (196)	N = 251 admitted for AF ablation, 115 with OSA (AHI ≥ 5/hr)	N = 136 without OSA	Prospective case control	30 months	Level 3 device	ECG + Holter + patient symptoms	AF recurrence occurred more often in the OSA group (65.2 vs. 45.6 %; p=0.003)	OSA diagnosed by single night level 3 device.
Farrehi et al, 2015 (197)	N = 247 consecutive ablation patients, 94 with reported prior OSA (group A), 121 high risk for OSA on STOP-BANG (group B)	N = 32 low risk OSA on STOP-BANG (group C)	Prospective case control	100 days	History of prior PSG or STOP-BANG	Patient event monitor	Patients in the low risk OSA group (group C) were more likely to remain free of AF than those in the known OSA group (group A) p = 0.006; or in groups A and B combined, p = 0.002.	Prior OSA diagnosis by PSG was patient-reported and severity was unknown. Some patients were treated with CPAP but neither CPAP compliance nor efficacy was objectively assessed.
Matiello et al, 2010 (194)	N = 174 sequential PVI patients without prior PSG, n = 42 with OSA	n = 132 without OSA	Prospective case control	1 year	Berlin + Level 1 PSG	Serial Holter	Arrhythmia-free probability at one year was 48.5% in patients with low BQ score or AHI < 10/h, 30.4% in the non-severe OSA group (10 < AHI < 30/h) and 14.3% in the severe OSA group (AHI >or= 30). P< 0.001 for the low risk vs severe group.	OSA diagnosis based on initial screening with Berlin Questionnaire, then PSG in high risk patients only, hence a proportion of the control group likely to have OSA.
Chilukuri et al, 2010 (198, 216)	N = 109 PVI patients, 48 high risk on BQ	61 low risk on BQ	Prospective case control	11 months	BQ	ECG, Event monitor for symptomatic patients	58% of OSA patients had a 90% reduction in AF burden after a 3 month blanking period, as compared with 77% without OSA (P = 0.036)	OSA diagnosed on BQ only which has poor diagnostic accuracy in AF patients
Jongnarangsin et al, 2008 (199, 217)	N = 324 PVI patients, 32 of	292 patients without known OSA	Prospective case control	7 months	Prior PSG	ECG and 3 day event recorder	Patients without OSA were more likely to be free from arrhythmia at the end of the	Patients were not screened for OSA, OSA diagnosed on the basis of previous

	whom had known prior OSA						follow up period (7M), 63% vs 41%, p = 0.02.	PSG only, hence likely significantly underdiagnosed.
Tang et al, 2009 (202)	N = 178 PVI patients, 104 high risk on BQ	74 low risk on BQ	Prospective case control	1 year	BQ	Confirmed AF on ECG and Holter monitor beyond 3M post ablation	No difference in AF recurrence between high risk and low risk for OSA groups on BQ (25.0% vs 24.3%, p = 0.855)	OSA diagnosed on BQ only which has poor diagnostic accuracy in AF patients
Ng et al, 2011 (195)	Total of 6 studies, n = 958 with OSA	N = 3,037 without OSA	Meta-analysis of AF recurrence post catheter ablation	6 – 32 months	BQ or PSG	Various	Overall, patients with OSA have a 25% greater risk of AF recurrence after catheter ablation (risk ratio 1.25, 95% confidence interval 1.08 to 1.45, p = 0.003).	Heterogeneous diagnostic methods utilised for OSA and AF recurrence.

AF: Atrial fibrillation, BG: Berlin questionnaire, ECG: electrocardiogram, OSA: Obstructive sleep apnoea, PSG: Polysomnography, STOP-BANG: STOP-BANG questionnaire,

Table 10: Treatment Studies

Treatment Studies post ablation / Cardioversion

Ref	N	Study Population	Control(s)	Study Design	Follow-up	OSA Dx	Outcome Measure	Result	Limitations
Patel et al, 2010 (4)	3000	N = 315, PVAI + OSA, on CPAP	N = 325 PVAI + OSA, not on CPAP. N = 2360, PVA, without known OSA.	Prospective case control	32 +/- 14months	Prior diagnosis of OSA on prospectively collected database	AF recurrence on event monitor or Holter monitor	79% CPAP, 68% non-CPAP were free from AF, HR 8.81 p < 0.001	Patients were not actively screened for OSA. Observational design.
Kanagala et al, 2003 (5)	118	cardioversion patients with a prior PSG, N = 12 with OSA on CPAP	N = 29 with OSA, not using CPAP N = 79 randomly selected cardioversion patients with no prior sleep study	Prospective case control	12 months	Prior PSG	AF recurrence on clinical evaluation or ECG	Recurrence was 82% in untreated OSA patients, 42% in treated OSA patients (n = 12, p=0.013) and 53% controls (n = 79, p=0.009).	Controls not tested and may have had occult OSA. Observational design.
Fein et al, 2013 (6)	32.	N = 32 PVI patients with OSA on a prior PSG (AHI>15), using CPAP	Three comparison groups: N = 30 PVI patients with OSA not using CPAP; N = 30 PVI patients without a prior dx of OSA; N = 22 medically managed patients with OSA on CPAP	Retrospective analysis of ablation database.	12 months	Prior PSG	AF recurrence on ECG, telephone call	CPAP therapy was associated with a higher AF-free survival rate (71.9% vs. 36.7%; p = 0.01). AF recurrence rate of CPAP-treated patients was similar to the group of patients without OSA (HR: 0.7, p = 0.46).	Unclear whether controls may have had occult OSA. Observational design.
Naruse et al, 2013 (7)	153	N = 82 PVI patients with OSA on CPAP	N = 34 PVI patients with OSA, not using CPAP N = 37 PVI patients without OSA	Prospective case control	18.8 ± 10.3 months	PSG	AF recurrence on ECG	AF free survival was significantly increased in the CPAP group compared to the OSA (no CPAP) group (p = 0.17), and was not significantly different from the No OSA group (p= 0.33).	Observational design.
Caples et al, 2019 (203)	25	N = 12 DCCV patients with OSA,	N = 13 DCCV patients with OSA, randomised to usual care	RCT	12 months	PSG	AF recurrence	There was no difference in AF recurrence between the two groups	Very small patient numbers, Select group (ESS > 10 or significant

		randomised to CPAP							pulmonary/cardiac disease excluded)
Neilan et al, 2013 (184)	720	N = 71 PVI patients with OSA, on CPAP	N = 71 PVI patients with OSA, not using CPAP N = 578 PVI patients without OSA	Prospective case control	42 months	Standardised questionnaire (not specified) +/- “formal sleep study” (not specified)	AF on ECG or prolonged monitoring	In a multivariable model, the presence of SA (hazard ratio 2.79, CI 1.97 to 3.94, P<0.0001) and untreated SA (hazard ratio 1.61, CI 1.35 to 1.92, P<0.0001) were highly associated with AF recurrence	OSA likely underdiagnosed. Diagnostic pathway not specified. Observational design.
Srivali et al, 2019	429	N = 269 CPAP users, undergoing ablation/cardioversion	N = 160 CPAP non-users, undergoing ablation/cardioversion	Retrospective case control	Nil	PSG	AF on ECG	no effect of CPAP treatment of SDB on time to recurrence of AF post-AF intervention	Retrospective design
Shukla et al, 2015 (200)	1087 OSA patients post PVI	CPAP group	Non-CPAP group	Metanalysis of 7 prospective case control studies, 5 of them post PVI	Median 12 months (range: 7 to 42 months)	PSG (all studies)	Various	CPAP was associated with a significant reduction in AF recurrence (relative risk: 0.58, 95% CI: 0.51 to 0.67; heterogeneity chi-square p ¼ 0.91, I2 ¼ 0%)	Heterogeneity in AF diagnosis, CPAP compliance not reported.
Deng et al, 2018 (204)	1217 patients with AF following catheter ablation	CPAP group (n = 619, 50.86%)	non-CPAP group (n = 598, 49.14%)	Metanalysis of 7 case control studies and 3 small RCTs	16.33 ± 10.34 months	PSG or BQ/PSG	Various	AF recurrence was increased in the CPAP non-user group (24.88% vs 42.47%; RR 0.60; 95% CI 0.51–0.70; *p* < 0.001)	Heterogeneity in AF diagnosis, CPAP compliance not reported.
Qureshi et al, 2015 (201)	N = 1247 with OSA and AF undergoing	698 on CPAP	549 without CPAP	Metanalysis of 8 studies: 7 prospective case control and one RCT	unreported	PSG (all studies)	AF recurrence	44% lower risk of recurrent AF in patients with OSA who used CPAP versus those who did not, pooled RR, 0.56; 95% CI, 0.47 to 0.68; p <0.001	OSA severity not reported.

	catheter ablation,								
Yang et al, 2020 (205)	2134 Rhythm control strategy patients	CPAP group	Non-CPAP group	Meta-analysis of 9 prospective case control studies	Mean 20.4 months, range 7 to 42 months	PSG or prior documentation	AF recurrence	CPAP therapy reduced AF recurrence (RR = 0.63; 95% CI, 0.56–0.72).	Heterogeneity in AF diagnosis, CPAP compliance not reported. OSA severity not reported.
Congrete et al, 2018 (206)	4572 Patients with OSA and AF undergoing catheter ablation	CPAP group	Non-CPAP group	Meta-analysis of 7 prospective case control	unreported	PSG (5 studies) or BQ (2 studies)	AF recurrence on ECG, Holter, event monitor or prolonged ECG monitoring.	OR of recurrent AF in patients with OSA was 1.70 (95% CI, 1.40-2.06, CPAP was significantly associated with decreased risk of recurrent AF with pooled OR of 0.28 (0.19-0.40)	Heterogeneity in AF diagnosis, CPAP compliance not reported. OSA severity not reported.

AF: Atrial fibrillation, BQ: Berlin questionnaire, CPAP: Continuous positive airway pressure, DCCV: Direct current cardioversion, ECG: Electrocardiogram, OSA: Obstructive sleep apnoea, OR: Odds ratio, PSG: Polysomnography, PVAI: Pulmonary vein antrum isolation, RCT: Randomised control trial, RR: Relative risk

Table 10 (Continued) Treatment Studies: Effect of CPAP on AF Burden

Ref	N	Study Population	Control	Study Design	Follow-up	OSA Dx	Outcome	Result	Limitations
Holmqvist et al, 2015 (152)	10,132	AF patients with OSA (n = 1841)	AF patients without OSA (n = 8291)	Retrospective case control	2 years	Prior known diagnosis of OSA	AF progression, hospitalisations, cardiovascular outcomes	OSA patients on CPAP were less likely to progress to more permanent forms of AF compared with OSA patients without (HR, 0.66; 95% CI, 0.46-0.94; P = .021). No difference in all-cause death, hospitalisations, CV death, stroke or bleeding between CPAP and no CPAP OSA groups	Controls not screened for OSA. Patients with OSA had more significant co-morbidities. PSG data not available.
Traaen et al 2021(144)	108	AF Outpatients from cardiology clinics or referred for ablation: CPAP for 5 months	54 CPAP, 54 Supportive care	RCT	5 months	AHI ≥ 15/hr diagnosed by 2 nights home polygraphy	Change in AF burden as measured via implantable loop recorder	No significant difference in AF burden between the 2 groups	Patients with an ESS ≥ 15 were excluded. Likely underpowered. OSA diagnosed on polygraphy.
Abe et al, 2010 (157)	316	Sleep clinic patients with AHI > 20/hr	Nil	Prospective cohort	Nil	PSG	Nocturnal arrhythmia on diagnostic PSG compared with a subsequent CPAP study	16 patients demonstrated PAF on PSG before CPAP, 1 patient only on CPAP ($p < 0.001$)	Patients recruited from sleep study referrals not on the basis of AF.
Abumuamar et al, 2019 (218)	100	Consecutive cardiology clinic AF outpatients, treated with CPAP	Nil	Prospective cohort	6 months	AHI ≥ 5/hr (mean AHI taken from 2 x level 2 sleep studies)	Holter result at 3 and 6 months compared to baseline	atrial ectopy count/24 hr significantly decreased in patients with paroxysmal AF compared to baseline (median (IQR) 351 (2049) to 31 (113), P=0.016, n = 14	No untreated control group.
Craig et al, 2009 (193, 219)	83	Men with moderate to severe OSA 43 underwent one month of therapeutic CPAP	N = 43 on CPAP vs n = 40 on sham CPAP	RCT	One month	PSG (ODI > 10/hr)	Dysrhythmias during 24 hour ECG recording pre and post CPAP	No difference in dysrhythmias in CPAP vs no CPAP. Reduction in mean HR on CPAP was noted.	AF was not analysed independently but was included in “SVT” supraventricular tachycardia category.

AF: Atrial fibrillation, CPAP: Continuous Positive Airway Pressure, CTI: Cavo-tricuspid isthmus, DCCV: Direct Current Cardioversion, ESS: Epworth Sleepiness Score, OSA: Obstructive sleep apnoea, PSG: Polysomnography, PVAI: Pulmonary vein antrum isolation,

2.0 Clinical Screening Tools for Obstructive Sleep Apnoea in a population with Atrial Fibrillation: A Diagnostic Accuracy Trial

This study was published as:

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2.1 ABSTRACT

Background: Although Obstuctive Sleep Apnoea (OSA) is a known risk factor for Atrial Fibrillation (AF), there is a paucity of data around its diagnosis and management in patients with AF.

Study Objectives: 1) To compare the diagnostic accuracy of commonly used OSA screening tools in an AF population, including a level 3 portable sleep study device, 2) To examine the epidemiology of OSA in a hospital cohort with AF.

Methods: 107 patients with AF recruited from two tertiary centres underwent a panel of OSA screening tools and in-laboratory polysomnography (PSG) in randomised order.

Results: Oxygen desaturation index (ODI) derived from a Level 3 portable sleep study device performed best for moderate to severe and severe OSA, with excellent diagnostic accuracy (AUC 0.899, 95% CI 0.838 – 0.960 and AUC 0.925, 95% CI 0.859 – 0.991 respectively). Sixty-seven patients (62.6%) were newly diagnosed with OSA (31.8% mild, 18.7% moderate, 12.1% severe). Study results are summarised in figure 7 (graphical abstract).

Conclusions: Undiagnosed OSA is highly prevalent in a hospital AF cohort. However it is characterised by a relative paucity of symptoms, markedly limiting the usefulness of history or screening questionnaires. This is the first study to find that a level 3 home sleep study device shows excellent diagnostic accuracy in AF patients. This finding may inform AF management guidelines.

Keywords: Polygraphy, Level 3 sleep study, Apnea Hypopnea Index, Oxygen Desaturation Index, ApneaLink.

2.2 BRIEF SUMMARY

Current Knowledge/Study Rationale:

- Obstructive Sleep Apnoea (OSA) is a known risk factor for Atrial Fibrillation (AF). Despite this, international AF guidelines lack clarity around the approach to the diagnosis and management of OSA.

Study Impact:

- Our study demonstrates that traditional OSA symptoms including snoring, self-reported sleepiness and obesity are inadequate for the detection of moderate to severe OSA in an AF population. A level 3 portable sleep study device showed excellent diagnostic accuracy in a hospital-based AF population, and may be useful as a screening tool in AF patients.

2.3 INTRODUCTION

The association between Obstructive Sleep Apnoea (OSA) and Atrial Fibrillation (AF) is well described (150, 151, 155). Studies consistently show a higher prevalence of OSA amongst AF patients as compared with controls, for example 62 vs 38% (142). Animal and human experimental studies have confirmed that OSA increases AF inducibility, both acutely in response to individual apnoeic events and via chronic atrial remodelling pathways (2, 177, 220). Several non-randomised studies report that OSA increases the risk of AF recurrence following cardioversion and ablative procedures, a risk which appears to be mitigated by effective OSA treatment (4-6, 200, 201). OSA is an independent risk factor for ischaemic stroke in AF patients (221).

Although clinical guidelines acknowledge the role of OSA as a risk factor for atrial fibrillation (AF), they lack clarity in the approach to its diagnosis and management (9, 10, 222, 223). Guidelines of the AHA/ACC/HRS suggest that weight loss is recommended for obese patients with AF along with modification of risk factors, including OSA (10). However, the diagnostic strategy by which to identify OSA is not elaborated in the guidelines, and the treatment of OSA in non-obese patients is not discussed. Recently published guidelines from the European Heart Rhythm Association / European Society of Cardiology (EHRA/ESC) recommend that optimal management of OSA may be considered to reduce AF incidence, progression, recurrence, and symptoms. However, they also stipulate that how and when to test for OSA in AF patients remain unknown (223). These inconsistencies highlight a paucity of evidence around screening and management of OSA in AF patients.

The gold standard investigation for the diagnosis of OSA, in-laboratory polysomnography (PSG), is a resource-intensive investigation requiring overnight admission in a specialist centre and may be inaccessible to many patients. In practice, AF patients may be referred for PSG at the discretion of their treating physician, on the basis of clinical suspicion of OSA. However, it is unclear how to identify which AF patients are most at risk of OSA. A recently published study highlighted the prevalence of undiagnosed OSA in patients awaiting AF ablation, and concluded that more research is required to identify the optimal method to test for sleep Apnea in AF patients (224).

The primary aim of this study was to evaluate the validity of a number of commonly used OSA screening tools in patients with AF, including: snoring, obesity, daytime hypersomnolence, airway crowding, symptom-based questionnaires and a Level 3 portable sleep study performed at home. A secondary aim was to examine the epidemiology of OSA in a hospital cohort with AF.

2.4 METHODS

Approval was obtained from the Northern Sydney Local Health District Human Research Ethics Committee (HREC/16/HAWKE/25), and the North Shore Private Hospital Ethics Committee (approval number 2016-012). All patients gave their informed written consent to participate in the study. The trial was registered with the Australian New Zealand Clinical Trials Registry (ANZCTR): 12616001016426.

Patients were recruited via two hospital-based clinical pathways: 1) Emergency Department presentations with confirmed AF, 2) Pulmonary Vein Isolation (PVI) waitlist in the Departments of Cardiology at two specialist centres. All patients had an electrocardiogram (ECG) documented history of ≥1 episode of AF in the last 12 months. PVI patients were sequentially recruited over the duration of the study period (July 2016 – Sep 2019). Due to large numbers of ED presentations during the study period, ED patients were sequentially recruited within three discrete time intervals during the study period (July 2016 – Nov 2016, Sep 2017 – Feb 2018, July 2018 – Dec 2018). Exclusion criteria are outlined in the study flowchart (Figure 9).

All patients undertook a baseline interview for the collection of demographic and anthropometric data including age, sex, ethnicity, Body Mass Index (BMI) and neck circumference. Comorbidities and AF risk factors were documented from patient interview and corroborating medical record review, including the presence of diabetes, ischemic heart disease (IHD), hypertension, congestive cardiac failure (CCF), CHA_2DS_2-VASc score, AF type (paroxysmal vs persistent/permanent) family history of AF, thyroid disease, alcohol excess. Paroxysmal AF was defined as an episode of AF self-terminating within 7 days. Other forms of AF were considered as persistent/permanent. Echocardiographic data, when available, was reviewed for patient ejection fraction, atrial size and valvulopathies.

All patients underwent a panel of commonly used OSA screening tools and full in-laboratory polysomnography (PSG) as the diagnostic reference within a week of one another, in randomised order. Randomisation was undertaken using computer-

generated random number software. The diagnostic accuracy of each screening tool was compared to in-laboratory PSG for various levels of OSA severity. OSA screening tools were as follows: the presence of patient-reported snoring, obesity (BMI ≥ 30 kg/m^2), airway crowding (Modified Mallampati score ≥ 3), self-reported daytime somnolence as measured by the Epworth Sleepiness Scale (ESS), Stop-Bang questionnaire score, Berlin questionnaire "high risk", and results from a Level 3 portable home sleep apnoea test (HSAT) (ApneaLink Air^{TM}, ResMed Ltd) performed in the patient's home. Clinical screening tools are summarised in Table 4. Test characteristics (sensitivity (Sns), specificity (Spc), positive and negative predictive values (PPV, NPV) and receiver operating characteristic (ROC) area under the curve (AUC)) were compared to results from PSG.

2.4.1 Sample Size Calculation

Sample size estimates were obtained by the method of evaluating confidence intervals for likelihood ratios for diagnostic test studies (225). We hypothesise that ApneaLink will be clinically useful as a screening tool if the upper limit of the confidence interval for the negative likelihood ratio is no greater than 0.2. We used an estimated AF prevalence of 65%, based on a previous study of OSA in an Australian AF population (though this study was limited to AF patients with normal ejection fraction) (142). Sensitivity and specificity for the ApneaLink device for the detection of moderate or severe OSA (AHI > 15) have been documented at 0.947 and 1.0 respectively in a non-AF population (226). Therefore required at least 40 patients with OSA and 40 patients without OSA to complete the final analysis. Taking into account the expected

prevalence of 65%, a total of 88 patients are required. To offset an expected withdrawal rate up to 20% we aimed to recruit a total of 110 patients for the study.

2.4.2 Polysomnography (PSG)

PSG was performed and analysed in a single tertiary referral centre by experienced technicians who were blinded to the screening tool results. PSG was scored according to American Academy of Sleep Medicine (AASM) 2012 criteria. An Apnoea was defined as complete (≥ 90%) reduction in airflow, lasting ≥ 10 seconds. A hypopnea was defined as a partial (≥ 30%) reduction in airflow, lasting ≥10 seconds, associated with either an arousal from sleep or an oxygen desaturation of ≥ 3% from baseline.

2.4.3 Sleep Apnea Severity definitions

The Apnoea/hypopnea index (AHI) is the primary metric used to classify sleep Apnea severity. It is defined as the number of Apnoeas plus hypopneas occurring per hour of sleep time (for PSG) or recording time (for level 3 or 4 devices which do not have EEG capability and are therefore unable to detect the presence of sleep). An AHI of 5 to <15/hr is classified as mild OSA; an AHI of 15 to <30/hr is classified as moderate OSA and an AHI ≥ 30/hr is classified as severe OSA.

2.4.4 Level 3 portable sleep study device

The ApneaLink Air device (ResMed, Australia) is a portable, Level 3 sleep study device comprising four channels: pulse oximetry (heart rate and oxygen saturation), airflow via a nasal cannula pressure transducer and respiratory effort measured via a chest band with pneumatic sensor (figure 9). Application of the device was demonstrated to patients in a clinic setting, following which patients were issued with a loan device to use overnight in their own home. Automated software analysis was used to derive sleep parameters including the AHI and 3% ODI. The oxygen desaturation index (ODI), measured by pulse oximetry, is the average number of oxygen desaturations (3%) from baseline per hour of sleep time (for PSG) or recording time (for level 3 or 4 devices). ApneaLink automatic scoring software has previously demonstrated good diagnostic accuracy compared with concurrent PSG in a sleep centre population (AUC 0.87, SE 0.06) (227).

2.4.5 Patient-Centred Assessment of Sleep Tests

A subset of patients (n=29) completed paired visual analogue questionnaires relating to patient-centred perceived qualities of in-laboratory polysomnography vs a Level 3 portable sleep study device (questionnaire reproduced in Appendix 1). Outcomes included test comfort, test convenience, perceived similarity to the patient's usual sleep pattern during the test and patient confidence in the test results.

2.4.6 Statistical Analysis

Data are presented as the mean +/- standard deviation (SD), or as a percentage of the total group. Continuous variables were compared between dichotomous groups

using independent t tests. Levene's test was used to assess homogeneity of variances. Categorical variables were compared using Chi^2 tests or Fisher's exact test, as applicable. A p value of <0.05 was considered statistically significant. Sensitivities, specificities, Receiver Operating Characteristics (ROC) curves and positive and negative predictive values were calculated using the statistical software package SPSS. ROC AUC was used to assess diagnostic accuracy according to the following thresholds: excellent: 0.9 – 1.0; good: 0.8 – 0.9; fair: 0.7 – 0.8; poor: 0.6 – 0.7; very poor: 0.5 – 0.6.

2.5 RESULTS

The study flowchart is outlined in Figure 9. Baseline characteristics are summarised in Table 11 by the presence of moderate to severe OSA. Baseline characteristics are also reported by recruitment stream (ED vs PVI, Table 15), and according to OSA of differing severities (Table 16, Table 17). There was no significant difference in the presence of moderate to severe OSA between the ER and PVI recruitment streams (31.0 Vs 30.1%, p=0.962).

2.5.1 OSA Clinical Screening Tools

A level 3 HSAT was the only screening tool to perform with good to excellent diagnostic accuracy across all severity categories. AHI derived from a Level 3 portable sleep study device performed best for the detection of OSA of any severity (AHI ≥ 5/hr): AUC 0.896 (95% CI 0.830 – 0.961). ODI derived from a Level 3 portable sleep study device performed best for the detection of moderate to severe OSA (AHI ≥ 15/hr):

AUC 0.899 (95% CI 0.838 – 0.960) as well as for severe OSA only (AHI ≥ 30/hr): AUC 0.925 (95% CI 0.859 – 0.991).

For moderate to severe OSA, snoring and self-reported hyper-somnolence measured via the ESS both performed with poor diagnostic accuracy. Obesity, Modified Mallampati score ≥3, and a Stop Bang or Berlin questionnaire score in the high risk category performed with fair diagnostic accuracy.

For severe OSA, two screening tools performed with good diagnostic accuracy. These are obesity (BMI ≥ 30 kg/m^2) with an AUC of 0.865 (95% CI 0.741 – 0.990), and a StopBang Questionnaire score in the "high risk" range (≥5): AUC 0.847 (0.733 – 0.961). A Berlin questionnaire in the high risk category performed with fair diagnostic accuracy, and snoring, self-reported hypersomnolence and a Modified Mallampati score ≥3 all performed with poor to very poor diagnostic accuracy.

Across all severity categories, the presence of snoring was a highly sensitive but not specific tool for the detection of OSA, though overall the presence of snoring showed poor to very poor diagnostic accuracy. ESS also showed poor to very poor diagnostic accuracy across all severity categories. Screening tool diagnostic accuracy characteristics are reported in Table 12 and in the Graphical Abstract (Figure 7).

2.5.2 Patient centred evaluation of Sleep Tests

A level 3 HSAT was perceived by patients as significantly more comfortable, more convenient and more conducive to replicating the patient's usual sleep pattern when compared to in-laboratory PSG (see Table 13). There was no difference in patient confidence in the test results.

2.5.3 OSA diagnosis

67 patients (62.6%) were newly diagnosed with OSA (31.8% mild, 18.7% moderate, 12.1% severe). The average AHI in the OSA group fell within the moderate range (20.4 ± 15.8/hr).

2.6 DISCUSSION

To the best of our knowledge this is the first study to validate a level 3 HSAT (also known as polygraphy) in an AF population, demonstrating its superiority to other OSA screening tools. Overall, a Level 3 HSAT showed the highest diagnostic accuracy at all levels of OSA severity: mild, moderate and severe. Previously these devices have been validated only in sleep clinic patients or those suspected to have OSA (227-229). We have demonstrated that AF patients represent a distinct clinical phenotype when compared with a sleep clinic population, and are less likely to have daytime symptoms or obesity, thus supporting the need and clinical relevance of test validation in the target population.

Importantly, many traditional OSA risk factors did not perform well as screening tools in this AF cohort, including some which are recommended in clinical guidelines. This gives caution to the use of self-reported snoring and daytime hypersomnolence, both of which performed with poor diagnostic accuracy for moderate to severe OSA, and very poor diagnostic accuracy for severe OSA. Similarly the presence of obesity, which is linked to OSA treatment in the AHA/ACC/HRS guidelines, performed with only fair diagnostic accuracy for moderate to severe OSA, though with good diagnostic accuracy for severe OSA.

Self-reported hyper-somnolence via the ESS has been shown in three prior studies of AF patients to be poorly predictive of OSA (146, 147, 230), though to the best of our knowledge this is the first study to report the diagnostic accuracy of self-reported snoring or obesity as OSA screening tools in an AF population against the gold standard of PSG.

2.6.1 Diagnostic Accuracy of Questionnaires and patient-reported symptoms

This study adds to the very limited available data on the diagnostic accuracy of screening questionnaires in AF patients. Both the StopBang and Berlin Questionnaires overall performed with only fair diagnostic accuracy for moderate to severe OSA, (AUC 0.787 (95% CI 0.688 – 0.886) and 0.761 (95% CI 0.659 – 0.864) respectively, results which are broadly consistent with one previously published study (230). The diminished performance of these questionnaires likely reflects the paucity of traditional OSA symptoms in an AF group.

Despite an AUC of only 0.639, a Stop-Bang Score ≥ 3 (intermediate to high risk) has a very high negative predictive value for the exclusion of moderate to severe OSA (NPV 90.0 for AHI ≥ 15/hr). This characteristic in particular would make a Stop Bang ≥ 3 a useful screening tool for regional or under-resourced areas where a level 3 device may not be accessible. In addition, the high NPV lends itself to a tiered screening strategy whereby StopBang could be utilised initially, followed by a level 3 device for those patients with a StopBang ≥ 3. For every 100 patients screened with this approach, 29 would return a negative StopBang result and therefore could forego the ApneaLink test. However for every 100 patients screened with this tiered stragegy, 3 patients an AHI > 15/hr would be missed.

Some screening tools, notably the presence of obesity, performed differently across different levels of OSA severity. This raises the question of what level of OSA severity is clinically significant in AF, an issue which is confounded by variable OSA definitions and diagnostic methods in the literature to date. The significance of OSA severity in AF patients is an area for future research.

2.6.2 Level 3 HSAT (polygraphy) vs Overnight oximetry

In this study, ODI as well as AHI was derived from a Level 3 portable sleep study device. Two prior studies have assessed ODI from overnight oximetry alone as a screening tool for OSA in cardiac patients, including one in an AF population (80, 231). In a group of 439 AF patients, Linz et al showed an AUC of 0.951 (95% CI: 0.929–

0.972) for the detection of moderate to severe OSA (80). In both mentioned studies, pulse oximetry data was collected as a component of PSG, in a sleep laboratory setting: a highly controlled environment less susceptible to signal loss than the home setting. In addition, when studies are performed concurrently there is no effect from night-to-night variability. These two factors are likely to at least partly explain the slightly lower AUC we found for ODI derived from a Level 3 device, performed on a different night to PSG in the home setting. Our study of ODI via polygraphy, performed in a home setting, represents an important next step for OSA diagnosis in AF patients. Unlike overnight oximetry, a level 3 device also has the capacity to distinguish obstructive from central apneas, which may be advantageous in a cardiovascular patient cohort.

2.6.3 Epidemiology of OSA in a hospital based AF cohort

We confirm that the prevalence of OSA in AF population was very high, with a total of 62.6% of patients newly diagnosed with OSA. Of note, patients were recruited solely on the presence of AF and not on the basis of any sleep symptoms nor OSA risk factors. The prevalence in our cohort is somewhat lower than in a recently published study which used home peripheral arterial tonometry (PAT) rather than the gold standard investigation (in-laboratory PSG) to diagnose OSA (224).

Despite the very high population prevalence of OSA, only a small proportion of patients (8 out of 230 contacted patients, 4.3%) were excluded on the basis of active OSA treatment. This highlights the significant under-diagnosis of OSA in this population,

and the need for a high index of suspicion amongst treating clinicians. This is consistent with a large cohort study of AF patients, which found only 17% had a diagnosis of OSA on the basis of physician report and medical record review, without active OSA screening (232). By contrast, studies which have sequentially screened AF patients, regardless of OSA symptoms, have identified a much higher prevalence eg 66%, 82%, (146, 224) in keeping with our study.

Taken together, the high population prevalence of OSA amongst AF patients, its under-diagnosis in this group and the paucity of traditional daytime symptoms emphasise the need for a simple, cost effective and accurate OSA screening tool in this population.

2.6.4 Patient centred evaluation of sleep tests

Patients' subjective experience of a Level 3 portable sleep study performed in their own home was that it resulted in sleep more similar to their usual sleep pattern. This is biologically plausible since the level 3 study allows the study to be performed in the patient's usual sleeping environment, less encumbered by leads. This finding aligns with previous studies which have shown that in-laboratory PSG artificially increases the severity of sleep disordered breathing by increasing supine sleep (233). There was also a statistically significant increase in patient comfort and perceived convenience with the Level 3 device when compared to in-laboratory PSG.

2.6.5 Limitations

Although our study provides novel findings, we acknowledge some important limitations. We performed PSG on one night only. This does not account for variations in sleep apnea severity from night-to-night, such as those caused by variations in sleep position. Of note, the ApneaLink device used in this study does not record sleeping position, and therefore this could not be compared to PSG. It is possible that this study has under-estimated the diagnostic accuracy of a Level 3 HSAT since it was performed on a different night and different setting to PSG. However this is necessary in a real-world scenario and hence to allow translation to clinical practice, we performed the portable sleep study in the patient's own home rather than the sleep laboratory.

Although we have documented patient reasons given (Figure 2) for the 20% who declined to participate, it is possible that this has introduced a bias into the study, which may have impacted on the prevalence data in particular. We cannot exclude the possibility that patients with OSA symptoms or risk factors may have been more likely to participate. We recruited AF patients from 2 streams: namely ED presentations and PVI waitlists. As there were some significant differences between these groups (see Table 5, supplementary material), this may have introduced a bias. We employed this strategy in order to replicate a clinically relevant range of AF patients. Finally, our study does not address the question of whether treating OSA in AF patients improves health outcomes, a critically important factor when considering screening strategies, and this warrants further research. Randomised control trials addressing this question are ongoing.

2.7 CONCLUSIONS

Our study demonstrates that traditional OSA symptoms including snoring, self-reported sleepiness and obesity are inadequate for the detection of moderate to severe OSA in an AF population. A level 3 HSAT showed excellent diagnostic accuracy in a hospital-based AF population, and may be useful as a screening tool in AF patients. Testing with a level 3 HSAT was perceived by patients as more comfortable, convenient and more closely matched to their usual sleep pattern than in-laboratory polysomnography.

Figure 7, GRAPHICAL ABSTRACT: ROC curves depicting the diagnostic accuracy of OSA screening tools at various levels of severity.

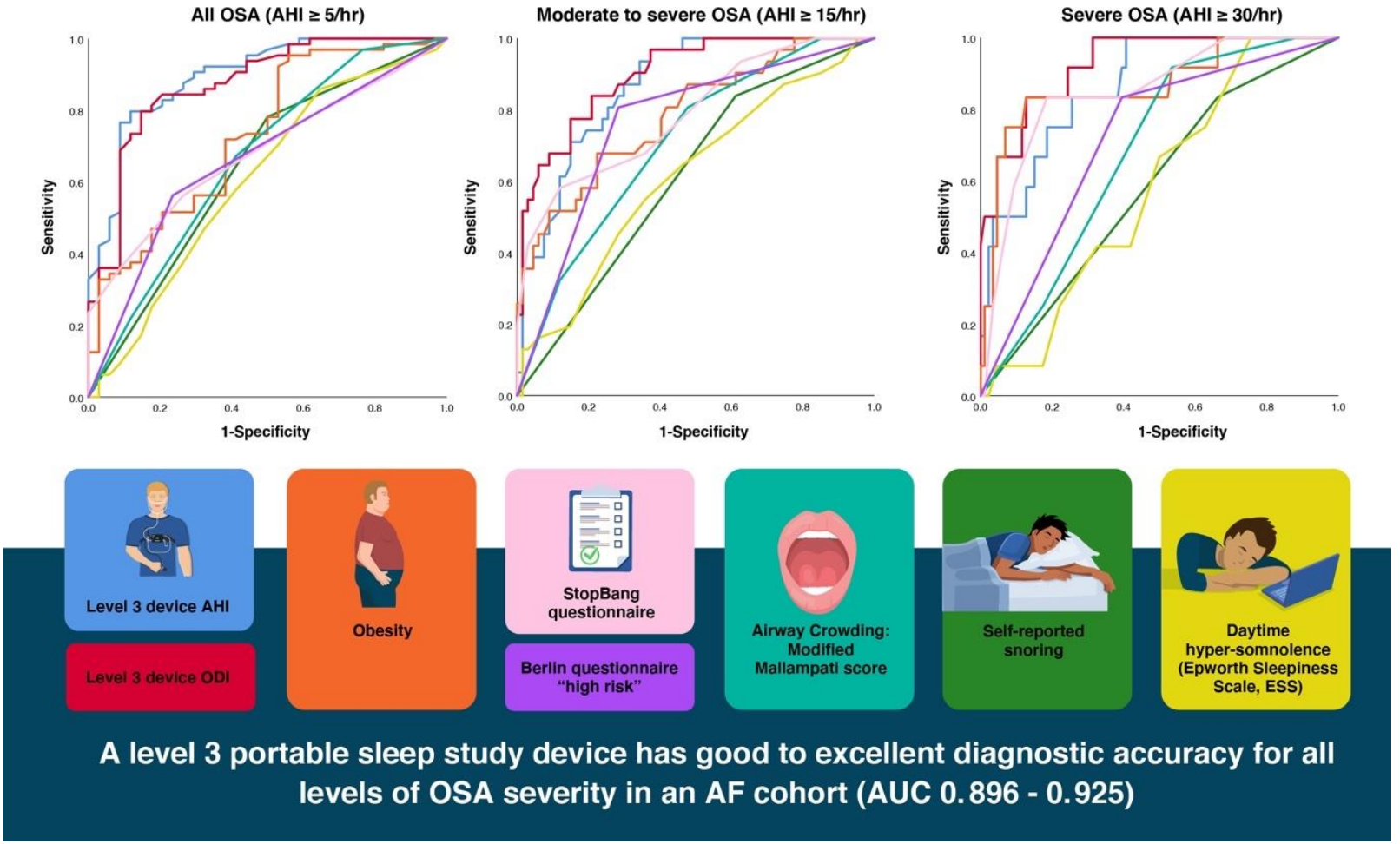
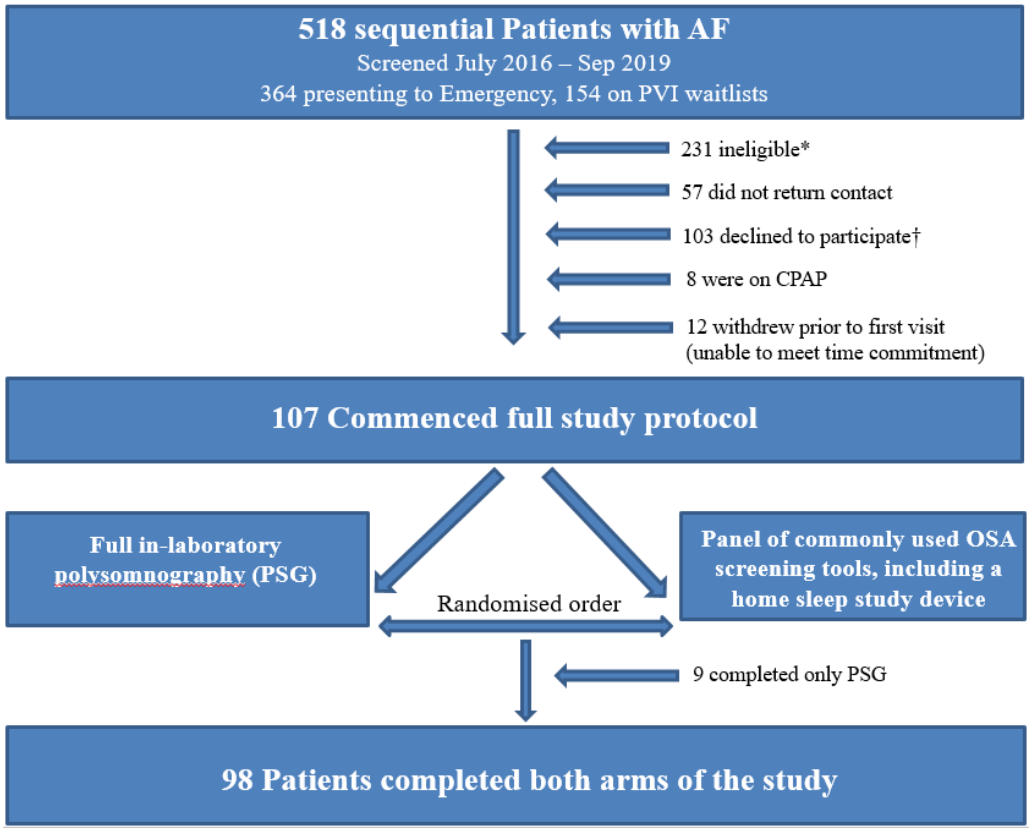


Figure 8: Study Flowchart



***231 patients ineligible. Reasons:**
43: no definite history of documented AF
67 : significant geriatric health issues
29: active malignancy
25: repeat presentations
24: geographically remote and unable to travel to the study
12: end stage organ disease
8: significant cognitive impairment
7: significant mental illness
6: active substance abuse
1: deceased
1: intubated
8: otherwise unable to provide written informed consent.

****103 patients declined. Reasons given:**
30 (29.1%): no reason given
22 (21.4%): too busy / no time
16 (15.6%): not interested
9 (8.7%): diagnostic sleep study already performed
7 (6.8%): too unwell to participate / too many medical appointments
6 (5.8%): no OSA symptoms
4 (3.9%): already diagnosed with OSA (not on treatment)
10 (1.0%): other reason

Figure 9: Level 3 portable sleep study device (Apnea Link™, Resmed Ltd)

An example of the Level 3 Sleep Study device (Apnealink, Resmed) which was administered in the patients' own home.

Table 11: Baseline characteristics of AF patients with and without moderate to severe OSA (AHI ≥ 15/hr).

Characteristic	N (%) or Mean ± SD			
	Total	AHI < 15/hr	AHI ≥ 15/hr	p Value
	n = 107	n = 74	n = 33	
General Demographics				
Recruitment stream: ER	58 (54.2)	40 (54.1)	18 (54.5)	0.962
Age (years)	61.3 ± 11.7	60.2 ± 12.1	63.88 ± 10.3	0.130
Male	70 (65.4)	45 (60.8)	25 (75.8)	0.133
Ethnicity: Caucasian	99 (92.5)	68 (91.2)	31 (93.9)	0.870
Phenotypic Characteristics				
BMI (kg/m^2)	27.2 ± 4.2	25.8 ±3.3	30.4 ± 4.2	< 0.001*
Neck Circumference (cm), n = 105	40.0 ± 4.7	39.1 ± 3.9	42.1 ± 5.8	0.003*
Modified Mallampati Score (n=106)	2.7 ± 0.9	2.5 ± 0.9	3.1 ± 0.7	0.001*
OSA Symptoms				
ESS	6.1 (3.4)	5.7 ± 3.3	6.9 ± 3.4	0.079
Self-reported Snoring	69 (64.5)	43 (58.1)	26 (78.8)	0.039*
Co-morbidities/AF risk factors				
Alcohol Excess (≥10SD/week), n = 105	26 (24.2)	17 (23.3)	9 (28.1)	0.730
Thyroid disease	17 (15.9)	15 (20.3)	2 (6.1)	0.135
Family history of AF	33 (30.8)	27 (36.5)	6 (18.9)	0.015*
Mod-severe MS/Prosthetic heart valve	3 (2.8)	2 (2.7)	1 (3.0)	0.865
Hypertension	44 (41.1)	22 (29.7)	22 (66.7)	<0.001*
Diabetes	5 (4.7)	2 (2.7)	3 (9.1)	0.169
IHD	5 (4.7)	2 (2.7)	3 (9.1)	0.169
CCF	18 (16.8)	8 (10.8)	10 (30.3)	0.013*
Cerebrovascular Disease	2 (1.8)	2 (2.7)	0 (0)	0.476
Peripheral Vascular disease	3 (2.8)	3 (4.1)	0 (0)	0.327
CHA_2DS_2-Vasc Score	1.6 ± 1.3	1.5 ± 1.2	2.0 ± 1.4	0.038*
AF characteristics				
Paroxysmal	102 (95.3)	73 (98.6)	29 (87.9)	0.015*

Persistent/Permanent	5 (4.7)	1 (1.4)	4 (12.1)	0.015*
High burden (≥ 10 episodes AF / last 12M)	34 (31.8)	24 (32.4)	10 (30.3)	0.827
Anti-arrhythmic therapy	88 (82.2)	60 (81.0)	28 (84.8)	0.638
Anti-coagulant therapy	87 (81.3)	60 (81.0)	27 (81.8)	0.730
Echocardiographic parameters				
Cardiac Ejection Fraction (%) (n=79)	57.5 ± 8.6	58.8 ± 7.7	54.6 ± 9.8	0.075
Left atrial diameter (cm) (n=57)	4.1 ± 0.6	4.0 ± 0.6	4.3 ± 0.6	0.211
Left atrial area (cm^2) (n=50)	24.3 ± 5.2	23.4 ± 5.2	26.6 ± 4.7	0.048*
Questionnaires				
Berlin Questionnaire “high risk” (n=106)	44 (41.5)	19 (25.7)	25 (75.8)	<0.001*
Stop Bang Questionnaire score	3.5 ± 1.7	3.0 ± 1.3	4.7 ± 1.7	<0.001*
Sleep Parameters: from PSG				
AHI	13.5 ± 15.5	5.2 ± 4.3	31.9 ± 15.5	<0.001*
ODI	7.1 ± 10.6	2.1 ± 2.3	18.4 ± 13.1	<0.001*
CAI	0.6 ± 1.5	0.2 ± 0.5	1.4 ± 2.5	<0.001*

AHI: Apnoea Hypopnea Index, BMI: Body Mass Index, CAI: Central Apnoea Index, CCF: Congestive Cardiac Failure, ER: Emergency Room, ESS: Epworth Sleepiness Scale, IHD: Ischemic Heart Disease, MS: Mitral Stenosis, ODI: Oxygen desaturation index, PVI: Pulmonary Vein Isolation procedure waitlist, SD: Standard drinks.

Table 12: Sensitivity and Specificity of clinical OSA screening tools in an AF cohort, at various levels of OSA severity, n = 98: Excellent: 0.9 – 1.0, good: 0.8 – 0.9, fair: 0.7 – 0.8, poor: 0.6 – 0.7, very poor: 0.5 – 0.6.

	AnyOSA (AHI ≥ 5/hr) +ve: n = 64 (65.3%), –ve: n = 34 (34.7%)					**Moderate - Severe OSA (**AHI ≥ 15/hr) +ve: n = 31 (31.6%), –ve: n = 67 (68.4%)					**Severe OSA (**AHI ≥ 30/hr) +ve: n = 12 (12.3%), –ve: n = 86 (87.6%)				
	Sns (%)	**Spc (%)**	**PPV**	**NPV**	**AUC (95%CI)**	**Sns (%)**	**Spc (%)**	**PPV**	**NPV**	**AUC (95%CI)**	**Sns (%)**	**Spc (%)**	**PPV**	**NPV**	**AUC (95%CI)**
Self-reported Soring	78.1	50.0	74.6	54.8	0.641 (0.22 – 0.522)	83.9	38.8	38.8	83.9	0.613 (0.498 – 0.729)	83.3	33.8	14.9	93.5	0.585 (0.424 – 0.746)
Obesity (BMI ≥ 30)	32.8	94.1	91.3	42.7	0.732 (0.627 – 0.837)	51.6	89.6	69.6	80.0	0.785 (0.686 – 0.883)	83.3	84.9	43.5	97.3	0.865 (0.741 – 0.990)
Modified Mallampati Score ≥ 3	67.2	58.8	75.4	48.8	0.665 (0.548 – 0.782)	80.6	52.2	43.9	85.4	0.708 (0.602 – 0.813)	91.7	46.5	19.3	97.6	0.683 (0.554 – 0.812)
Elevated Epworth Sleepiness Scale (≥ 11)	8.8	91.2	66.7	34.8	0.608 (0.487 – 0.730)	16.1	94.0	55.6	70.8	0.615 (0.495 – 0.735)	8.3	90.7	11.1	87.6	0.584 (0.441 – 0.726)
Stop Bang Score intermediate to high risk (≥ 3)	77.6	38.5	68.4	50.0	0.580 (0.465 – 0.695)	90.9	37.0	39.5	90.0	0.639 (0.532 – 0.747)	92.3	31.2	15.8	96.7	0.617 (0.474 – 0.761)
Stop Bang Score “high risk” (≥ 5)	36.0	91.2	88.5	43.1	0.683 (0.579 – 0.787)	58.1	88.1	69.2	82.0	0.787 (0.688 – 0.886)	83.3	81.4	38.5	97.2	0.847 (0.733 – 0.961)
Berlin questionnaire “high risk”	56.3	76.5	81.8	48.1	0.664 (0.552 – 0.775)	80.7	71.6	56.8	88.9	0.761 (0.659 – 0.864)	83.3	60.5	22.7	96.3	0.719 (0.577 – 0.861)
Level 3 sleep study: AHI															
Cut off AHI 5.15	79.7	88.2	92.7	69.8	0.896 (0.830 – 0.961)										
Cut off AHI 8.75						80.6	74.6	59.5	89.2	0.868 (0.799 – 0.937)					

Cut off AHI 10.95											83.3	74.4	31.2	97.0	0.866 (0.774 - 0.958)
Level 3 sleep study: ODI															
Cut off ODI 4.95	84.4	79.4	88.5	73.0	0.874 (0.799 – 0.948)										
Cut off ODI 8.30						83.9	79.1	65.0	91.4	0.899 (0.838 – 0.960)					
Cut off ODI 13.75											83.3	87.2	47.6	97.4	0.925 (0.859 – 0.991)

AHI: Apnea Hypopnea Index, NPV: Negative Predictive Value, ODI: Oxygen Desaturation Index, PPV: Positive Predictive Value, Sns: Sensitivity, Spc: Specificity

Table 13: Subjective Patient Assessment of in-laboratory Polysomnography Vs a Level 3 Portable Sleep Study Device at home: Results from paired visual analogue scales (1-10) in a subset of 29 patients.

	In-laboratory PSG	Level 3 portable Sleep Study Device	Mean difference (95% CI)	P value
How comfortable did you find the study?	5.9 ± 2.4	7.2 ± 1.7	-1.2 (-2.3 - -0.2)	0.018*
How convenient did you find the study?	7.0 ± 2.5	8.2 ± 1.1	-1.3 (-2.2 - -0.4)	0.008*
How closely did your sleep on the study night match your normal sleep pattern at home?	5.1 ± 2.3	7.3 ± 2.1	-2.2 (-3.3 - -1.1)	<0.001*
How confident were you in the results of the study?	7.5 ± 1.9	7.5 ± 1.7	0.000 (-0.8 – 0.8)	1.000

PSG: Polysomnography

Table 14: Summary of assessed OSA screening tools

Clinical Screening tool	Description	Previously validated against PSG in an AF cohort?
Level 1 Sleep Study (Polysomnography)	Diagnostic montage of biological channels performed overnight in a laboratory setting; includes: EEG, EOG, EMG, ECG, airflow, air pressure, respiratory and abdominal effort, SaO2, HR, limb movement, snore probe, position sensor	Gold standard investigation
Self-reported Snoring	Presence of snoring as reported by the patient or patient's bed partner	No
Obesity	BMI ≥ 30 kg/m^2	No
Modified Mallampati Score	Visual assessment of airway crowding performed with the patient sitting directly opposite the examiner, mouth open and tongue maximally protruded. Class 1: Faucial pillars, soft palate and uvula visible; Class II: Faucial pillars and soft palate visible. Uvula obscured by tongue; Class 3: Only the soft palate is visible; Class IV: Soft palate not visible (234).	No
Epworth Sleepiness Scale (ESS)	Validated self-administered questionnaire of 8 questions in which the patient is asked to rank their usual chances of falling asleep or dozing in a series of daytime scenarios. Each question is subjectively scored from 0 -3, for a maximum overall score of 24, minimum of 0 (167). A score ≥11 indicates excessive daytime somnolence.	Yes, in on prospective cohort and one retrospective analysis of prospectively collected data. ESS very poorly predicted sleep disordered breathing for all levels of OSA severity (AUC: 0.48-0.56) (146), and moderate OSA only (AUC 0.50) (230).
Stop Bang Score	Validated questionnaire of 8 dichotomous variables related to OSA: snoring, tiredness, observed apnoea, high BP, BMI, age, neck circumference and male gender. Score of 0-2 – low risk for moderate to severe OSA (AHI ≥ 15/hr), score of 5 – 8 = high risk of moderate to severe OSA (AHI ≥ 15/hr) (235).	Yes, with fair diagnostic accuracy for moderate OSA in one study (AUC 0.75, CI 0.66 – 0.86) (230).
Berlin questionnaire	Validated questionnaire assessing three domains: snoring, daytime somnolence or fatigue and obesity or hypertension. Positive responses in 2 out of 3 domains confer a "high risk" score (236).	Yes, with poor diagnostic accuracy for moderate OSA only (AUC 0.64, CI 0.52 – 0.75) (230). Also assessed in small

		subsets of AF patients in two validation studies: (n=44), Sensitivity 86%, Specificity 89% (150), (n=30), Sensitivity 100%, Specificity 30% (202).
Level 3 sleep study, also known as polygraphy	Portable sleep study device including at least 4 channels, usually airflow, respiratory effort via thoracic band, oximetry and heart rate.	No
Level 3 sleep study derived Apnoea Hypopnea Index (AHI)	Number of apnoeas and hypopneas per hour of recording time. Scoring of events may be via automated software or can be manually scored by a trained technician.	No
Level 3 sleep study derived Oxygen desaturation Index (ODI)	Number of oxygen desaturations from baseline, usually a drop of ≥ 3%.	No, ODI from a home-based test has not previously been assessed. ODI derived from laboratory PSG has previously been assessed in an AF cohort, with a 91% sensitivity and 83% specificity to detect moderate to severe OSA (AHI ≥ 15/hr) using a cut-off value of 4.1/hr, AUC 0.951, 95% CI: 0.929-0.972 (80)

EEG: Electro-encephalogram, EOG: Electro-oculogram, EMG: Electromyogram, ECG: Electrocardiogram, AHI: Apnoea Hyopnea Index, ODI: Oxygen Desaturation

Table 15: Baseline characteristics of AF patients by recruitment stream (ER presentations vs PVI waitlist)

Characteristic	N (%) or Mean ± SD			
	Total n = 107	ER presentation n = 58	PVI waitlist n = 49	p Value
General Demographics				
Age (years)	61.3 ± 11.7	62.7 ± 12.5	59.7 ± 10.4	0.181
Male	70 (65.4)	33 (56.9)	37 (75.5)	0.044*
Ethnicity: Caucasian	99 (92.5)	53 (91.4%)	46 (93.9%)	0.624
Phenotypic Characteristics				
BMI (kg/m^2)	27.2 ± 4.2	26.6 ± 4.0	27.8 ± 4.3	0.142
Neck Circumference (cm), n = 105	40.0 ± 4.7	39.2 ± 4.8	41.0 ± 4.5	0.050*
Modified Mallampati Score (n=106)	2.7 ± 0.9	2.7 ± 0.8	2.7 ± 0.9	0.761
OSA Symptoms				
ESS	6.1 (3.4)	5.6 ± 3.5	6.4 ± 3.3	0.328
Self-reported Snoring	69 (64.5)	35 (60.3)	34 69.4)	0.330
Co-morbidities/AF risk factors				
Alcohol Excess (≥10SD/week), n = 105	26 (24.2)	12 (20.7)	14 (28.6)	0.295
Thyroid disease	17 (15.9)	11 (19.0)	6 (12.2)	0.366
Family history of AF	33 (30.8)	12 (20.7)	21 (42.9)	0.033*
Mod-severe MS/Prosthetic heart valve	3 (2.8)	2 (3.4)	1 (2.0)	0.660
Hypertension	44 (41.1)	26 (44.8)	18 (36.7)	0.397
Diabetes	5 (4.7)	1 (1.7)	4 (8.2)	0.116
IHD	5 (4.7)	2 (3.4)	3 (6.1)	0.514
CCF	18 (16.8)	11 (19.0)	7 (14.3)	0.519
Cerebrovascular Disease	2 (1.8)	0 (0)	2 (4.1)	0.120
Peripheral Vascular disease	3 (2.8)	2 (3.4)	1 (2.0)	0.660
CHA_2DS_2-Vasc Score	1.6 ± 1.3	1.8 ± 1.3	1.4 ± 1.2	0.044*
AF characteristics				
Paroxysmal (cf persistent/permanent)	102 (95.3)	55 (94.8)	47 (95.9)	0.790
Persistent/Permanent	5 (4.7)	3 (5.2)	2 (4.1)	0.790
High burden (≥ 10 episodes AF/ last 12M)	34 (31.8)	10 (17.2)	24 (49.0)	< 0.001*
Anti-arrhythmic therapy	88 (82.2)	48 (82.8)	40 (81.6)	0.879

Anti-coagulant therapy	87 (81.3)	46 (79.3)	41 (83.7)	0.564
Echocardiographic parameters				
Cardiac Ejection Fraction (%) (n=79)	57.5 ± 8.6	56.6 ± 9.2	58.1 ± 7.9	0.429
Left atrial diameter (cm) (n=57)	4.1 ± 0.6	4.1 ± 0.7	4.1 ± 0.6	0.683
Left atrial area (cm^2) (n=50)	24.3 ± 5.2	23.3 ± 4.1	25.1 ± 5.8	0.236
Questionnaires				
Berlin Questionnaire "high risk" (n=106)	44 (41.5)	27 (46.6)	17 (34.7)	0.282
Stop Bang Questionnaire score	3.5 ± 1.7	3.4 ± 1.7	3.7 ± 1.6	0.345
Sleep Parameters: all derived from PSG				
AHI	13.5 ± 15.5	12.6 ± 13.2	14.4 ± 17.6	0.564
ODI	7.1 ± 10.6	7.1 ± 10.8	7.1 ± 10.6	0.988
CAI	0.6 ± 1.5	0.6 ± 1.5	0.5 ± 1.5	0.656
Moderate to Severe OSA (AHI > 15/hr)	33 (30.8)	18 (31.0)	15 (30.1)	0.962

AHI: Apnoea Hypopnea Index, BMI: Body Mass Index, CAI: Central Apnoea Index, CCF: Congestive Cardiac Failure, ER: Emergency Room, ESS: Epworth Sleepiness Scale, IHD: Ischemic Heart Disease, MS: Mitral Stenosis, ODI: Oxygen desaturation index, PVI: Pulmonary Vein Isolation procedure waitlist, SD: Standard drinks.

Table 16: Baseline characteristics of AF patients with and without OSA (AHI ≥ 5/hr).

Characteristic	N (%) or Mean ± SD			
	Total (n = 107)	OSA absent (AHI < 5/hr) n = 40 (37.3%)	Any OSA (AHI ≥5/hr) n = 67 (62.6%)	p Value
General Demographics				
Recruitment stream: ER	58 (54.2)	21 (52.5)	37 (55.2)	0.470
Age (years)	61.3 ± 11.7	58.2 ± 13.0	63.15 ± 10.5	0.047*
Male	70 (65.4)	22 (55.0)	48 (71.6)	0.080
Ethnicity: Caucasian	99 (92.5)	38 (95.0)	61 (91.0)	0.323
Phenotypic Characteristics				
BMI (kg/m^2)	27.2 ± 4.2	25.0 ± 3.5	28.5 ± 4.0	< 0.001*
Neck Circumference (cm), n = 105	40.0 ± 4.7	39.0 ± 4.5	40.7 ± 4.8	0.078
Modified Malampatti Score (n=106)	2.7 ± 0.9	2.4 ± 1.0	2.9 ± 0.8	0.009*
OSA Symptoms				
ESS	6.1 (3.4)	5.5 ± 3.8	6.4 ± 3.2	0.195
Self-reported Snoring	69 (64.5)	18 (45.0)	51 (76.2)	0.002*
Co-morbidities/AF risk factors				
Alcohol Excess (≥10SD/week), n = 105	26 (24.2)	13 (32.5)	13 (23.6)	0.191
Thyroid disease	17 (15.9)	12 (30.0)	5 (7.5)	0.003*
Family history of AF	33 (30.8)	15 (37.5)	18 (26.9)	0.141
Mod-severe MS/Prosthetic heart valve	3 (2.8)	0 (0)	3 (4.5)	0.337
Hypertension	44 (41.1)	10 (25.0)	34 (50.7)	0.009*
Diabetes	5 (4.7)	2 (5.0)	3 (4.5)	0.901
IHD	5 (4.7)	1 (2.5)	4 (6%)	0.411
CCF	18 (16.8)	5 (12.5)	13 (19%)	0.356
Cerebrovascular Disease	2 (1.8)	0 (0)	2 (3.0)	0.27
Peripheral Vascular disease	3 (2.8)	3 (7.5)	0 (0)	0.023*
CHA_2DS_2-Vasc Score	1.6 ± 1.3	1.4 ± 1.1	1.8 ± 1.4	0.115

AF characteristics				
Paroxysmal	102 (95.3)	40 (100.0)	62 (92.5)	0.091
Persistent/Permanent	5 (4.7)	0 (0)	5 (7.5)	0.091
High burden (≥ 10 episodes AF in the last 12M)	34 (31.8)	9 (22.5)	25 (37.3)	0.111
Anti-arrhythmic therapy	88 (82.2)	34 (85.0)	54 (80.6)	0.564
Anti-coagulant therapy	87 (81.3)	33 (82.5)	54 (80.6)	0.807
Echocardiographic parameters				
Cardiac Ejection Fraction (%) (n=79)	57.5 ± 8.6	59.7 ± 5.7	56.1 ± 9.7	0.075
Left atrial diameter (cm) (n=57)	4.1 ± 0.6	4.0 ± 5.3	4.2 ± 6.8	0.188
Left atrial area (cm^2) (n=50)	24.3 ± 5.2	22.7 ± 4.9	25.6 ± 5.2	0.048*
Questionnaires				
Berlin Questionnaire “high risk” (n=106)	44 (41.5)	8 (20.0)	36 (53.7)	0.002*
Stop Bang Questionnaire	3.5 ± 1.7	2.8 ± 1.7	4.0 ± 1.8	0.001*
Sleep Parameters: all derived from PSG				
AHI	13.5 ± 15.5	1.8 ± 1.4	20.4 ± 15.8	< 0.001*
ODI	7.1 ± 10.6	0.6 ± 0.7	11.0 ± 11.8	< 0.001*
CAI	0.6 ± 1.5	0.1	0.8	0.016*

AHI: Apnoea Hypopnea Index, BMI: Body Mass Index, CAI: Central Apnoea Index, CCF:

AHI: Apnoea Hypopnea Index, CAI: Central Apnoea Index, Congestive Cardiac Failure, ER: Emergency Room, ESS: Epworth Sleepiness Scale, IHD: Ischemic Heart Disease, MS: Mitral Stenosis, ODI: Oxygen desaturation index, PVI: Pulmonary Vein Isolation procedure waitlist, SD: Standard drinks

Table 17: Baseline characteristics of AF patients with and without severe OSA (AHI ≥ 30/hr).

Characteristic	N (%) or Mean ± SD			
	Total	AHI < 30/hr	AHI ≥ 30/hr	p Value
	(n = 107)	n = 94	n = 13	
General Demographics				
Recruitment stream: ER	58 (54.2)	52 (55.3)	6 (46.1)	0.371
Age (years)	61.3 ± 11.7	61.2 ± 11.6	62.0 ± 12.4	0.823
Male	70 (65.4)	58 (61.7)	12 (92.3)	0.024*
Ethnicity: Caucasian	99 (92.5)	86 (91.5)	13 (100.0)	0.977
Phenotypic Characteristics				
BMI (kg/m^2)	27.2 ± 4.2	26.4 ± 3.6	32.8 ± 4.0	<0.001*
Neck Circumference (cm), n = 105	40.0 ± 4.7	39.3 ± 4.1	45.8 ± 5.5	0.002*
Modified Malampatti Score (n=106)	2.7 ± 0.9	2.6 ± 0.9	3.1 ± 0.6	0.085
OSA Symptoms				
ESS	6.1 (3.4)	6.0 ± 3.5	6.5 ± 2.8	0.528
Self-reported Snoring	69 (64.5)	59 (62.8)	10 (76.9)	0.250
Co-morbidities/AF risk factors				
Alcohol Excess (≥10SD/week), n = 105	26 (24.2)	23 (25.0)	3 (23.1)	0.859
Thyroid disease	17 (15.9)	16 (17.0)	1 (7.7)	0.634
Family history of AF	33 (30.8)	31 (33.0)	2 (1.5)	0.089
Mod-severe MS/Prosthetic heart valve	3 (2.8)	2 (2.1)	1 (7.7)	0.364
Hypertension	44 (41.1)	35 (37.2)	9 (69.2)	0.028*
Diabetes	5 (4.7)	4 (4.3)	1 (7.7)	0.582
IHD	5 (4.7)	4 (4.3)	1 (7.7)	0.582
CCF	18 (16.8)	13 (13.8)	5 (38.4)	0.042*
Cerebrovascular Disease	2 (1.8)	2 (2.1)	0 (0)	0.771
Peripheral Vascular disease	3 (2.8)	3 (3.2)	0 (0)	0.675
CHA_2DS_2-Vasc Score	1.6 ± 1.3	1.6 ± 1.3	1.9 ± 1.2	0.341
AF characteristics				
Paroxysmal (cf persistent/permanent)	102 (95.3)	92 (97.9)	10 (76.9)	0.012*
Persistent/Permanent	5 (4.7)	2 (2.1)	3 (23.1)	0.012*
High burden (≥ 10 episodes AF/last 12M)	34 (31.8)	31 (33.0)	3 (23.0)	0.074
Anti-arrhythmic therapy	88 (82.2)	78 (83.0)	10 (76.9)	0.416

Anti-coagulant therapy	87 (81.3)	75 (79.8)	12 (92.3)	0.252
Echocardiographic parameters				
Cardiac Ejection Fraction (%) (n=79)	57.5 ± 8.6	57.9 ± 8.2	54.5 ± 11.2	0.244
Left atrial diameter (cm) (n=57)	4.1 ± 0.6	4.0 ± 0.6	4.6 ± 0.7	0.014*
Left atrial area (cm^2) (n=50)	24.3 ± 5.2	23.9 ± 5.0	28.4 ± 6.1	0.064
Questionnaires				
Berlin Questionnaire "high risk" (n=106)	44 (41.5)	34 (36.2)	10 (76.9)	0.020*
Stop Bang Questionnaire	3.5 ± 1.7	3.8 ± 1.5	5.2 ± 1.6	0.001*
Sleep Parameters: all derived from PSG				
AHI	13.5 ± 15.5	8.7 ± 7.9	47.7 ± 13.2	<0.001*
ODI	7.1 ± 10.6	3.6 ± 4.2	32.3 ± 8.9	<0.001*
CAI	0.6 ± 1.5	0.3 ± 0.9	2.3 ± 3.2	<0.001*

AHI: Apnoea Hypopnea Index, BMI: Body Mass Index, CAI: Central Apnoea Index, CCF: Congestive Cardiac Failure, ER: Emergency Room, ESS: Epworth Sleepiness Scale, IHD: Ischemic Heart Disease, MS: Mitral Stenosis, ODI: Oxygen desaturation index, PVI: Pulmonary Vein Isolation procedure waitlist, SD: Standard drinks

3.0 Does Obstructive Sleep Apnoea modulate Cardiac Autonomic Function in Paroxysmal Atrial Fibrillation?

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3.1 ABSTRACT

Purpose: The autonomic nervous system may mediate acute apnoea-induced atrial fibrillation (AF). We compared cardiac autonomic function in paroxysmal atrial fibrillation (PAF) patients with and without obstructive sleep apnoea (OSA).

Methods: Case control study of 101 patients with PAF recruited at two tertiary centres. All patients underwent in-laboratory polysomnography. ECG signal demonstrating “steady state” sinus rhythm (ie with arrhythmic beats and respiratory events excluded) was included in the analysis. Cardiac autonomic function was assessed via measures of heart rate variability (HRV) and reported by sleep stage (REM vs Non-REM) for patients with and without OSA.

Results*:* 65 (66.3%) of patients were male, mean age 61.5 ± 11.6 years, mean BMI 27.1 ± 4.3kg/m^2. Global measures of HRV (triangular index, total power) did not differ between PAF patients with and without OSA in either REM or non-REM sleep. Frequency domain analysis during non-REM sleep in PAF patients with OSA showed increased cardiac parasympathetic modulation (HF-nu: 39.1 ± 15.7 vs 48.0 ± 14.6, p = 0.008*) and reduced cardiac sympathetic modulation (LF-nu 54.1 ± 19.7 vs 43.7 ± 18.0, p = 0.012*, LF/HF ratio: 2.1 ± 2.0 vs 1.2 ± 1.0, p = 0.007*). Results remained significant after adjusting for age, sex and BMI (adjusted p values 0.024, 0.045 and 0.018 respectively). There were no differences in HRV parameters during REM sleep.

Conclusions: This is the first study of HRV in PAF patients with and without OSA. Our results indicate limited differences in HRV between groups. However, this work suggests a chronic increase in parasympathetic nervous modulation and relative reduction in sympathetic modulation in PAF patients with OSA during steady-state non-REM sleep.

3.2 INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is associated with increased risk of stroke and congestive heart failure (237). Mounting evidence suggests that dysregulation of the cardiac autonomic axis plays an integral role in arrhythmogenesis (187).

OSA is a highly prevalent sleep disorder characterised by upper airway collapse during sleep and is found in up to 63% of AF patients (238). Attempting to breathe against an obstructed upper airway results in intermittent hypoxia, intra-thoracic pressure swings and activation of the autonomic nervous system; these acute perturbations are thought to trigger and maintain episodes of AF (239, 240), and may lead to long term atrial remodelling (240, 241).

Understanding the influence of OSA on autonomic function in patients with AF may inform treatment strategies that mitigate pro-arrhythmic autonomic influences. Heart Rate Variability (HRV) reflects beat-to-beat variation in heartbeat intervals influenced by the combined effects of the sympathetic and parasympathetic nervous system (242). The study of HRV provides a non-invasive method to assess cardiac autonomic function (242). We aimed to assess whether in a paroxysmal atrial fibrillation (PAF) cohort the presence of OSA is associated with altered autonomic function. We hypothesised that PAF patients with OSA will show altered HRV parameters indicative of the influence of OSA on cardiac autonomic function.

3.3 METHODS

3.3.1 Study population

Sequential AF patients were recruited via two centres as part of a prospective diagnostic accuracy study for sleep apnoea in patients with AF (238). Approval for this trial was obtained from the Northern Sydney Local Health District Human Research Ethics Committee (HREC/16/HAWKE/25), and the North Shore Private Hospital Ethics Committee (approval number 2016-012). The study was performed in accordance with the 1964 Helsinki Declaration and its later amendments. All patients gave their informed written consent to participate in the study. The trial was registered with the Australian New Zealand Clinical Trials Registry (ANZCTR): 12616001016426.

Patients were sequentially recruited via two pathways: emergency department admissions with AF, and pulmonary vein isolation waitlists at two tertiary centres between July 2016 and September 2019. All patients had a history of AF (≥ 2 episodes in the past 12 months) and underwent in-laboratory polysomnography (PSG) to investigate OSA. Patients with a previous known diagnosis of sleep apnoea were excluded.

3.4 Data collection

3.4.1 Polysomnography

Polysomnographic recordings were performed and scored by experienced Sleep Scientists using Compumedics PSG4 V4.1 software (Compumedics, Australia), according to the American Academy of Sleep Medicine (AASM) criteria (243). An

apnoea was defined as complete (≥ 90%) reduction in airflow, lasting ≥ 10 seconds. A hypopnea was defined as a partial (≥ 30%) reduction in airflow, lasting ≥10 seconds, associated with either an arousal from sleep or an oxygen desaturation of ≥ 3% from baseline. Sleep apnoea was defined as the average number of apnoeas and/or hypopneas per hour (Apnoea Hypopnea Index (AHI)) ≥5/hr. Other standard parameters of OSA severity were generated including ODI (oxygen desaturation index): average number of desaturations per hour > 3% below baseline, and %T<90: the percent of sleep time with SaO_2 < 90%. OSA severity was defined as mild (AHI ≥5 – 14.9/hr), moderate (AHI ≥15 – 29.9/hr) and severe (AHI ≥30/hr).

3.4.2 Holter monitor processing

Electrocardiographic (ECG) signals from the polysomnographic recording were processed using Holter software analysis for ectopic beat detection (SpaceLabs Sentinel v11.5.1.12779 and Pathfinder SL version 1.9.2.11104, Snoqualmie, WA 98065, United States). Three traces were excluded as the ECG quality was insufficient for Holter software analysis. Since heart rate variability (HRV) is ordinarily performed during sinus rhythm, six traces were excluded as patients were in AF for the vast majority (≥ 90%) of the study night. Patients with shorter runs of AF were included, though the periods of AF were excluded from the analysis (three patients, with 1.8, 22.4 and 3.1% of the night spent in AF respectively).

3.4.3 Heart Rate Variability analysis

Following Holter analysis, ECG signals were analysed following the guidelines of Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (242). QRS detection was performed to a resolution of 1ms (equivalent to a sample rate of 1000Hz). HRV analysis was performed using a validated algorithm (244) using MATLAB 2017, version 9.2.0.538062 (R2017a), Natick, Massachusetts: The MathWorks Inc. Analysis was performed over 2-minute epochs averaged across each sleep stage (NREM and REM) of the entire ECG signal. Epochs with mixed sleep stages were excluded, as were periods of arousal, apnoeas, hypopneas, respiratory event related arousals as well as artefact as per previously published (245-247). A 15 second interval following obstructive respiratory events was excluded to control for acute post-event autonomic perturbations. Furthermore, periods of cardiac arrhythmia including atrial and ventricular ectopic beats were excluded from the HRV analysis (2.65% of total beats). If the excluded periods of an epoch exceeded 12 seconds (10% of epoch length) then the complete epoch was excluded. Patients were excluded from further analysis if > 90% of 2 minute epochs were excluded on the basis of arrhythmia or sleep apnoea events (3 patients). A total of 89 studies were therefore included in the HRV analysis (Figure 10).

3.4.4 Time and Frequency domain measures of HRV

Time domain measures of HRV provide the simplest of method to evaluate variations in heart rate. These include (a) HRV triangular index (HRVi) indicative of overall HRV (b) RMSSD which is the root mean square of successive differences in NN intervals and (c) pNN50, the proportion of successive NN intervals which differ by more than 50ms. Both RMSSD and pNN50 are short term measures, and are estimates of high

frequency variations in heart rate; these measures reflect parasympathetic modulation of the heart (242, 248).

Frequency domain measures of HRV provide information on sympathetic and parasympathetic modulation of beat-to-beat fluctuations in the heart rate. Analysis was performed using a Lomb periodogram method and the spectral bands for HRV were investigated in the range of 0-0.4 Hz: very low frequency (VLF) at 0 to 0.04 Hz, low frequency (LF) at 0.04 – 0.15 Hz and high frequency (HF) power at 0.15 to 0.4 Hz (242). LF and HF were also expressed in normalized units, LF-nu and HF-nu respectively (242). The HF component of HRV, synchronous with respiration, is considered a strong marker of parasympathetic modulation (242). The interpretation of the LF component of HRV is more controversial, however when expressed in normalised units (nu) is a marker of sympathetic modulation. We have applied this methodology in evaluating the level of sympathetic and parasympathetic modulation at the atrial site (242). A summary of time and frequency domain HRV variables is provided in Table 18.

3.5 Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 27.0, Armonk, NY: IBM Corp. HRV parameters which were not normally distributed were natural-log transformed to normalise their skewed distributions. Data are presented as the mean +/- standard deviation (SD), or as mean (interquartile range (IQR)) for non-normally distributed data. HRV parameters were compared using t-tests (continuous variables) or chi-square tests (categorical variables) as appropriate.

Analysis of Covariance (ANCOVA) was performed to adjust for age, sex and BMI. Correlations between HRV parameters and standard measures of OSA severity (AHI, ODI and T<90%) were performed. This was an exploratory analysis of the comparison of multiple HRV parameters reflecting different aspects of ANS modulation, therefore we did not adjust the significance level for multiple comparisons. We considered a p value of < 0.05 statistically significant.

3.6 RESULTS

3.6.1 Patient characteristics

A total of 101 AF patients underwent overnight polysomnography. Patients with OSA demonstrated a higher BMI and were predominantly male compared to the no-OSA group. They also had increased hypertension but reduced thyroid disease and peripheral vascular disease. There were no significant differences in other cardiovascular comorbidities including diabetes, ischaemic heart disease (IHD), congestive cardiac failure (CCF) and cerebrovascular disease (CVD), although the OSA group did have a lower ejection fraction (55.5 ± 9.7 vs 59.6 ± 1.1%, p = 0.027). The OSA group also had an increased left atrial area (25.5 ± 5.3 vs 22.3 ± 4.5 cm^2, p = 0.032) and increased proportion of “high burden AF”, defined as > 12 self-reported episodes in the last 12 months. CHA_2DS_2-Vasc Scores were not significantly different between the groups (1.4 ± 1.2 vs 1.7 ± 1.4, p = 0.270). Neither were there significant differences in anti-arrhythmic medications between groups. Although nine patients were excluded from the final HRV analysis, excluded patients were not significantly

different from the group in terms of key baseline characteristics including age, sex and BMI. Baseline characteristics are presented in Table 19.

3.6.2 Atrial Fibrillation characteristics

There were no significant differences in the presence of arrhythmia (AF beats, Ventricular ectopic beats (VEBs) and Supraventricular ectopic beats (SVBs)) between AF patients with and without OSA using a cut-off AHI of 5/hr (see Table 20). On subgroup analysis however, PAF patients with severe OSA (AHI ≥ 30/hr) had more AF beats and Ventricular Ectopic Beats (VEBs) than those without severe OSA (22.7 ± 42.8% vs 3.7 ± 17.9%, p = 0.006*, 1.7 ± 3.8 vs 0.3 ± 0.9%, p = 0.004* respectively). Similarly, ANOVA for OSA severity groups showed that PAF patients with severe OSA had a higher % AF beats than patients with no OSA or moderate OSA (mean difference 19.8 ± 7.3%, p = 0.040; 22.7 ± 8.3%, p = 0.036 respectively, see figure 11) and that PAF patients with severe OSA had a higher %VEBs than patients with mild or moderate OSA (mean difference 1.6 ± 0.5%, p = 0.019; 1.6 ± 0.6%, p = 0.035 respectively). There were no significant differences in SVEs across OSA severity groups.

3.6.3 Heart rate variability in PAF patients with and without OSA

In non-REM sleep, time domain measures of HRV did not differ between OSA and no-OSA groups (Table 20). However, we saw selective differences in frequency domain measures (Table 21). Specifically, PAF patients with OSA showed increased

parasympathetic modulation (HF-nu: 48.0 ± 14.6 vs 39.1 ± 15.7, p = 0.01*) and reduced sympathetic modulation (LF-nu 43.7 ± 18.0 vs 54.1 ±19.7, p = 0.01*). Consistent with these results, the LF/HF ratio showed a relative decrease in parasympathetic modulation (1.2 ± 1.0 vs 2.1 ± 2.0, p = 0.007*) (Table 21). Furthermore, these results remained significant after adjusting for age, sex and BMI.

In REM sleep, time domain measures of HRV did not differ between OSA and no-OSA groups (AHI ≥ or < 5/hr) (Table 3) in PAF patients. PAF patients with OSA showed increased parasympathetic modulation (HF-nu 32.6 ± 16.0 vs 40.5 ± 17.4, p = 0.036), however significance was not maintained after adjusting for age, sex and BMI (Table 4). We extended the analysis to include OSA at different severity levels (AHI < or > 15/hr, AHI < or > 30/hr), although the above changes were not significant in these groups (see tables 22-25)

3.6.4 HRV correlations with markers of OSA

We examined correlations between HRV parameters and AHI, as well as other markers of OSA severity, including those that reflect hypoxic burden (ODI and %T<90). In REM sleep, there was a weak negative correlation between LF-nu and all markers of OSA severity (AHI, ODI and %T<90). Correlation analysis of other HRV (time and frequency) measures with OSA severity metrics were not significant (see Tables 26 and 27).

In non-REM sleep, we saw a weak negative correlation between average NN interval and ODI as well as %T<90. Correlations of other time and frequency HRV measures

with markers of OSA severity (AHI, ODI and T<90%) were not significant. (Tables 26 and 27)

3.7 DISCUSSION

To our knowledge, this is the first study to compare HRV parameters in PAF patients with and without OSA. We found some evidence that PAF patients with OSA showed increased cardiac parasympathetic modulation (HF-nu) and blunted cardiac sympathetic modulation (LF-nu and LF/HF ratio) compared to PAF patients without OSA. The pathophysiological mechanism behind this finding needs further investigation but may provide future avenues for anti-arrhythmic therapeutic research. That these findings were limited to non-REM sleep is not surprising, given that REM sleep is a time of cardiovascular instability which may potentially mask differences in HRV between the groups.

Overall HRV (HRVi and total power) did not differ between PAF patients with and without OSA. Reduced overall HRV reflects a less adaptable ANS and is a strong independent predictor of mortality, in particular after myocardial infarction (249-257) and congestive heart failure (258-262). Similarly, studies in AF patients show an association between depressed overall HRV and adverse outcome (263-268). According to the Task Force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology, a triangular index <15 indicates a severely depressed sinus node activation. In our entire cohort of AF patients, the triangular index was, perhaps not surprisingly, well below this critical number (during

non-REM and REM sleep), although was similar between PAF patients with and without OSA.

Experimental studies indicate changes in the ANS play a critical role in facilitating arrhythmic events and that concomitant modifiable risk factors such as OSA may further trigger AF (240). Our short term HRV analysis indicate there were no differences in overall HRV in PAF patients with and without OSA in any of the sleep stages. These results are in line with our recent systematic review that revealed nocturnal short term measures of overall HRV were similar between patients with and without OSA (269) and therefore may extend to patient populations with PAF.

OSA events are well known to precipitate acute autonomic responses. For example, the initial apnoeic period is characterised by vagally-driven bradycardia, followed by a sympathetically-driven surge in heart rate and blood pressure with an accompanying arousal at the conclusion of the apnoeic event (189). In this study we deliberately excluded OSA events and the immediate post-apnoeic period (15 seconds) from the analysis in order to exclude the acute autonomic perturbations that accompany these events. This was done in order to compare chronic autonomic changes between the groups during a period of “steady state” sinus rhythm. Accordingly, we used short term measures of HRV with a two minute epoch. This was designed to maximise the availability of steady state ECG available for analysis, due to the frequency of excluded arrhythmic and respiratory events.

Additionally, particular anti-arrhythmic medications including Flecainide (class 1c) and β-blockers (class 11) are known to impact HRV through their effect on the ANS. For

example, Flecainide has been shown to reduce HRV time-domain parameters (270). In our study, the use of anti-arrhythmic medications in each individual class was not significantly different between the two groups, though the dosage and administration times were not measured. Further, certain co-morbidities including acute myocardial infarction, diabetic neuropathy, heart transplantation and tetraplegia are known to significantly alter the function of the autonomic nervous system and hence HRV(270). In our study, we corrected for the effect of age, sex and BMI. Most measured co-morbidities were not significantly different between groups, with the exception of hypertension, thyroid disease and peripheral vascular disease (see table 2). Little is known about the influence of these particular conditions on HRV. However, one study demonstrated an increase in time domain and frequency domain HRV parameters in AF patients with hypertension compared to patients with hypertension alone (271).

Several physiological studies demonstrated the importance of the autonomic nervous system in mediating sleep-apnoea-induced AF. For example, vagal activation during the intra-thoracic pressure changes caused by acute apnoeic events shortens the atrial effective refractory period, thus increasing AF inducibility (177). In a dog-model, Ghias et al showed that after ablation of cardiac parasympathetic innervation, there was a significant decrease in apnoea-induced AF. This also occurred with sympatho-vagal blockade (272). Similarly, Linz et al showed in a pig model that the application of negative tracheal pressure induced AF via a shortening of the atrial refractory period, and that this effect was negated by parasympathetic deactivation, either in the form of atropine administration or vagotomy (177). During an acute obstructive apnoea, the profound vagal activation followed by combined sympathetic activation is thought to trigger and maintain AF. Experimental studies in chronic intermitted

hypoxia show AF vulnerability depends principally on parasympathetic activation, furthermore, parasympathetic activation has been identified as the major pro-arrhythmogenic mechanism in the rodent model (273). Our data are line with this body of work, where PAF patients with OSA show increased parasympathetic modulation compared to PAF patients without OSA.

In addition to a major parasympathetic component, the sympathetic nervous system is also likely to contribute to AF promotion. However, in our study of PAF patients we did not see elevated sympathetic modulation. Rather, our results suggest a blunted cardiac sympathetic modulation in PAF patients with OSA compared to PAF patients without OSA. This is somewhat surprising given that elevated sympathetic activity is well documented in OSA (269) and chronic intermittent hypoxia (274, 275). However, one study in rats exposed to chronic intermittent hypoxia demonstrated elevated AF vulnerability that was accompanied by an elevated cholinergic response and damped beta-adrenergic response of the atrial myocardium (273). It is possible that sympathetic activation maybe less important compared to parasympathetic activation in promoting AF due to elevated spatial dispersion of atrial refractoriness during parasympathetic activation (276). Furthermore, the blunted sympathetic modulation in PAF patients with OSA in our study maybe associated with a ceiling effect driven by higher intrinsic adrenergic tone (273).

3.7.1 Arrhythmia Analysis

The study methodology provided an opportunity to compare the presence of nocturnal arrhythmia between AF patients with and without OSA, although this was not a primary aim of the study. On patient recall at interview, patients in the OSA group reported a higher incidence of “high burden” AF, defined as ≥ 10 episodes in the past 12 months (8/36 patients (22%) vs 23/62 patients (37.1%), p = 0.039. On the sleep study night, there was no significant difference in % AF beats between the OSA and no-OSA groups, although the trend towards increased %AF beats in the OSA group was noted (2.9 ± 16.6 vs 8.1 ± 26.4 %, p = 0.283. On subgroup analysis however, patients with severe OSA (AHI > 30/hr) had more AF beats and more ventricular ectopic beats, but not supraventricular ectopic beats on nocturnal polysomnography. Similarly, PAF patients with severe OSA had a higher % AF beats than patients with no OSA or moderate OSA (mean difference 19.8 ± 7.3%, p = 0.040; 22.7 ± 8.3%, p = 0.036 respectively, figure 11). These findings of higher AF burden according to OSA severity are consistent with the findings of Mehra et al (155), showing that nocturnal arrhythmia including AF and VEBs were more common in patients with severe sleep disordered breathing, also using a cut-off of AHI > 30/hr. To our knowledge our study is the first to replicate this finding in a cohort of patients with PAF with and without OSA.

3.7.2 Limitations

Although this study provides some novel insights into the HRV profile of those with OSA and PAF, there are limitations to the study. 24- Hour holter recording is ideal for HRV analysis, accounting for both diurnal and nocturnal variability (242). For this study HRV parameters were derived from nocturnal polysomnograpy and thus are subject to all the usual autonomic perturbations of sleep, which may explain the

selective differences seen across time and frequency domain measures. Further, we were unable to control for differences in undiagnosed conduction disturbances between the two groups, including, for example, the presence of sinus nodal disease which has a high prevalence in AF patients (277). However, we analysed only periods of sinus rhythm in order to minimise the contribution of AV nodal dysfunction. Our study contained some patients who had undergone previous PVI: patients had, on average, undergone 0.4 ± 0.6 previous PVI procedures. Since PVI may cause neuronal damage to the intrinsic cardiac nervous system (278), caution must be used when extrapolating the results to other groups. Although we excluded periods of arrhythmia, it is possible that autonomic disturbances related to the arrhythmia may have preceded or persisted beyond these events. It is also possible that HRV parameters may have been impacted by autonomic disruptions from acute obstructive respiratory events in the OSA group. We attempted to allow for this by excluding ECG trace during and immediately following sleep apnoea events from the analysis, however we excluded a post-event period of 15 seconds and it is possible autonomic disturbance may persist beyond this interval. In addition, some sub-criterion respiratory events are likely to have remained in the analysis.

3.7.3 Clinical Implications

There is mounting evidence that the perturbations during OSA have a profound influence on the myocardium.(241) Atrial remodelling leading to changes to the electrical conduction and ANS activation is thought to trigger and maintain AF.(241) Our work shows altered autonomic function in PAF patients with co-morbid OSA which we believe supports previous observations that progression of AF is promoted by the

presence of modifiable risk factors such as OSA.(240, 241). Treatment of OSA may modulate autonomic function and protect the atrial myocardium from pro-arryhthmic autonomic influences from OSA. Therefore, future studies should look to replicate our findings in a larger cohort and determine the effect of OSA therapy on modulation of the ANS and whether indeed such interventions may mitigate arrhythmogenesis in PAF.

3.8 CONCLUSIONS

This is the first study to compare sympatho-vagal balance, assessed by HRV, in PAF patients with and without OSA. Our results indicate limited differences in HRV between groups. However, we found some evidence of increased parasympathetic modulation and decreased sympathetic modulation in the OSA group. Altered autonomic function in this group may promote arrhythmogenesis and impair antiarrhythmic therapy. Elucidating influence of OSA on autonomic function in patients with AF may inform treatment strategies that mitigate pro-arrhythmic autonomic influences. Future studies should look to replicate our findings in a larger cohort and determine the effect of OSA therapy on modulation of the ANS.

Figure 10: Study Flowchart

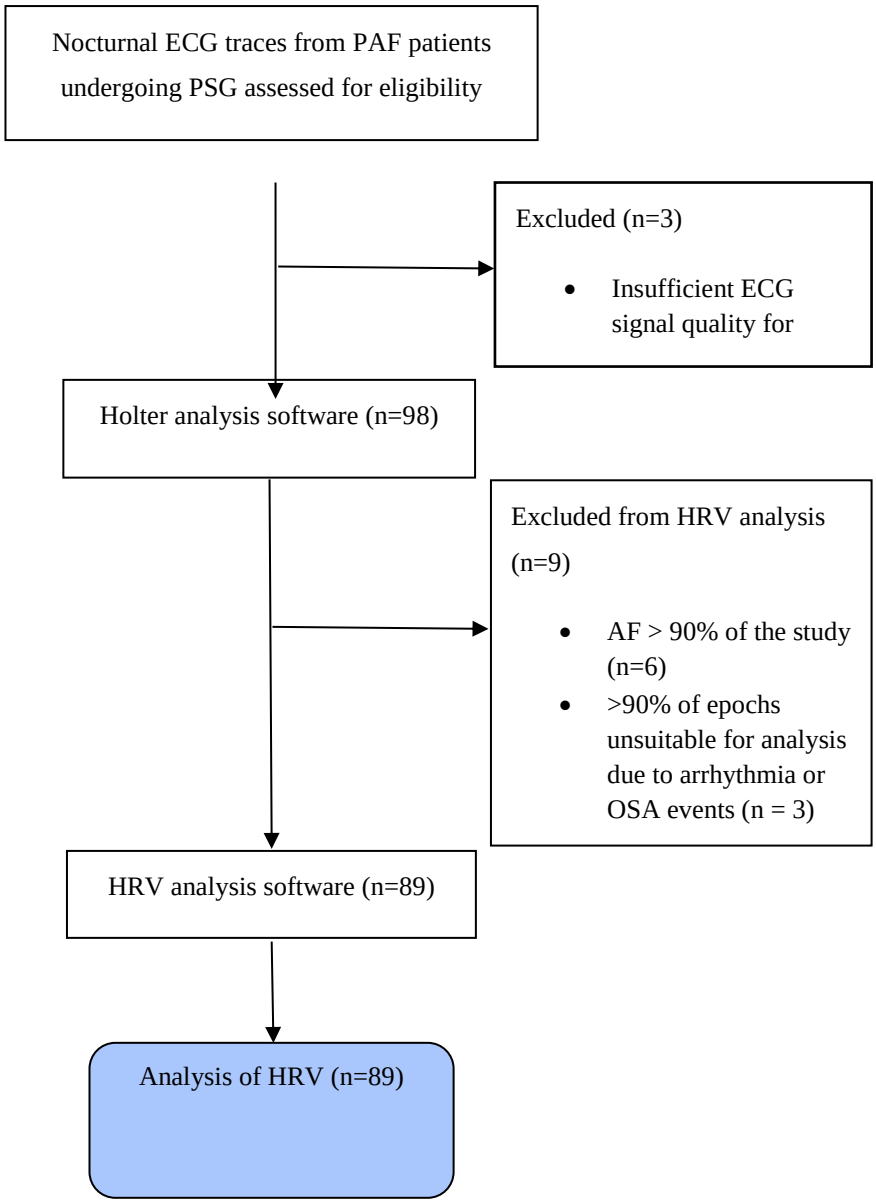


Table 18: Summary of Time and Frequency Domain HRV Parameters

HRV Parameter (units)	Description
Time Domain	
NN interval (ms)	Interval between R wave peaks for two normal successive beats
Average NN interval (ms)	Average time interval between normal successive R waves
RMSSD (ms)	Square root of the mean squared differences of successive NN intervals
pNN50 (%)	Proportion of NN intervals which differ by more than 50ms
Triangular Index (nu)	Integral of the density of the RR interval histogram divided by its height, a measure of total HRV
Frequency Domain	
High Frequency (ms^2)	Power in the 0.15-0.40Hz band
High Frequency, Normalised Units (%)	HF power divided by power ≥0.04Hz
Low Frequency (ms^2)	Power in the 0.04-0.15Hz band
Low Frequency Normalised Units (%)	LF power divided by power ≥0.04Hz
Very Low Frequency (ms^2)	Power less than 0.04Hz
LF/HF Ratio (nu)	Low frequency power divided by high frequency power
Total Power	Power from 0 to Nyquist frequency

Table 19: Baseline characteristics of AF patients with and without OSA (AHI ≥ 5/hr)

Characteristic	N (%) or Mean ± SD			
	Mean (SD) or n (%)	AHI < 5/hr	AHI ≥ 5/hr	p Value
	n = 98	n = 36	n = 62	
General Demographics				
Recruitment stream: ER	54 (55.1)	19 (52.8)	35 (56.5)	0.834
Age (years)	61.5 ± 11.6	58.9 ± 12.5	63.0 ± 10.8	0.098
Male	65 (66.3)	19 (52.8)	46 (74.2)	0.045*
Ethnicity: Caucasian	91 (92.9)	34 (94.4)	57 (91.9)	0.384
Phenotypic Characteristics				
BMI (kg/m^2)	27.1 ± 4.3	24.7 ± 3.5	28.5 ± 4.2	<0.001*
Neck Circumference (cm)	40.0 ± 4.9	38.8 ± 4.7	40.7 ± 4.9	0.065
Modified Mallampati Score	2.7 ± 0.9	2.4 ± 0.9	2.8 ± 0.8	0.028*
Co-morbidities/AF risk factors (n=99)				
Alcohol Excess (≥10SD/week), n = 105	21 (21.4)	12 (33.3)	11 (17.8)	0.136
Thyroid disease	16 (16.3)	11 (30.6)	5 (8.1)	0.009*
Family history of AF	29 (29.6)	13 (36.1)	16 (25.8)	0.203
Mod-severe MS/Prosthetic heart valve	3 (3.0)	2 (2.9)	1 (3.1)	0.865
Hypertension	38 (38.8)	8 (22.2)	31 (50.0)	0.010*
Diabetes	4 (4.1)	2 (5.6)	3 (4.8)	0.876
IHD	4 (4.1)	1 (2.8)	3 (8.3)	0.619
CCF	18 (18.4)	5 (13.8)	13 (21.0)	0.431
Cerebrovascular Disease	2 (2.0)	0 (0)	2 (3.2)	0.530
Peripheral Vascular disease	3 (3.1)	3 (8.3)	0 (0)	0.047*
CHA_2DS_2-Vasc Score	1.6 ± 1.3	1.4 ± 1.2	1.7 ± 1.4	0.270
Anti-coagulant therapy	78 (79.6)	30 (83.3)	49 (79.0)	0.792
AF characteristics				

Paroxysmal	90 (91.8)	36 (100.0)	57 (91.9)	0.080
High burden (≥ 10 episodes AF last 12M)	31 (31.6)	8 (22.2)	23 (37.1)	0.039*
Prior PVI (number)	0.4 ± 0.6	0.33 ± 0.05	0.40 ± 0.64	0.570
Prior Cardioversion (number)	1.0 ± 1.5	0.64 ± 1.18	1.16 ± 1.57	0.086
Anti-arrhythmic therapy				
Prescribed anti-arrhythmic medication?	78 (79.6)	30 (83.3)	50 (80.6)	0.794
Number of anti-arrhythmic medications	1.05 (0.6)	1.06 (0.63)	1.06 (0.67)	0.948
Class 1 anti-arrhythmic	29 (29.6)	11 (30.6)	18 (29.0)	0.873
Class 2 anti-arrhythmic	30 (30.6)	11 (30.6)	19 (30.6)	0.993
Class 3 anti-arrhythmic	28 (28.6)	9 (0.25)	19 (30.6)	0.646
Class 4 anti-arrhythmic	9 (9.2)	3 (8.3)	6 (9.7)	0.824
Class 5 anti-arrhythmic	3 (3.1)	1 (2.8)	2 (3.2)	0.901
Echocardiographic parameters (n=74)				
Cardiac Ejection Fraction (%)	57.1 ± 8.7	59.6 ± 1.1	55.5 ± 9.7	0.027*
Left atrial diameter (cm) (n=53)	4.1 ± 6.3	3.9 ± 0.5	4.2 ± 0.7	0.105
Left atrial area (cm^2) (n=46)	24.2 ± 5.2	22.3 ± 4.5	25.5 ± 5.3	0.032*
OSA Symptoms				
ESS	6.2 ± 3.4	5.7 ± 3.8	6.4 ±3.1	0.349
Self-reported Snoring	64 (65.3)	18 (50.0)	46 (74.2)	0.027*
Sleep Parameters: from PSG				
AHI (/hr)	13.8 ± 15.9	1.7 ± 1.4	20.8 ± 16.3	<0.001*
ODI (/hr)	7.4 ± 10.9	0.8 ± 1.5	11.2 ± 12.2	<0.001*
CAI (/hr)	0.6 ± 1.5	0.1 ± 1.2	0.8 ± 1.8	0.018*
AI (/hr)	2.4 ± 5.3	0.2 ± 0.3	3.7 ± 6.3	<0.001*
HI (/hr)	11.4 ± 13.2	1.5 ± 1.4	17.1 ± 13.8	<0.001*
Presence of Arrhythmia on PSG				
AF (% of total beats)	6.2 ± 23.4	2.9 ± 16.6	8.1 ± 26.4	0.283
SVEB (% of total beats)	0.6 ± 1.6	0.9 ± 2.0	0.5 ± 1.4	0.136
VEB (% of total beats)	0.5 ± 1.7	0.5 ± 1.4	0.4 ± 1.8	0.826

AF: Atrial Fibrillation, AHI: Apnoea Hypopnea Index, BMI: Body Mass Index, CAI: Central Apnoea Index, CCF: Congestive Cardiac Failure, ER: Emergency Room, ESS: Epworth Sleepiness Scale, IHD: Ischaemic Heart Disease, MS: Mitral Stenosis, ODI: Oxygen desaturation index, PVI: Pulmonary Vein Isolation procedure waitlist, SD: Standard drinks, SVE: Supraventricular Ectopic Beats, VE: Ventricular Ectopic Beats

Figure 11: AF beats as a percent of total beats by OSA Severity

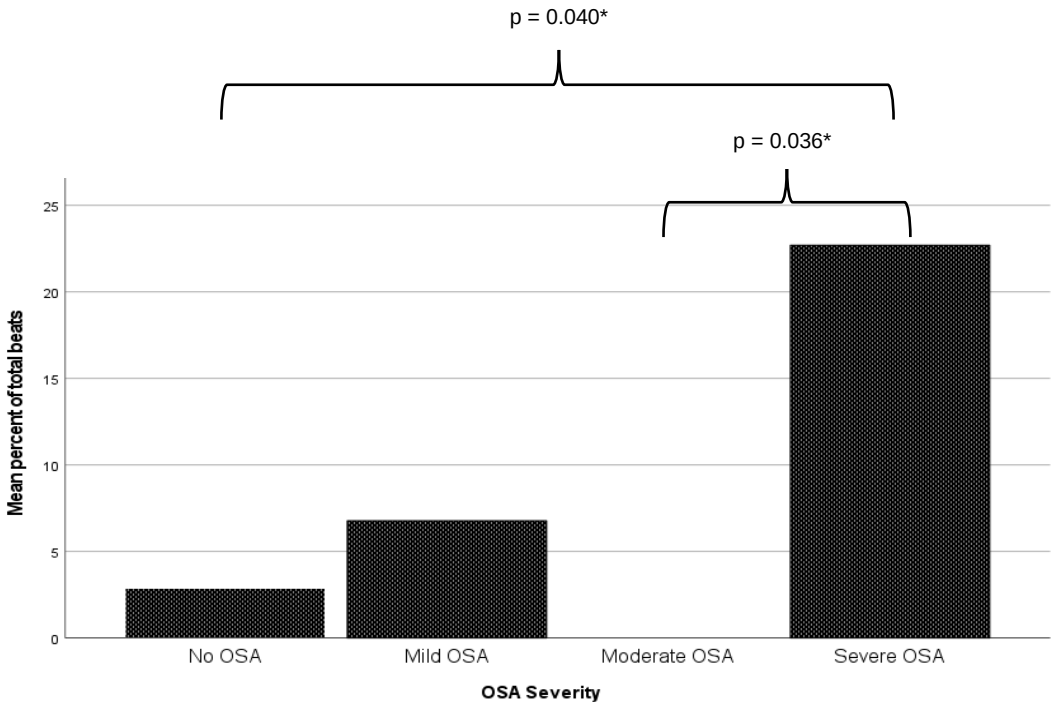


Figure 11 Legend: Patients with no OSA (AHI ≤ 5/hr, n=36) had 2.9 ±16.6% AF beats, patients with mild OSA (AHI 5 – 14.9/hr, n=31) had 6.7 ± 23.6% AF beats, patients with moderate OSA (AHI 15 – 29.9/hr, n=18) had 0.0 ± 0.0% AF beats, and those with severe OSA (AHI ≥30/hr, n =13) had 22.7 ± 42.8% AF beats.

Table 20: HRV Time-Domain Parameters by OSA Status in a cohort with Atrial Fibrillation

	All patients	No OSA AHI < 5/hr	OSA AHI > 5/hr	P value	P value (adjusted for age, sex, BMI)
	n = 89	**n = 35**	**n = 54**		
Average NN interval (ms)					
Non-REM	1080.2 ± 162.9	1062.0 ± 133.9	1091.9 ± 179.4	0.401	0.475
REM	1067.2 ± 166.4	1041.2 ± 136.7	1084.3 ± 182.5	0.243	0.492
†RMSSD (ms)					
Non-REM	28.7 (23.1)	27.3 (20.7)	30.9 (23.6)	0.447	0.570
REM	26.7 (22.7)	20.4 (20.8)	25.3 (23.5)	0.376	0.374
†pNN50 (%)					
Non-REM	5.5 (14.7)	4.5 (12.2)	6.2 (15.9)	0.063	0.061
REM	2.8 (12.3)	1.9 (11.1)	3.3 (17.2)	0.772	0.631
Triangular Index (nu)					
Non-REM	10.8 ± 4.3	10.7 ± 4.4	10.8 ± 4.4	0.975	0.612
REM	11.7 ± 4.6	11.7 ± 4.6	11.6 ± 4.7	0.885	0.541

Data are presented as mean ± SD or median (IQR). Natural log-transformed data are indicated by †

Non-REM: non-rapid eye movement; REM: rapid eye movement; Average NN interval: average of N wave to N wave variation, RMSSD: square root of the mean squared differences of successive NN intervals, pNN50: percentage of successive NN intervals that differ by more than 50ms, Triangular Index: integral of the density of the RR interval histogram divided by its height.

Table 21: HRV Frequency-Domain Parameters by OSA Status in a cohort with Atrial Fibrillation

	All patients	No OSA AHI < 5/hr	OSA AHI > 5/hr	P value	P value (adjusted for age, sex, BMI)
	n = 89	n = 35	n = 54		
† High Frequency (ms^2)					
Non-REM	333.3 (437.8)	238.8 (913.9)	403.5 (723.7)	0.643	0.730
REM	223.3 (437.8)	206.6 (344.1)	239.8 (531.1)	0.530	0.426
High Frequency, Normalised Units (%)					
Non-REM	44.5 ± 15.6	39.1 ± 15.7	48.0 ± 14.6	0.008*	0.024*
REM	37.4 ± 17.2	32.6 ± 16.0	40.5 ± 17.4	0.036*	0.143
† Low Frequency (ms^2)					
Non-REM	336.1 (863.9)	339.6 (1155.7)	327.6 (760.1)	0.447	0.559
REM	302.9 (817.5)	358.5 (1103.7)	298.8 (831.0)	0.533	0.904
Low Frequency Normalised Units (%)					
Non-REM	47.8 ± 19.2	54.1 ±19.7	43.7 ± 18.0	0.012*	0.045*
REM	55.2 ± 22.1	60.4 ± 20.8	51.8 ± 22.5	0.076	0.228
†Very Low Frequency (ms^2)					
Non-REM	470.0 (860.0)	603.8 (1055.1)	445.2 (605.6)	0.135	0.148
REM	865.4 (1322.0)	954.9 (1548.9)	826.5 (1307.6)	0.417	0.663
LF/HF Ratio (nu)					
Non-REM	1.5 ± 1.5	2.1 ± 2.0	1.2 ± 1.0	0.007*	0.018*
REM	2.3 ± 2.2	2.9 ± 2.6	2.0 ± 1.9	0.063	0.108
† Total Power					
Non-REM	1352.7 (2078.9)	1183.2 (1514.3)	1109.0 (1573.3)	0.526	0.987
REM	1128.2 (1498.7)	1439.0 (2360.6)	1318.0 (2137.8)	0.666	0.988

Data are presented as mean (SD) or median (IQR). Natural log-transformed data are indicated by †

High frequency: Power in the 0.15-0.40Hz band, High frequency normalised units: HF power divided by power ≥0.04Hz, Low Frequency: Power in the 0.04-0.15Hz band, Low Frequency normalised units: LF power divided by power ≥0.04Hz Very low frequency: Power less than 0.04Hz, LF/HF, Low frequency/high frequency ratio: Low frequency power divided by high frequency power, Total Power: Power from 0 to Nyquist frequency.

Table 22: HRV Time-Domain Parameters by OSA Status (AHI < or ≥15/hr) in a cohort with Atrial Fibrillation

	All patients	No OSA/Mild OSA AHI < 15/hr	Moderate to Severe OSA AHI ≥ 15/hr	P value	P value (adjusted for age, sex, BMI)
	n = 89	**n = 64**	**n = 25**		
Average NN interval (ms)					
Non-REM	1080.2 ± 162.9	1097.6 ± 166.5	1035.7 ± 147.1	0.053	0.074
REM	1067.2 ± 166.4	1080.9 ±169.6	1029.9 ± 154.7	0.105	0.076
†RMSSD (ms)					
Non-REM	28.7 (23.1)	28.3 (38.5)	30.9 (20.7)	0.231	0.180
REM	26.7 (22.7)	22.8 (24.0)	23.4 (19.5)	0.375	0.616
†pNN50 (%)					
Non-REM	5.5 (14.7)	5.6 (18.7)	4.8 (13.6)	0.369	0.827
REM	2.8 (12.3)	2.9 (14.4)	2.8 (6.0)	0.211	0.351
Triangular Index (nu)					
Non-REM	10.8 ± 4.3	11.1 ± 4.4	9.9 ± 4.2	0.135	0.162
REM	11.7 ± 4.6	12.1 ± 4.6	10.6 ± 4.8	0.093	0.170

Data are presented as mean ± SD or median (IQR). Natural log-transformed data are indicated by †

Non-REM: non-rapid eye movement; REM: rapid eye movement; Average NN interval: average of N wave to N wave variation, RMSSD: square root of the mean squared differences of successive NN intervals, pNN50: percentage of successive NN intervals that differ by more than 50ms, Triangular Index: integral of the density of the RR interval histogram divided by its height.

Table 23: HRV Frequency-Domain Parameters by OSA Status (AHI < or ≥15/hr) in a cohort with Atrial Fibrillation

	All patients	No OSA/Mild OSA AHI < 15/hr	Moderate to Severe OSA AHI ≥15/hr	P value	P value (adjusted for age, sex, BMI)
	n = 89	**n = 64**	**n = 25**		
† High Frequency (ms^2)					
Non-REM	333.3 (437.8)	314.6 (1116.8)	396.7 (570.8)	0.320	0.111
REM	223.3 (437.8)	217.4 (421.4)	225.8 (491.4)	0.635	0.554
High Frequency, Normalised Units (%)					
Non-REM	44.5 ± 15.6	43.7 ± 15.0	46.5 ± 17.1	0.463	0.889
REM	37.4 ± 17.2	35.6 ± 16.4	42.3 ± 18.8	0.111	0.388
† Low Frequency (ms^2)					
Non-REM	336.1 (863.9)	354.9 (1251.8)	307.6 (369.7)	0.095	0.063
REM	302.9 (817.5)	337.9 (1118.6)	289.9 (630.5)	0.126	0.127
Low Frequency Normalised Units (%)					
Non-REM	47.8 ± 19.2	49.8 ± 17.7	42.6 ± 22.3	0.116	0.457
REM	55.2 ± 22.1	58.0 ± 20.5	47.6 ± 25.0	0.054	0.150
†Very Low Frequency (ms^2)					
Non-REM	470.0 (860.0)	505.2 (1076.6)	439.4 (518.0)	0.072	0.031
REM	865.4 (1322.0)	1019.3 (1508.0)	618.8 (1240.9)	0.036*	0.023*
LF/HF Ratio (nu)					
Non-REM	1.5 ± 1.5	1.6 ± 1.6	1.3 ± 1.2	0.426	0.996
REM	2.3 ± 2.2	2.5 ± 2.3	1.9 ± 2.1	0.285	0.562
† Total Power					
Non-REM	1352.7 (2078.9)	1375.5 (3401.3)	1363.2 (1315.0)	0.191	0.079
REM	1128.2 (1498.7)	1610.6 (2946.8)	1442.6 (2010.1)	0.199	0.181

Data are presented as mean (SD) or median (IQR). Natural log-transformed data are indicated by †

High frequency: Power in the 0.15-0.40Hz band, High frequency normalised units: HF power divided by power ≥0.04Hz, Low Frequency: Power in the 0.04-0.15Hz band, Low Frequency normalised units: LF power divided by power ≥0.04Hz Very low frequency: Power less than 0.04Hz, LF/HF, Low frequency/high frequency ratio: Low frequency power divided by high frequency power, Total Power: Power from 0 to Nyquist frequency.

Table 24: HRV Time-Domain Parameters by OSA Status (AHI < or ≥30/hr) in a cohort with Atrial Fibrillation

	All patients	AHI < 30/hr	Severe OSA AHI ≥ 30/hr	P value	P value (adjusted for age, sex, BMI)
	n = 89	**n = 81**	**n = 8**		
Average NN interval (ms)					
Non-REM	1080.2 ± 162.9	1092.1 ± 157.1	959.9 ± 182.7	0.028*	0.018*
REM	1067.2 ± 166.4	1075.5 ± 161.5	974.3 ± 205.2	0.124	0.056
†RMSSD (ms)					
Non-REM	28.7 (23.1)	29.6 (27.2)	26.7 (42.2)	0.732	0.799
REM	26.7 (22.7)	22.8 (22.7)	25.5 (108.2)	0.298	0.396
†pNN50 (%)					
Non-REM	5.5 (14.7)	5.7 (15.0)	3.5 (6.4)	0.555	0.888
REM	2.8 (12.3)	2.9 (13.5)	2.6 (3.7)	0.392	0.220
Triangular Index (nu)					
Non-REM	10.8 ± 4.3	10.7 ± 4.4	11.0 ± 3.6	0.876	0.594
REM	11.7 ± 4.6	11.6 ± 4.6	11.8 ± 5.7	0.936	0.631

Data are presented as mean ± SD or median (IQR). Natural log-transformed data are indicated by †

Non-REM: non-rapid eye movement; REM: rapid eye movement; Average NN interval: average of N wave to N wave variation, RMSSD: square root of the mean squared differences of successive NN intervals, pNN50: percentage of successive NN intervals that differ by more than 50ms, Triangular Index: integral of the density of the RR interval histogram divided by its height.

Table 25: HRV Frequency-Domain Parameters by OSA Status (AHI < or ≥30/hr) in a cohort with Atrial Fibrillation

	All patients	No OSA/Mild OSA AHI < 30/hr	Severe OSA AHI > 30/hr	P value	P value (adjusted for age, sex, BMI)
	n = 89	**n = 81**	**n = 8**		
† High Frequency (ms^2)					
Non-REM	333.3 (437.8)	321.2 (703.4)	355.6 (1345.8)	0.642	0.664
REM	223.3 (437.8)	217.4 (386.6)	401.5 (33331.1)	0.236	0.354
High Frequency, Normalised Units (%)					
Non-REM	44.5 ± 15.6	44.9 ± 15.2	40.1 ± 19.9	0.405	0.081
REM	37.4 ± 17.2	37.0 ± 16.8	42.0 ± 22.5	0.466	0.481
† Low Frequency (ms^2)					
Non-REM	336.1 (863.9)	319.2 (989.3)	342.3 (780.2)	0.953	0.890
REM	302.9 (817.5)	301.2 (830.9)	328.3 (836.6)	0.610	0.851
Low Frequency Normalised Units (%)					
Non-REM	47.8 ± 19.2	47.9 ± 18.5	46.6 ± 27.3	0.861	0.624
REM	55.2 ± 22.1	56.1 ± 21.6	45.5 ± 26.8	0.229	0.133
†Very Low Frequency (ms^2)					
Non-REM	470.0 (860.0)	493.6 (877.5)	374.8 (628.4)	0.971	0.648
REM	865.4 (1322.0)	890.5 (1310.2)	618.8 (815.0)	0.809	0.835
LF/HF Ratio (nu)					
Non-REM	1.5 ± 1.5	1.5 ± 1.6	1.6 ± 1.2	0.807	0.293
REM	2.3 ± 2.2	2.4 ± 2.2	1.9 ± 2.2	0.608	0.481
† Total Power					
Non-REM	1352.7 (2078.9)	1374.6 (2329.6)	1573.3 (2862.1)	0.744	0.937
REM	1128.2 (1498.7)	1576.9 (2573.7)	1664.9 (6913.2)	0.470	0.663

Data are presented as mean (SD) or median (IQR). Natural log-transformed data are indicated by †

High frequency: Power in the 0.15-0.40Hz band, High frequency normalised units: HF power divided by power ≥0.04Hz, Low Frequency: Power in the 0.04-0.15Hz band, Low Frequency normalised units: LF power divided by power ≥0.04Hz Very low frequency: Power less than 0.04Hz, LF/HF, Low frequency/high frequency ratio: Low frequency power divided by high frequency power, Total Power: Power from 0 to Nyquist frequency

Table 26: HRV Time-Domain Pearson correlations with OSA parameters

	PSG AHI		PSG ODI		%T<90	
	R value	P value	R value	P value	R value	P value
Average NN interval						
Non-REM	-0.169	0.112	-.215	0.043*	-.211*	0.047*
REM	-0.095	0.386	-0.151	0.167	-0.160	0.140
† **RMSSD**						
Non-REM	0.043	0.692	0.032	0.768	0.087	0.415
REM	0.137	0.207	0.099	0.366	0.101	0.354
† **pNN50**						
Non-REM	0.104	0.336	0.082	0.450	0.050	0.644
REM	-0.065	0.551	-0.110	0.312	-0.008	0.943
Triangular Index						
Non-REM	-0.022	0.841	-0.048	0.658	0.008	0.942
REM	-0.017	0.878	-0.038	0.727	0.006	0.957

Natural log-transformed data are indicated by †

PSG: polysomnogram, AHI: Apnea Hypopnea Index, ODI: Oxygen Desaturation Index, %T<90: percent of sleep time with haem-oxygen saturation < 90%, Non-REM: non-rapid eye movement; REM: rapid eye movement; Average NN interval: average of N wave to N wave variation, RMSSD: square root of the mean squared differences of successive NN intervals, pNN50: percentage of successive NN intervals that differ by more than 50ms, Triangular Index: integral of the density of the RR interval histogram divided by its height.

Table 27: HRV Frequency-Domain Pearson correlations with OSA parameters

	PSG AHI		PSG ODI		%T<90	
	R value	P value	R value	P value	R value	P value
† **High Frequency**						
Non-REM	-0.001	0.993	0.001	0.995	0.128	0.233
REM	0.122	0.262	0.090	0.409	0.095	0.386
High Frequency Normalised Units						
Non-REM	0.036	0.738	0.082	0.443	0.059	0.582
REM	0.182	0.094	0.190	0.079	0.114	0.296
†**Low Frequency**						
Non-REM	-0.063	0.559	-0.084	0.435	0.060	0.579
REM	-0.017	0.876	-0.041	0.708	-0.011	0.917
Low Frequency Normalised Units						
Non-REM	-0.141	0.187	-0.192	0.071	-0.164	0.125
REM	-.219	0.043*	-.219	0.042*	-.215	0.046*
†**Very Low Frequency**						
Non-REM	-0.095	0.377	-0.101	0.344	-0.006	0.954
REM	-0.071	0.518	-0.056	0.608	-0.021	0.845
LF/HF Ratio						
Non-REM	-0.083	0.437	-0.106	0.323	-0.102	0.341
REM	-0.143	0.188	-0.134	0.217	-0.109	0.317
† **Total Power**						
Non-REM	-0.028	0.793	-0.037	0.730	0.094	0.379
REM	0.017	0.875	-0.004	0.969	0.020	0.857

Natural log-transformed data are indicated by †

PSG: polysomnogram, AHI: Apnea Hypopnea Index, ODI: Oxygen Desaturation Index, %T<90: percent of sleep time with haem-oxygen saturation less than 90%; Non-REM: non-rapid eye movement, REM: rapid eye movement, High frequency: Power in the 0.15-0.40Hz band, High frequency normalised units: HF power divided by power ≥0.04Hz, Low Frequency: Power in the 0.04-0.15Hz band, Low Frequency normalised units: LF power divided by power ≥0.04Hz, Very low frequency: Power less than 0.04Hz, LF/HF, Low frequency/High frequency ratio: Low frequency power divided by High frequency power, Total Power: Power from 0 to Nyquist frequency.

4.0 A Pilot Study of the Acceptance, Compliance and Efficacy of Mandibular Advancement Splint Therapy in Atrial Fibrillation Patients with Obstructive Sleep Apnoea

4.1 ABSTRACT

Introduction*:* International Atrial Fibrillation (AF) management guidelines recommend assessment for and treatment of underlying Obstructive Sleep Apnoea (OSA) (10, 223). However, compliance with Continuous Positive Airway Pressure (CPAP) therapy may be suboptimal in cardiovascular patients (111). Mandibular Advancement Splint (MAS) therapy is the leading treatment alternative to CPAP, however there is little data on its use in AF patients.

Aims: This is a pilot study of MAS therapy for OSA in AF patients. Primary outcomes were patient acceptance, compliance and MAS efficacy. Secondary outcomes included AF burden, MAS patient-centred evaluation and side effects, quality of life, and change in 24 hour ambulatory BP. In addition, the feasibility of tools for the assessment of AF recurrence was assessed.

Methods: Patients with AF and OSA were treated MAS over a 6 month period. Polysomnography (PSG) was performed at baseline and after 6 months of MAS therapy. Patient acceptance was defined as the proportion of patients who continued to use the MAS after an initial one-week lead-in period. Compliance was defined as the proportion of patients who achieved ≥ 4 hours of MAS usage on ≥ 70 % of nights, as assessed by the inbuilt compliance recorder (DentiTrac, Braebon). MAS efficacy was assessed via the polysomnographic change in Apnea Hypopnea Index (AHI) with the device in situ at six months when compared with baseline. Feasibility of tools for the assessment of AF recurrence was evaluated by adherence with and efficacy of a number of methods for AF detection.

Results*:* 12 Patients were included in this pilot study, of whom 9 (75%) were male, with a mean age of 65.5 ± 10.2 years and mean BMI 29.6 ±4.8 kg/m^2. 10 out of 12 patients continued to use the MAS device after one week, giving an acceptance rate of 83.3%. 80% of patients who used the device met the pre-determined compliance threshold of ≥ 4 hours of usage on ≥ 70 % of nights at 3 and 6 months. Of the 10 patients who continued to use the MAS at 6 months, 60% met the liberal criteria for MAS response, and 40% met the strict criteria for MAS response. Of the 8 patients who demonstrated an improvement in AHI with MAS in situ, the average reduction in AHI was 17.1 (±12.4) /hr, or 48%. A daily at-home ECG device (AliveCor Kardia) showed the best performance in detecting AF recurrence (in 58% of patients).

Conclusions: Results from this pilot study suggest that MAS therapy has a high level of acceptance, compliance and efficacy in AF patients. These data provide valuable insights to inform the design of future randomised control trial.

4.2 INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia worldwide, and incurs a substantial public health burden through increased stroke risk and hospitalisation (279). International guidelines for the management of AF recommend aggressive, holistic risk factor management, including identification and treatment of obstructive sleep apnoea (OSA) (10). However, the gold standard therapy for the management of OSA, known as Continuous Positive Airway Pressure (CPAP) therapy, is poorly tolerated by some patients. This has proven particularly true in cardiovascular populations (111). In addition, the modest number of randomised control trials conducted to date looking at cardiovascular endpoints with CPAP therapy have failed to demonstrate a benefit, perhaps due to the low levels of CPAP compliance common to all trials, and particularly in cardiovascular patients (13, 14, 51).

Mandibular advancement splint (MAS) therapy, while less effective at lowering the Apnoea Hypopnoea Index (AHI), is generally better tolerated than CPAP (92). Therefore MAS therapy may be more effective at reducing the overall sleep apnoea burden, if it is worn for a greater proportion of the night. MAS therapy may help to answer the important clinical question of whether the treatment of OSA may improve outcomes in AF patients, and most significantly whether treating OSA can improve AF burden. As yet there are no studies of MAS therapy for the treatment of OSA in patients with atrial fibrillation. We hypothesised that MAS therapy will show high levels of patient acceptance, compliance and efficacy in an AF population.

AF burden is most sensitively assessed with continuous ECG monitoring, such as that afforded by an implantable loop recorder device. This is because AF episodes are intermittent and can be asymptomatic, thus undetectable by the patient. However, loop recorders are invasive, costly, and must be implanted by a specialist practitioner. Hence large scale studies with these devices would be highly resource-intensive. In this pilot study we aimed to review a number of alternative methods for the acquisition of AF recurrence data, including serial 24 hour Holter monitoring, patient symptom diary, medical record review and the use of an at-home ECG device.

4.3 AIMS

We sought to evaluate patient acceptance, compliance and efficacy of MAS therapy in an AF population; these constituted the primary outcomes of the study. Secondary outcomes included AF burden, MAS patient-centred evaluation assessment and side effects, quality of life, and change in 24 hour ambulatory BP. As this was a pilot study, we also sought to evaluate the feasibility of AF detection methods ahead of a future larger randomised control trial. To do this we posed two questions: 1) What are the patient compliance rates with a selection of AF assessment tools? And 2) How effective is each tool at identifying AF recurrence?

4.4 METHODS

4.4.1 Study Ethics

Approval was obtained from the Northern Sydney Local Health District Human Research Ethics Committee (HREC/16/HAWKE/25), and the North Shore Private

Hospital Ethics Committee (approval number 2016-012). All patients gave their informed written consent to participate in the study. The trial was registered with the Australian New Zealand Clinical Trials Registry (ANZCTR): 12618001081202.

4.4.2 Patient recruitment

Patients were recruited via three clinical pathways: Emergency department presentations with confirmed AF (33%), Pulmonary Vein Isolation (PVI) waitlists (58%), or direct referrals from treating Sleep physicians (8%). Most patients (92%) had completed a prior study looking at diagnostic tools for OSA in an AF population (ACTRN12616001016426). All patients had an ECG documented history of ≥1 episode of AF in the last 12 months, and an Apnea Hypopnea Index (AHI) ≥10/hr on baseline in-laboratory polysomnography (PSG). Patients were excluded from the study if they were currently on active OSA treatment or if they met any of the following criteria: no definite history of documented AF, significant geriatric health issues (eg falls, frequent UTIs, impaired mobility), active malignancy, repeat presentations, geographical remoteness, end stage organ disease, significant cognitive impairment, significant mental illness, substance abuse, end stage organ disease, intubated, deceased or otherwise unable to provide written informed consent.

4.4.3 Study Outcomes

Patient acceptance was defined as MAS therapy persisting beyond one week after receipt of the device. Non-acceptance was therefore defined in those patients who did not continue MAS therapy after the first week. **Compliance** at 3 and 6 months

was defined as MAS usage for ≥ 4 hours on 70% of nights, as assessed by the inbuilt temperature sensor chip (DentiTrac, Braebon Medical). In addition, we reported average hours of usage per night (nights used) and average hours of usage per night (all nights). **Efficacy** was defined by the change in AHI from baseline with the MAS device in situ as assessed on in-laboratory PSG. Patients were considered MAS responders according to the following definitions previously established in the literature (30): 1): Liberal definition: AHI improved by ≥ 50% on PSG at 6 months when compared to baseline PSG or 2) Strict definition: AHI improved by ≥ 50% when compared to baseline PSG with a residual AHI < 10/hr. Secondary outcomes were as follows: i) AF recurrence, assessed via a number of methods: a) daily ECG recorded by the patient at home (AliveCor Kardia device), b) Holter monitor at baseline and 6 months, c) patient diary and d) medical record review ii) MAS patient-centred evaluation and side effects (assessed via questionnaires at 3 and 6 months) iii) quality of life as assessed by 3 validated questionnaires relating to sleep, general health and atrial fibrillation respectively (FOSQ-10, SF-36, AFEQT) at baseline, 3 and 6 months, iv) change in 24 hour ambulatory blood pressure (24hrABP). Study tools for AF recurrence were assessed for a) adherence rate and b) efficacy, defined as the number of patients in whom at least one episode of AF recurrence was detected.

4.4.4 Study Visits

The study protocol was conducted over a 6 month period. Patients underwent study visits at baseline, as well as 3 and 6 months after receipt of the MAS device. In addition, 3 dental visits were conducted following the baseline assessment for digital

dental scanning, MAS fitting, education about titration and review. The study flowchart is outlined in Figure 12. Study visits are summarised in Table 28.

4.4.5 Mandibular Advancement Splint (MAS) Device

The study device was a bi-bloc custom-made MAS whose coupling mechanism consists of a series of plastic straps, each incrementally shorter in length (Avant device, Somnomed Australia), see figure 13. Patients were initially reviewed by the study dentist to ensure suitability of dentition for MAS therapy, then a digital 3-D oral scan was performed and a custom-made MAS device manufactured and fit for each individual patient. Patients were instructed to progress through the series of straps at home until they reached the shortest tolerable strap, thus bringing the mandible to the furthest comfortable limit of protrusion. After six months of MAS therapy, a PSG was performed with the device in situ to assess its efficacy when compared to the patient's baseline PSG. MAS devices were fitted with an in-built, temperature sensitive compliance recorder (Dentitrak, Braebon) which facilitated the collection of objective adherence data.

4.4.6 Tools for the Assessment of AF recurrence: AliveCor Kardia, Holter Monitor, AF diary and Medical Record review

AliveCor Kardia is a validated, single lead 1, portable ECG recording device and associated smartphone application (280), which patients were invited to download to their own smartphone device. Patients were instructed to record a daily ECG at the same time each day, and additionally at any time of perceived AF symptoms. On

completion of each recording, patients emailed the ECG trace to the study investigators. ECGs were interpreted by the device's inbuilt algorithm; ECGs which returned a diagnosis of "atrial fibrillation" or "possible atrial fibrillation" were reviewed by the study physician to confirm the presence or absence of AF.

A Holter monitor is a portable ECG device which was worn by the patients over a 24 hour period. Holter monitors (Mortara H3+) were performed at baseline and six months. Holter devices were applied by trained cardiac technicians and interpreted by experienced cardiologists who were blinded to the study aims and outcomes. Patients were also asked to keep a diary of AF symptoms on a diary template which was provided at baseline. Patients were asked to record the date and time of any perceived AF episodes. In addition, the patient's medical record was reviewed by the study physician to capture any documented episodes of AF during the study period. This included hospital presentations or outpatient review with a confirmed AF episode during the study period. Adherence rates for AliveCor Kardia were calculated as the proportion of daily ECGs that were returned to the study investigators over a six month period. Adherence rates for Holter monitors were calculated as the proportion of scheduled Holters that were attended by the patient. AF diary adherence rates were defined as the proportion of AF diaries that were completed and returned to the study investigators.

4.4.7 Patient Reported Outcome Measures (PROMS)

MAS side effects and a patient-centred evaluation of MAS therapy were assessed via questionnaires at 3 and 6 months. The questionnaires were initially developed by Ryan et al and first published in 2005 (132). 8 treatment-related side effects were assessed. Patients indicated the frequency and severity of side effects according to the following scale: 0 = not at all, 1 = Rare, but hardly disturbing, 2 = Rare but disturbing, 3 = Often, but hardly disturbing, 4 = Often and disturbing, 5 = Always and strongly disturbing. The MAS patient-centred questionnaire addressed five points: claustrophobia, comfort, satisfaction, perceived efficacy and intention to continue the MAS long-term. Side Effects and Patient-centred Evaluation questionnaires are attached as Appendix 1.

4.4.8 Quality of Life

Quality of life was assessed by 3 validated questionnaires (FOSQ-10, SF-36 and AFEQT) at baseline, 3 and 6 months.

The FOSQ-10 is a psychometrically strong 10-item instrument which measures the impact of sleepiness on functional status. It comprises a number of subscales, 1) activity level, 2) vigilance, 3) intimacy and sexual relationships, 4) general productivity, and 5) social outcomes. Due to the limited number of items in each subscale it is reported as a single total score. Scores range from 5–20 points, with higher scores indicating better functional status (281).

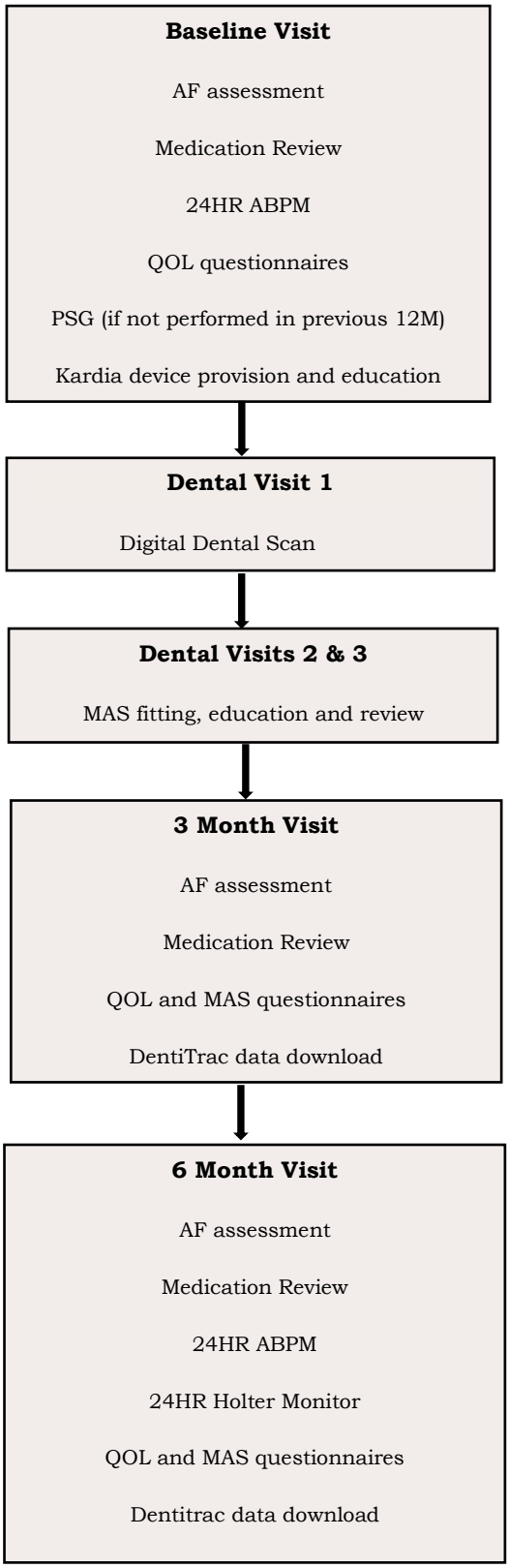
The SF-36 measures 8 general health domains: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions (282). Scores range from a minimum of 0 to a maximum of 100. Lower scores indicate more disability i.e., a score of zero is equivalent to maximum disability and a score of 100 is equivalent to no disability.

The Atrial Fibrillation Effect on Quality of Life (AFEQT) score is a validated tool which assesses AF-related quality of life in four domains: Symptoms, Daily Activities, Treatment Concern, and Treatment Satisfaction (283). Scores range from a minimum of 0 to a maximum of 100, with 100 representing optimal quality of life. Changes in AFEQT score of + or −5 points are considered clinically meaningful changes in patients' health (284) .

4.4.9 Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 27.0, Armonk, NY: IBM Corp. Results were presented as mean ± standard deviation or as percentages. Differences between measurements at baseline, 3 and 6 months were compared using one way ANOVA. We considered a p value of < 0.05 statistically significant.

Figure 12: Study Flowchart



ABPM: Ambulatory Blood Pressure Monitoring, MAS: Mandibular Advancement Splint, PSG: polysomnography, QOL: Quality of Life

Figure 13: Example of the Avant MAS device (Somnomed Australia) utilised in the study

The Avant MAS device (Somnomed Australia) is a fully customised, bibloc device. Note the coupling mechanism consisting of a plastic strap, which is also deigned to limit mouth opening.

Table 28: Summary of Study Visits:

	Baseline Assessment (Sleep Clinic)	**Dental Visit 1: SCAN (Dentist)**	**Dental Visit 2: FITTING (Dentist)**	**Dental Visit 3: MAS Review (Dentist)**	**3 month Visit (Sleep Clinic)**	**6 month Visit (Sleep Clinic)**
Alivecor Kardia: Daily ECG setup (baseline) and/or review (3 and 6 M)	√				√	√
24 hour Holter recording	√					√
AF diary set up (baseline) and/or review (3 and 6 M)	√				√	√
24 hour ambulatory BP	√					√
AFEQT Questionnaire	√				√	√
SF36 Questionnaire	√				√	√
FOSQ10 Questionnaire	√				√	√
AF Medication Review	√				√	√
Dental assessment and Scan		√				
MAS fitting and titration advice			√	√		
Chart review for AF since last visit					√	√
Interview for patient-reported AF since last visit					√	√
MAS subjective assessment Questionnaire					√	√
MAS side effects Questionnaire					√	√
PSG with MAS in situ						√
Compliance: download dentitrac					√	√
Echocardiogram	√					√

ABPM: Ambulatory Blood Pressure Monitoring, ECG: Electrocardiogram, MAS: Mandibular Advancement Splint, PSG: polysomnography, QOL: Quality of Life

4.5 RESULTS

12 Patients were included in this pilot study, of whom 9 (75%) were male. Mean age was 65.5 ± 10.2 years, and mean BMI in the overweight but not obese range (29.6 ±4.8 kg/m^2). Baseline characteristics are summarised in Table 29. When comparing PSG variables at baseline and with the MAS in situ for all patients who accepted MAS therapy, including responders and non-responders, only supine AHI in non-REM sleep was significantly different between the two groups (54.6 ± 27.6 at baseline vs 16.5 ± 16.1 with MAS in situ, $p < 0.001$), see table 30.

4.5.1 Primary Outcomes:

MAS Acceptance: 10 out of 12 patients continued to use the device after one week, giving an acceptance rate of 83.3%. 2 patients (16.7%) did not continue therapy after the initial week.

MAS compliance: Compliance was assessed for those patients who accepted therapy (10 patients). The compliance threshold (≥ 4 hours of usage on ≥ 70% of nights) was achieved in 8/10 (80%) of patients at both the 3 and 6 month time-points, see table 3. Average nightly usage at 3 months was 5.7 ± 2.1 hours (all days), and 6.6 ± 2.1 hours (days used). Average nightly usage at 6 months was 5.5 ± 2.0 hours (all days) and 6.7 ± 2.0 hours (days used). MAS daily compliance over six months is depicted as a heatmap in Figure 14.

MAS Efficacy: Of the 10 patients who continued to use the device at 6 months, 60% met the liberal criteria for MAS response (improvement in AHI ≥50%), and 40% met the stricter criteria for MAS response (AHI ≥50% *and* a residual AHI ≥10/hr). The average reduction in AHI at 6 months was 7.2 ± 24.1/hr (11.4 ± 82.2%); of the 8 patients who demonstrated an improvement in AHI, the average reduction in AHI was 17.1 ±12.4/hr, (48.0 ± 20.9%), see figure 14, Table 32. Two patients (20%) demonstrated an increase in the AHI at the 6 month PSG with MAS in situ. One of these patients (patient 4) gained 12kg in weight between his diagnostic study and his progress sleep study with MAS in situ; his BMI increased from 33.2kg/m^2 to 37.9kg/m^2. The second patient (patient 12) had limited REM sleep on his initial sleep study (34minutes, 10%) vs 54 minutes (18.6%) REM sleep on the study night with MAS in situ.

4.5.2 Secondary Outcomes:

AF recurrence and Feasibility of collection tools: Of the four instruments used to assess AF recurrence, daily ECG recording via the AliveCor Kardia device was most effective at detecting and documenting episodes of AF. At least 1 episode of AF was documented in 7/12 (58.3%) of patients, compared with 41.8%, 33.3% and 8.3% for patient diary, medical record review and Holter monitor respectively (Table 33). Patients recorded an average of 102.4 ± 28.3 ECGs over 180 days, giving a compliance rate of 52.9%. Of these, 17.8 ± 30.3 (19.2 ± 36.1%) demonstrated the presence of AF (Figure 16). Holter monitoring at 6 months detected at least one episode of AF in 1/12 patients (8.3%) with an adherence rate of 62.5%, table 34. Holter monitoring was significantly impacted by government-mandated “lockdowns” in

the setting of the global SARS-CoV-2 (COVID-19) pandemic. 9 out of 24 (37.5%) scheduled Holter monitors could not be performed. Hence the reported adherence rate is likely to represent an underestimate (table 32). Adherence rate for the AF diary was highest of all the examined tools at 79.2% (table 33).

MAS side effects and subjective evaluation: The most commonly reported side effects at 3 months were excessive salivation and tooth pain/discomfort. The vast majority of reported side effects reported at 3 months (23/24, 95.88%) were rated at the less severe/less frequent end of the scale between 0-3. One patient reported excessive salivation at grade 4 (often and disturbing). The most commonly reported side effects at 6 months were mouth dryness and tooth pain/discomfort. At 6 months, 22/25 (88%) of reported side effects were rated at the less severe/less frequent end of the scale between 0-3. Three reported side effects were assessed at grade 4 (Often and disturbing); these were: excessive salivation, mouth dryness and bite changes (see figure 17). All side effect data was gathered from the 10 patients who accepted the device (i.e. continued to use the device after one week). Both patients who did not continue the device after the first week were asked to complete part of the questionnaire outlining their reasons for discontinuation of the device. One patient reported reasons for stopping the device were: uncomfortable/cumbersome, claustrophobic, difficulty swallowing. The other patient declined to complete the questionnaire.

Patient-centred evaluation comprised 5 domains: claustrophobia, comfort, satisfaction, perceived efficacy and intention to continue the MAS long-term. At six

months 1/10 (10%) of patients reported claustrophobia, average overall comfort score fell between moderately comfortable (50%) and extremely comfortable (100%): 67.9 ± 18.5%, average overall satisfaction score fell between moderately satisfied (50%) and extremely satisfied (100%): 73.7 ± 26.1%, 6/10 (60%) of patients reported that the MAS was somewhat effective at reducing sleep apnoea symptoms and 4/10 (40%) reported that MAS therapy was extremely effective at reducing sleep apnoea symptoms and 7/10 (70%) indicated a definite intention to continue MAS therapy in the long term, see figure 18.

Quality of life: Quality of life questionnaire completion rates were high at 89%, 89% and 94% for the FOSQ-10, AFEQT and SF-36 respectively. Scores for the FOSQ-10, AFEQT and 7/8 domains of the SF-36 all demonstrated a non-significant improvement after 6 months of MAS therapy when compared to baseline. See tables 35 and 36.

Change in 24 hour ambulatory BP: There were no significant differences in 24 hour ambulatory blood pressure monitoring at 6 months compared to baseline. There was a non-significant drop in asleep systolic and asleep diastolic blood pressure with MAS therapy after 6 months. The difference remained non-significant in a subgroup of MAS responders (see table 37).

Table 29: Baseline Characteristics

Baseline Characteristic, n = 12	Mean (+/- SD) or Number (%)
Age (years)	65.5 (10.2)
Gender (male)	9 (75%)
BMI (kg/m2)	29.6 (4.8)
Neck Circumference (cm)	41.0 (4.8)
Modified Mallampati Score (tongue protruded)	3.1 (0.8)
Epworth Sleepiness Score	7.1 (4.3)
Baseline PSG AHI (/hr)	35.0 (20.8)
Baseline PSG 3% ODI (/hr)	29.7 (18.8)
Number of reported AF episodes last 12 months	10.2 (13.1)
Number of Cardioversions last 12 months	6.5 (13.2)
Number of PVIs last 12 months	1.3 (0.8)
CHA2DS2-VASc Score	1.6 (1.4)
Hypertension	7 (58.3)
Type 2 Diabetes Mellitus	0 (0)
Ischaemic Heart Disease	1 (8.3)
Congestive Cardiac Failure	3 (25)
Stroke/Transient Ischaemic Attack	0 (0)
Left Ventricular Ejection Fraction (%) (n=7)	58.7 (7.7)
Left Atrial Diameter (cm) (n = 6)	4.2 (1.0)

AHI: Apnoea Hypopnea Index, BMI: Body Mass Index, ODI: Oxygen Desaturation Index, PSG: Polysomnography, PVI: Pulmonary Vein Isolation

Table 30: Changes in Sleep Parameters with MAS in situ compared to baseline, including responders and non-responders (n = 10)

PSG Variable	Baseline	MAS in situ	P Value
AHI	33.8 ± 21.5	26.6 ± 25.8	0.505
ODI	30.0 ± 19.7	23.0 ± 26.4	0.511
HI	25.1 ± 22.9	22.6 ± 19.8	0.795
OAI	5.3 ± 7.3	2.8 ± 7.1	0.457
CAI	0.7 ± 0.8	0.7 ± 1.2	0.949
MAI	2.5 ± 6.2	0.5 ± 0.8	0.330
REM AHI	32.7 ± 30.1	31.1 ± 28.7	0.09
REM ODI	30.1 ± 28.8	28.2 ± 26.1	0.875
% Time < 90%	4.1 ± 4.8	7.2 ± 12.5	0.475
Minimum SaO2 (%)	82.0 ± 9.0	81.9 ± 11.5	0.983
TST (hrs)	317.3 ± 75.9	340.7 ± 70.6	0.485
Sleep Efficiency (%)	68.8 ± 14.4	72.1 ± 11.2	0.569
N1 (%)	14.4 ± 9.9	14.2 ± 10.5	0.953
N2 (%)	57.5 ± 10.3	57.3 ± 9.4	0.966
N3 (%)	12.3 ± 8.3	11.5 ± 9.3	0.851
REM Sleep (%)	15.9 ± 7.5	17.0 ± 6.3	0.719
AI (/hr)	35.0 ± 14.2	31.7 ± 23.1	0.708
Time Supine (mins)	79.5 ± 47.9	117 ± 121.7	0.373
% Sleep Time Supine	26.1 ± 16.2	33.3 ± 35.3	0.565
Supine AHI (Non-REM)	54.6 ± 27.6	16.5 ± 16.1	0.001
Supine AHI (REM)	36.2 ± 36.8	18.6 ± 20.1	0.201
% Responders (Strict Definition)	-	40	-
% Responders (Strict + Liberal Definition)	-	60	-

AHI: Apnoea Hypopnea index, AI: Arousal Index, CAI: Central Apnoea Index, HI: Hypopnea Index, MAI: Mixed Apnoea Index, OAI: Obstructive Apnoea Index, ODI: Oxygen desaturation index, PSG: Polysomnography, REM: Rapid Eye Movement, TST: Total Sleep Time

Table 31: MAS Compliance at 3 and 6 Months

Patient	Mean ± SD, or %							
	3 Months				6 Months			
	Average daily use: all days	Average daily use: days used	% of nights with > 4 hours of use:	Used for >4 hours on ≥ 70% of nights	Average daily use: all days	Average daily use: days used	% of nights with > 4 hours of use:	Used for >4 hours on ≥ 70% of nights
1	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
2	8.6 ± 1.5	8.7 ± 1.5	97.8	Y	8.3 ± 2.0	8.6 ± 2.0	95.6	Y
3	7.2 ± 2.2	7.8 ± 2.2	93.3	Y	7.3 ± 2.0	7.7 ± 2.0	95.0	Y
4	5.7 ± 2.4	5.9 ± 2.4	75.6	Y	5.7 ± 2.4	5.9 ± 2.4	78.3	Y
5	4.2 ± 3.7	6.9 ± 3.7	53.3	N	4.1 ± 3.7	7.0 ± 3.7	55.6	N
6	5.2 ± 1.7	5.2 ± 1.7	73.3	Y	6.0 ± 1.7	6.0 ± 1.7	85.0	Y
7	6.6 ± 1.3	6.6 ± 1.3	94.4	Y	6.8 ± 1.1	6.8 ± 1.1	96.7	Y
8	1.7 ± 2.2	4.0 ± 2.2	22.2	N	0.9 ± 1.8	4.0 ± 1.8	11.1	N
9	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
10	6.2 ± 1.4	6.3 ± 1.4	96.7	Y	6.3 ± 1.6	6.4 ± 1.6	92.2	Y
11	3.4 ± 3.8	7.0 ± 3.8	41.1	N	1.9 ± 3.3	7.0 ± 3.3	23.3	N
12	8.0 ± 0.8	8.0 ± 0.8	100.0	Y	8.0 ± 0.7	8.0 ± 0.7	100.0	Y
Average/ Percent	5.7 ± 2.1	6.6 ± 2.1	74.8	70%	5.5 ± 2.0	6.7 ± 2.0	61.1 ± 40.9	70%

Figure 14: Heat map of daily MAS compliance over 180 days in 12 patients

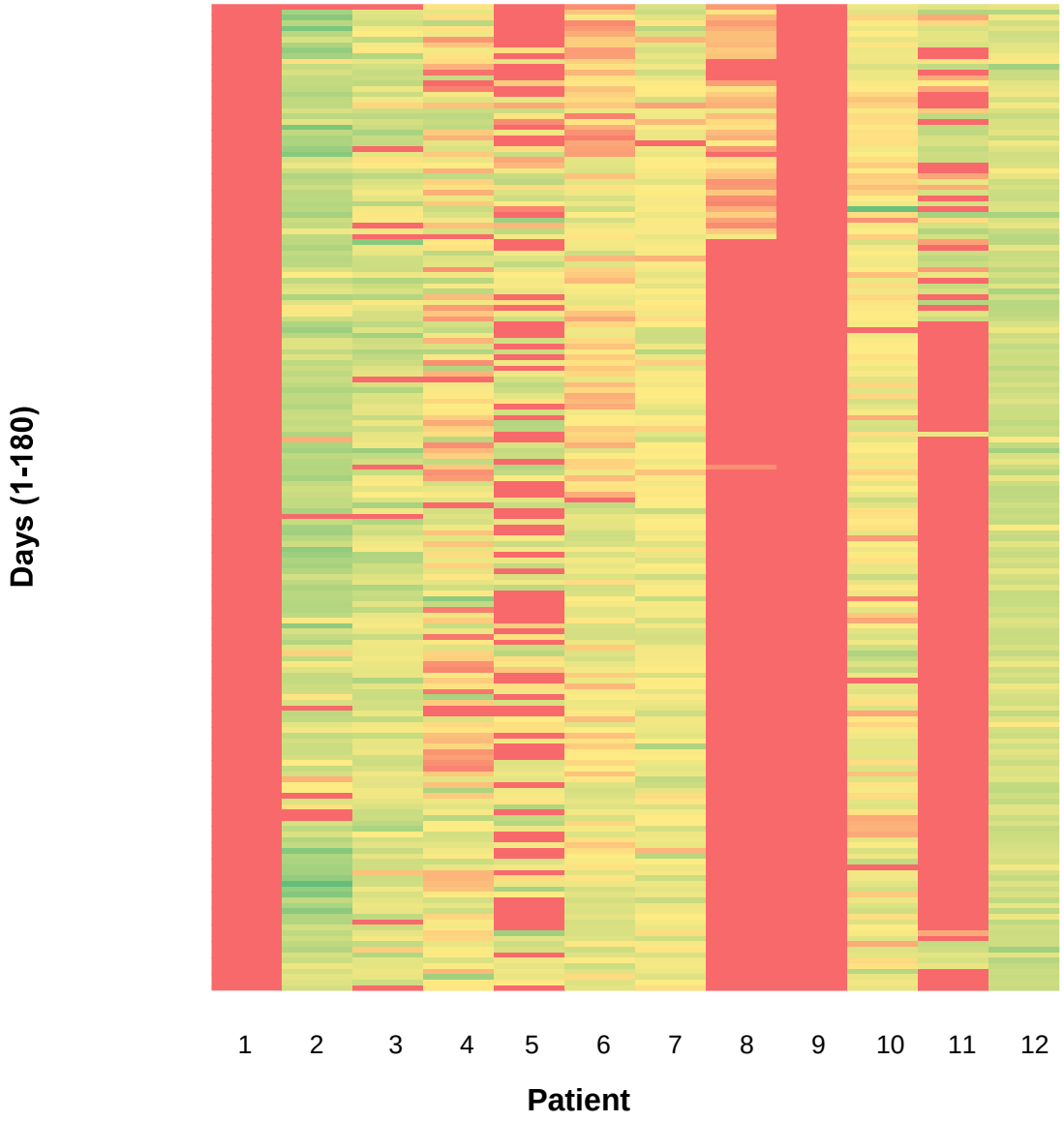


Figure 14 Legend: Hours of MAS usage per night

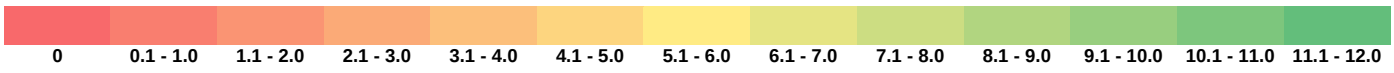
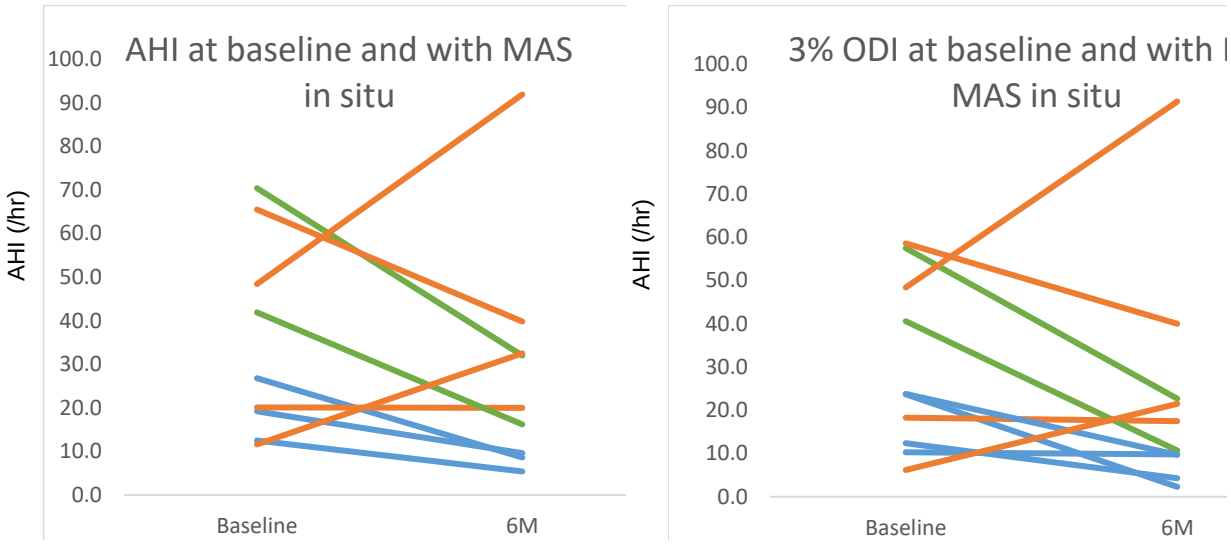


Figure 15: Change in AHI and ODI with MAS in Situ



Key: Blue = responders meeting strict definition only

Green = responders meeting both strict and liberal definition

Orange = Non-responders.

Table 32: MAS Efficacy

Patient	AHI Baseline (/hr)	AHI 6M (/hr)	Overall Change in AHI (/hr)	Change in AHI (improvers only) (/hr)	Overall %Reduction in AHI	% Reduction AHI (improvers only)	Responder (Strict Definition)	Responder (Liberal definition)
1	39.2	n/a	n/a	n/a	n/a	n/a	n/a	n/a
2	70.4	32.0	38.4	38.4	54.5%	54.5%	N	Y
3	26.8	8.6	18.2	18.2	67.9%	67.9%	Y	Y
4	48.4	91.9	-43.5	n/a	-89.9%	n/a	N	N
5	12.5	5.4	7.1	7.1	56.8%	56.8%	Y	Y
6	19.2	9.6	9.6	9.6	50.0%	50.0%	Y	Y
7	20.1	20.0	0.1	0.1	0.5%	0.5%	N	N
8	41.9	16.2	25.7	25.7	61.3%	61.3%	N	Y
9	15.3	n/a	n/a	n/a	n/a	n/a	n/a	n/a
10	65.5	39.8	25.7	25.7	39.2%	39.2%	N	N
11	21.9	10.1	11.8	11.8	53.9%	53.9%	Y	Y
12	11.6	32.5	-20.9	n/a	-180.2%	n/a	N	N
Average/ Total	**32.7**	**26.6**	**7.2**	**17.1**	**11.4%**	**48.0%**	**4 (40%)**	**6 (60%**
SD	20.3	25.8	24.1	12.4	82.2%	20.9%		

Note: patients 1 and 9 did not continue the device beyond one week of therapy. Responder (Strict Definition) = Reduction in AHI ≥50%, Responder (Liberal definition) = Reduction in AHI ≥50% AND a residual AHI < 10/hr.

Table 33: Adherence and Efficacy of Screening tools to detect AF recurrence

Screening tool for AF recurrence	Patient Adherence Rate	Number of patients in whom at least 1 episode of AF was detected over a 6 M period
Daily AlivecorKardia ECG Recording every day for six months	52.9%	7/12 (58.3%)
Holter monitor at baseline and 6 months	62.5%	1/12 (8.3%)
Patient AF diary	79.2%	5/12 (41.8%)
Medical record review at 3 and 6 months	n/a	4/12 (33.3%)

Figure 16: Daily at-home ECGs recorded by 12 AF patients over 180 days on the AliveCor Kardia device

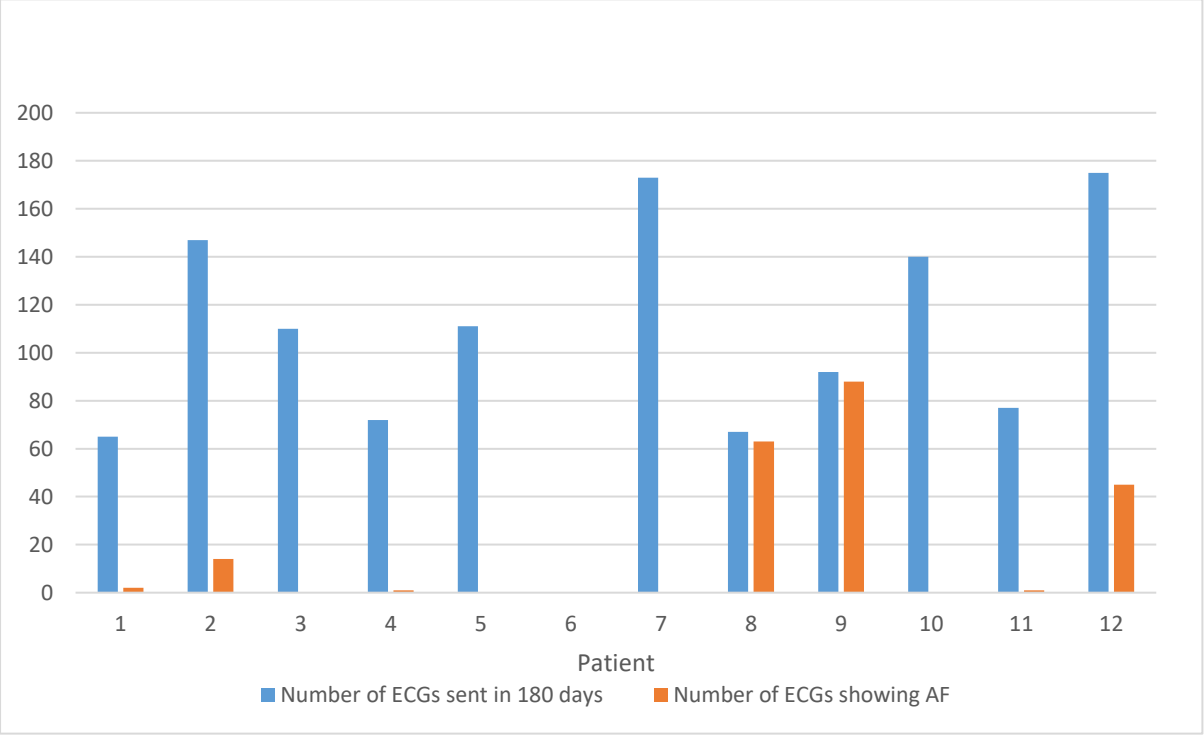
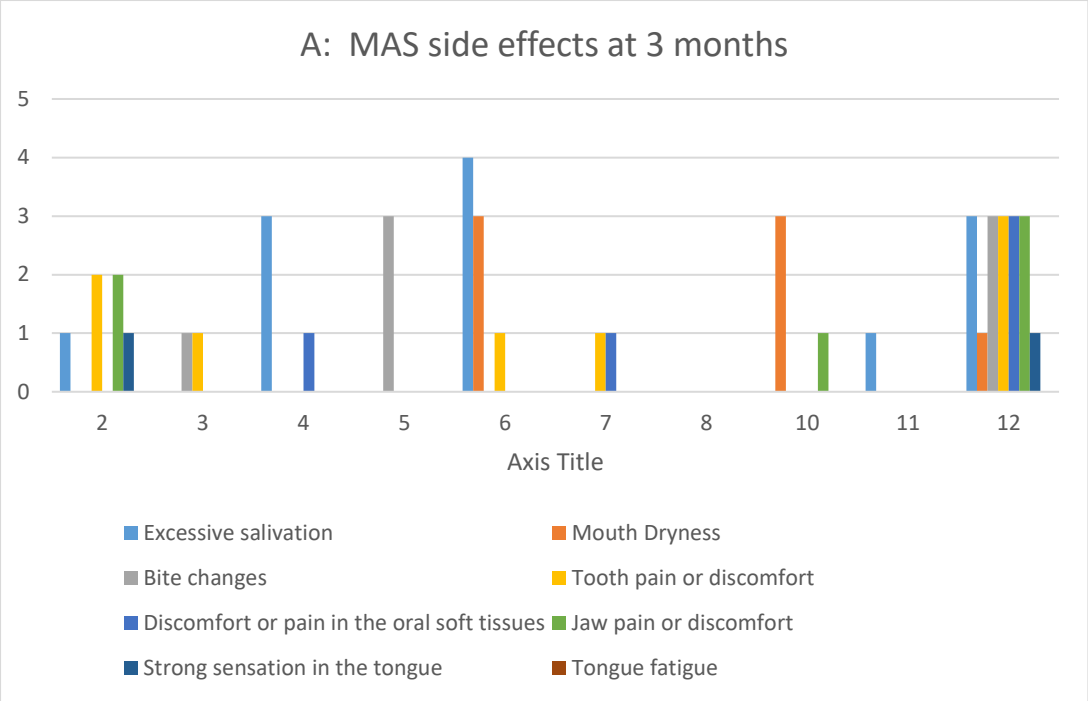


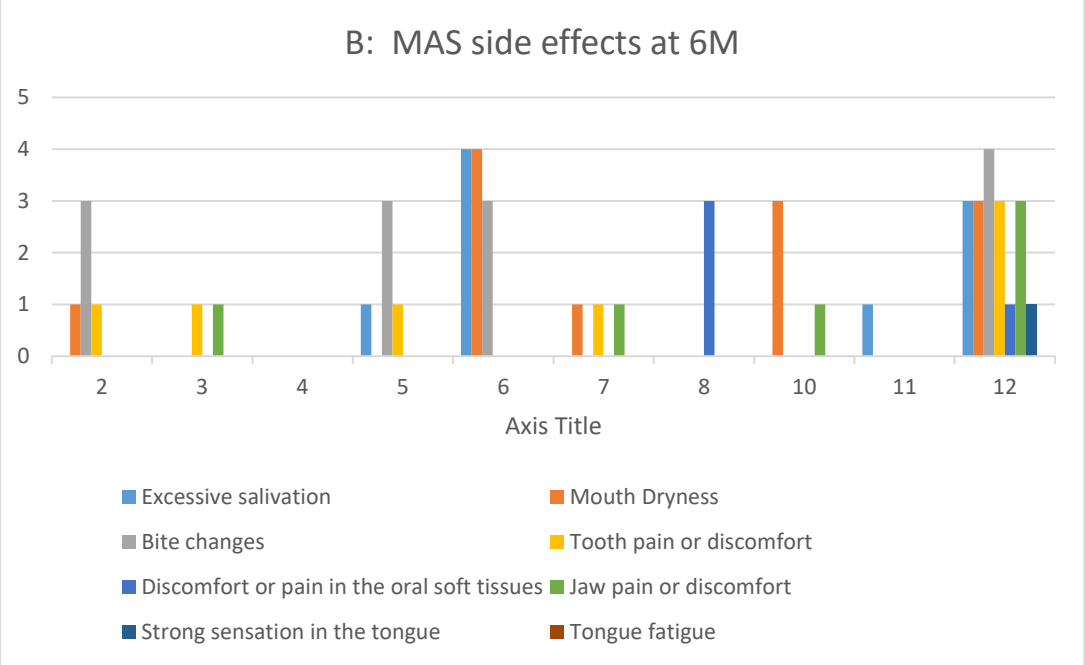
Table 34: Percent of Atrial Fibrillation as recorded on 24 hour Holter monitor at baseline and 6 months.

Patient Code	AF percent baseline	AF percent at 6M
1		
2	0	0
3		
4	0	
5		0
6	0	0
7		0
8	44	
9	0	
10	0	0
11	0	0
12	0	90

NB: greyed squares indicate that Holters could not be performed due to Sars-CoV-2 (COVID-19) government-mandated “lockdown” conditions.

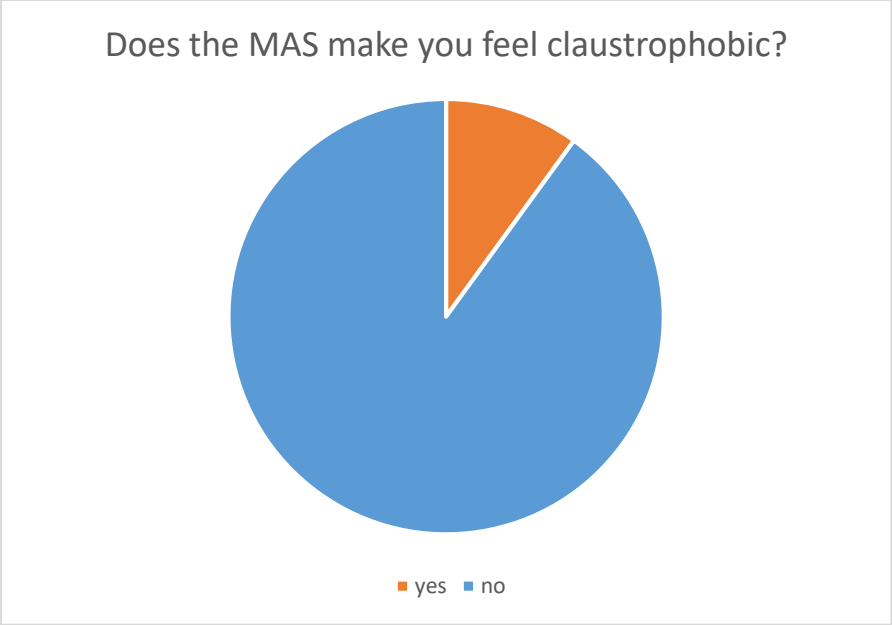
Figure 17: MAS Side Effects at 3 and 6 months in 12 patients with Atrial Fibrillation



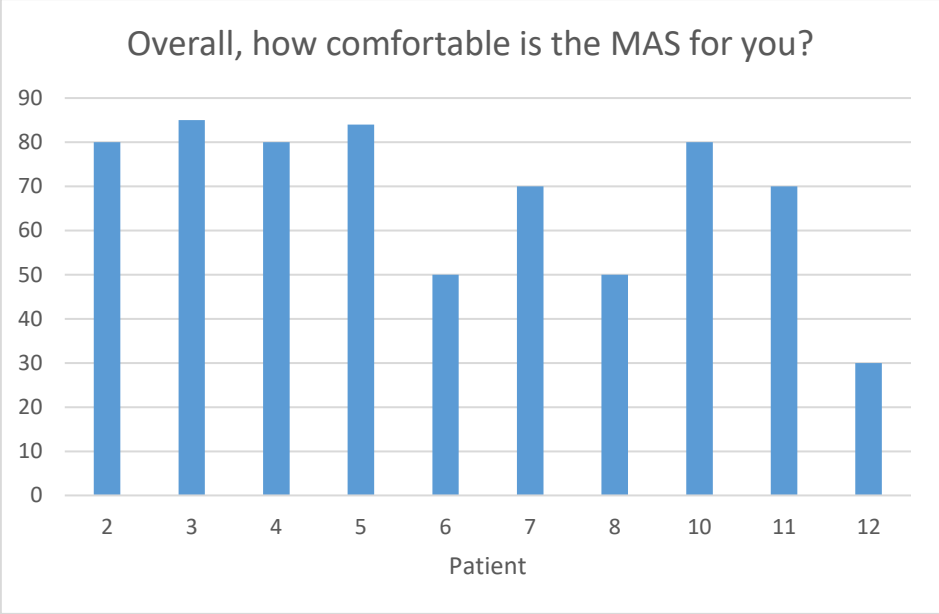


Key: 0 = not at all, 1 = Rare, but hardly disturbing, 2 = Rare but disturbing, 3 = Often, but hardly disturbing, 4 = Often and disturbing, 5 = Always and strongly disturbing NB: patients 1 and 9 did not tolerate the device, so no side effects were reported.

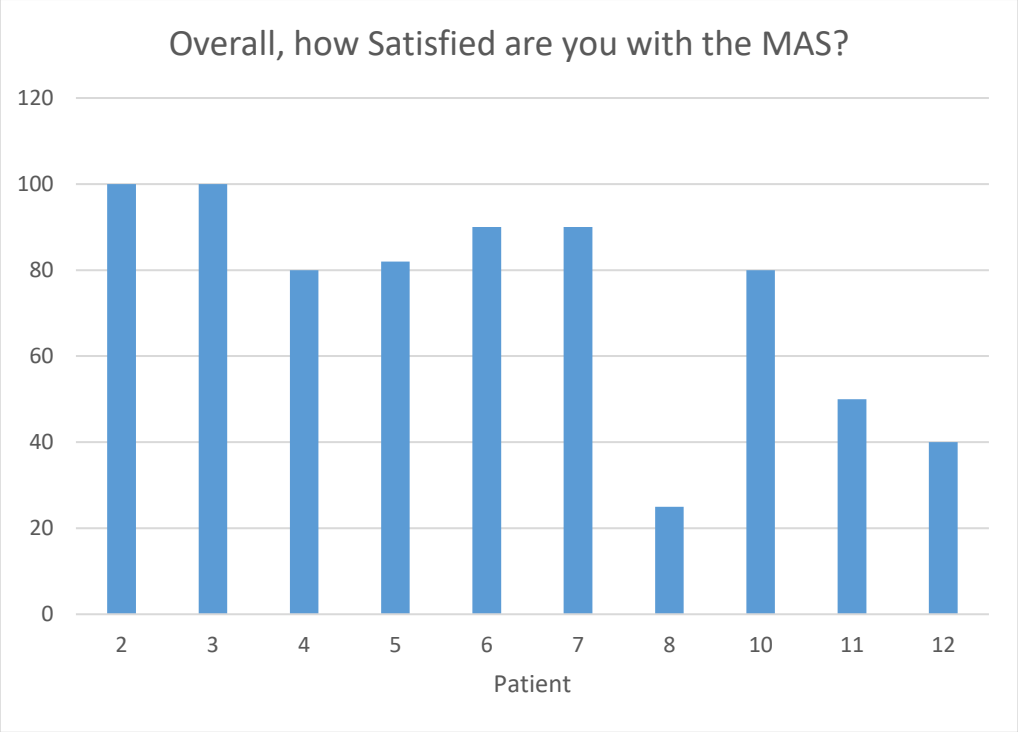
Figure 18: Patient Subjective evaluation of Mandibular Advancement Splint (MAS) therapy after 6 months:



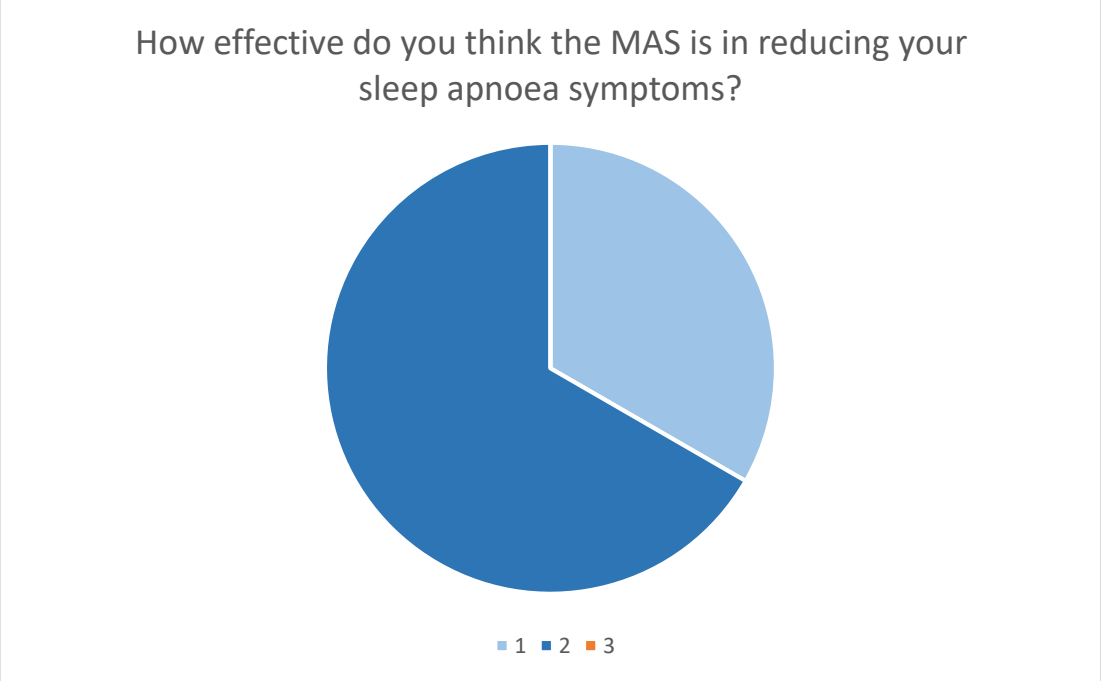
Key: yes (orange), no (blue)



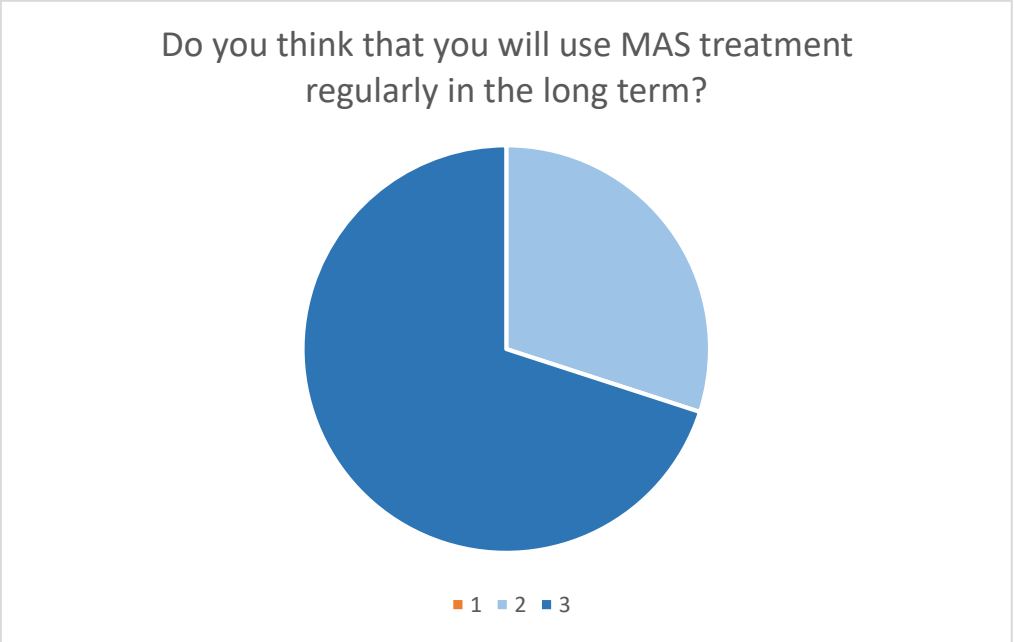
Key: Continuous scale from 1 – 100 where 0 = not comfortable at all, 50 = moderately comfortable, 100 = extremely comfortable



Key: Continuous scale from 1 – 100 where 0 = not satisfied, 50 = moderately satisfied, 100 = extremely satisfied



Key: 1 (light blue) = somewhat effective, 2 (dark blue) = very effective, 3 (orange) = not effective



Key: 1 (orange) = No, will not use MAS regularly, 2 (light blue) = Yes, may use MAS regularly, 3 (dark blue) = Yes, will definitely use MAS regularly

Table 35: Quality of Life scores (AFEQT and FOSQ10) at baseline, 3 and 6 months

	Baseline	3 Months	6 Months	P value
AFEQT	80.0 ± 16.0	74.3 ± 17.3	84.0 ± 14.5	0.411
FOSQ10	16.3 ± 2.3	17.2 ± 2.8	17.5 ± 3.4	0.634

Table 36: SF-36 Scores at Baseline, 3months and 6 months

Domain	**Baseline**	**3 Months**	**6 Months**	**P value**
Physical Functioning	75.4 ± 17.5	79.5 ± 18.1	87.4 ± 9.7	0.218
Role Limitations due to Physical Health	67.7 ± 29.1	76.1 ± 24.2	80.0 ± 26.0	0.542
Role Limitations due to emotional Problems	84.0 ± 22.0	82.6 ± 21.9	85.0 ± 15.6	0.962
Energy/Fatigue	52.6 ± 24.1	55.7 ± 26.4	59.0 ± 23.8	0.842
Emotional Well-being	73.3 ± 16.8	75.9 ± 16.4	73.9 ± 12.4	0.919
Social Functioning	79.2 ± 18.7	80.7 ± 21.9	75.0 ± 21.2	0.810
Pain	72.1 ± 28.0	82.7 ± 18.5	81.3 ± 18.1	0.473
General Health	63.3 ± 8.9	65.9 ± 14.8	64.5 ± 14.6	0.892

Table 37: 24 Hour Ambulatory Blood Pressure at Baseline and 6 Months

	Baseline	6 Months	P value
Overall systolic (cmH_2O)	128.5 ±14.4	126.3 ± 16.2	**0.764**
Overall diastolic (cmH_2O)	75.3 ± 5.6	75.8 ± 9.6	**0.894**
Awake systolic (cmH_2O)	132.1 ± 14.1	132.5 ± 15.3	**0.457**
Awake diastolic (cmH_2O)	78.4 ± 6.6	80.8 ± 8.7	**0.590**
Asleep systolic (cmH_2O)	119.2 ± 18.2	112.6 ± 17.7	**0.954**
Asleep diastolic (cmH_2O)	67.1 ± 71	64.9 ± 10.2	**0.512**

4.6 DISCUSSION

This is the first study to assess MAS treatment for OSA in patients with atrial fibrillation, and was conducted to inform the design of a future clinical trial. This pilot study provides a detailed spectrum of information about MAS therapy in AF patients, including MAS acceptance, compliance, efficacy, side effects, quality of life, cardiovascular parameters and AF recurrence. It also assesses the feasibility of research tools used to collect this information.

OSA is acknowledged as a treatable risk factor for AF, and may precipitate and perpetuate AF via a number of pathophysiological mechanisms. Intra-thoracic pressure changes caused by respiratory effort against an occluded upper airway may induce acute atrial wall mechanical stretch. Over time this leads to chronic atrial remodelling (285). Additionally, intermittent hypoxia leads to increased sympathetic nervous system activation; both of which are arrhythmogenic (286). Treatment of OSA as part of an holistic, aggressive risk factor reduction strategy has been shown to reduce AF recurrence after ablation (287). Only two small randomised controlled trials have assessed the impact of OSA treatment alone on AF burden. Caples et al looked at a small group of OSA patients randomised to CPAP (n=12) vs usual care (n=13) following cardioversion for AF, and found no difference in AF recurrence between groups (203). Similarly, Traaen et al treated 55 AF patients with moderate to severe OSA with CPAP and found no difference in AF burden measured by implantable loop recorder when compared to the control group (n = 54) (144). In both these studies CPAP compliance exceeded 4 hours per night, however these preliminary studies are small and larger RCTs are required. Other randomised studies looking at CPAP usage

in larger cardiovascular populations have found compliance rates to be well below the minimum recommended compliance threshold of 4 hours / night (13, 14, 51). In our study of MAS therapy for AF patients we found a comparatively high average nightly treatment usage time of 5.5 ± 2.0 hours. We found MAS efficacy rates to be generally consistent with that of previously reported studies (30), with 60% meeting the liberal criteria for MAS response (improvement in AHI ≥50%), and 40% the more rigorous criterion for MAS response (improvement in AHI ≥50% with a residual AHI ≤ 10/hr).

As with CPAP, which has inbuilt compliance data recorders, compliance with MAS therapy can now be objectively monitored via a temperature-sensitive data chip. A compliance threshold of > 4 hours / night on 70% of nights is commonly used in the clinical management of CPAP therapy and has similarly been applied to MAS therapy (120). In our study this threshold was achieved by 80% of patients who initially accepted therapy, at both 3 and 6 months. A previous study analysed compliance patterns in further detail, applying cluster analysis to identify discrete subtypes of MAS usage, namely consistent users, inconsistent users and non-users (118). In our study, a heat map of nightly compliance data (figure 13) reveals that most patients (70%) fit the pattern of consistent usage, ie. high usage hours on most nights of treatment, with one patient (patient 5) falling into the “inconsistent user” subtype (moderate-to-high usage on some nights with irregular non-usage nights). Two patients (patients 8 and 11) fell into the non-users subtype, in this case both patients used their MAS device very little after the initial 2 months (figure 13). Interestingly however, both these patients indicated that they would continue to use the MAS in the long term (figure 17). Only two patients (patients 1 and 9) did not accept the therapy, demonstrating no usage after the initial run-in period of one week.

MAS side effect profiling at multiple time points allowed us to evaluate the evolution of particular side effects over time. For example, excessive salivation became less prevalent between 3 and 6 months, whereas bite changes became more prevalent/more severe between 3 and 6 months. This early progression of changes are consistent with the known evolution of MAS side effects over time. Subtle dental movement is a common long-term side effect of MAS therapy, with treatment length associated with the magnitude of change (288).

The measurement of AF recurrence presents inherent challenges due to the intermittent nature of AF episodes, which may occur outside periods of monitoring. The gold standard for AF monitoring, implantable loop recorders, provide continuous 24 hour monitoring, which ensures that no episodes of paroxysmal AF will be missed. However, loop recorders are surgically implantable devices; they are thereby invasive and carry all the risks of implanted foreign bodies. In addition, they are resource intensive and must be implanted by specialist practitioners. In this study we have utilised four non-invasive methods to report on AF recurrence and compared the feasibility and results of all these methods. Alivecor Kardia is a validated portable single lead ECG recording device. It has been found to be three times more likely to detect incident AF in high risk patients than routine clinical care when used twice weekly, and has been suggested as a routine clinical screening tool (280). In our study, daily at-home ECG recordings detected more AF than the other non-invasive methods of AF screening with 19.2 ± 36.1% of all recorded ECGs demonstrating AF. At least one episode of AF was captured in 7 out of 12 patients, 58.3%. Alivecor

Kardia was therefore more effective than other methods of AF monitoring including serial Holter monitors at baseline and 6 months, patient diary or medical record review. Patients displayed a moderately high degree of compliance with the instructions to record a daily ECG, with an average of 102.4 ± 28.3 ECGs sent over a 180 day period. In addition, Alivecor Kardia has the added advantage of being portable and accessible to the patients in their own home. This had the unanticipated advantage in our study of allowing ongoing acquisition of daily ECGs despite government-mandated "lockdowns" during 2020/21 in the setting of the SARS-CoV-2 (COVID-19) pandemic, which prevented patients from leaving their homes to participate in other forms of ECG monitoring such as 24 hour Holter.

Health related quality of life as assessed by the SF-36 questionnaire showed improvements in 7 out of 8 domains at six months when compared to baseline, however, none of these results were statistically significant. This is likely due to the small sample size and the results should be repeated in a larger sample. Similarly, there were non-significant improvements in the AFEQT and FOSQ-10 after 6 months of MAS therapy when compared to baseline. Previous studies have shown comparable improvements in the SF-36 and the FOSQ-10 with both MAS and CPAP therapy (26, 289, 290). No studies have previously looked at AF–related quality of life, assessed by the AFEQT following OSA therapy. Implementation of the quality of life questionnaires was highly feasible, and when collected online via an automated system returned a completion rate of between 89 and 94%, suggesting that they could be successfully applied to a larger trial.

Similarly MAS patient-centred (subjective) assessment scores at six months were completed by all 10 patients who accepted the MAS with a completion rate of 100%.

Our study was not powered to detect blood pressure changes on therapy, but did allow assessment of the feasibility of including this outcome in a clinical trial. All patients tolerated the assessment with a completion rate of 100%. In our study there were no statistically significant changes in blood pressure, however a trend towards lower blood pressure during sleep after six months of MAS therapy may be observed. Animal studies have demonstrated that nocturnal blood pressure increases with recurrent occlusion of the upper airway, and that this increase in blood pressure persists into wake (192). Improvements in 24 hour blood pressure have been well demonstrated with both CPAP and MAS therapy in OSA patients, to a similar degree for both treatments (25, 26). With increasing statistical power, we would expect this finding to be replicated in a future, larger RCT of OSA treatment in AF patients.

In applying the results of this pilot study to the design of a proposed, larger randomised control trial, we have shown that MAS therapy has a high level of patient acceptance among AF patients, and that efficacy rates are similar to those demonstrated in other populations. The portable ECG device (AliveCor Kardia) was the most effective non-invasive device for the detection of AF recurrence, despite a modest daily compliance rate of 52.9%, Methods to improve adherence such as a daily text message reminder could be considered. Other secondary outcomes such as quality of life scores and PROMS as well as ambulatory blood pressure recordings were highly feasible with high compliance rates and could easily be applied to a larger trial.

4.7 CONCLUSION

This study provides an in-depth characterisation of MAS therapy in a cohort of AF patients. MAS showed a high level of acceptance and compliance, with efficacy rates in keeping with previously reported studies. Importantly, the compliance rate is much higher than that demonstrated for CPAP studies in cardiovascular populations, suggesting that MAS may have a significant role to play in the treatment of OSA in AF patients. The feasibility of outcome measurements were assessed, and in particular the use of a daily at-home ECG was identified as superior to other assessed methods for the identification and documentation of AF episodes. This pilot study provides important information to inform a larger randomised control trial, and suggests that MAS may have a significant role to play in addressing OSA as a risk factor in the treatment of atrial fibrillation.

5.0 Conclusions and Future Directions

This thesis manuscript has sought to address some of our knowledge deficits regarding the association between OSA and AF. Although international guidelines recommend treatment of underlying OSA in AF patients, optimal clinical pathways for its diagnosis and management are not established. Furthermore, possible mechanistic pathways that link these conditions, including cardiac autonomic dysregulation, and inflammation, remain poorly understood.

Chapter 2 reports a study of 107 sequential AF patients recruited from two Australian tertiary referral centres. Patients were recruited regardless of the presence or absence of any OSA symptoms, and patients with a known prior diagnosis of OSA were excluded. This is important and highlights the very high prevalence of undiagnosed OSA among a hospital-based AF cohort, even in those who are asymptomatic. All patients underwent full in-laboratory PSG, the gold standard investigation for OSA. This has been done in only very few previous prospective studies, yet is important considering the limited utility of screening by symptoms or questionnaires. We demonstrated a high prevalence (62.6%) of previously undiagnosed OSA amongst AF patients: (31.8% mild, 18.7% moderate, 12.1% severe) (291).

In addition to the prevalence findings, the study presented in Chapter 2 is the first study to report on the diagnostic accuracy of a level 3 portable sleep study device as a screening tool for OSA in patients with atrial fibrillation. We found a high level of diagnostic accuracy for moderate to severe OSA (AHI ≥ 15/hr) in an AF population

(AUC 0.899; 95% confidence interval, 0.838-0.960). Although the diagnostic accuracy of these devices has previously been reported in non-cardiac populations, the importance of validating the study in an AF cohort is highlighted by our finding that traditional OSA screening tools such as the presence of snoring, self-reported sleepiness and obesity perform poorly in an AF cohort. Further, we confirmed that commonly used questionnaires such as the Berlin questionnaire or STOP-BANG questionnaire perform with only poor to fair diagnostic accuracy in AF populations (164, 166, 291). This study therefore makes a significant contribution to clinical practice, since the level 3 portable sleep study is relatively inexpensive, portable and less resource-intensive when compared to PSG. Future studies should confirm its translation into clinical practice and feasibility for large-scale screening programs in AF patients, particularly in regional and remote areas.

In chapter 3 of this manuscript, heart rate variability, a marker of cardiac autonomic function, was used to compare AF patients with and without OSA (292). This study was conducted in order to further explore autonomic dysregulation as a possible mediator between OSA and AF. Overall, there were limited differences between the groups. However, there was some evidence of increased parasympathetic modulation and decreased sympathetic modulation in the OSA group during non-REM sleep. This exploratory study does not explain why an increase in chronic parasympathetic modulation was found in AF patients with OSA compared to those without, though possible explanations are discussed. However, these changes may support the hypothesis that OSA predisposes to the development and perpetuation of AF through perturbations in cardiac autonomic modulation, and this paves the way for further research in this area. Subsequent studies are required to look at the effect of OSA

treatment on cardiac autonomic modulation, and indeed whether this has an impact on AF burden and outcomes.

The final data chapter, Chapter 4, focussed on a treatment study of OSA in AF patients. Previous studies have shown that the usual first line therapy for OSA, continuous positive airway pressure (CPAP) therapy, has proven disappointing in terms of both compliance and outcomes in cardiovascular populations (12, 14, 210). Therefore, a pilot treatment study of mandibular advancement splint (MAS) therapy for OSA in AF patients was conducted. This study provides a detailed analysis of MAS therapy in an AF cohort, and showed that MAS therapy is associated with high levels of treatment acceptance and compliance in AF patients, with efficacy levels consistent with those in non-cardiovascular populations. The high average nightly treatment usage time of 5.5 ± 2.0 hours is encouraging when compared to average CPAP usage times found in previous large studies of cardiovascular populations, and suggests that MAS therapy may have an important role to play in OSA therapy for AF patients. Although only 60% of MAS users were technically classified as MAS responders, 70% of patients indicated that they would continue to use MAS in the long term, indicating a high level of patient-perceived benefit from MAS therapy. Future large RCT studies of OSA therapy in AF patients are required to assess the impact of effective OSA therapy on important AF outcomes, including AF burden, AF recurrence rates following rhythm control strategies and complications of AF, particularly embolic stroke. These trials should choose their target population well given that previous studies in cardiovascular populations have been criticised for looking at secondary preventive outcomes. In the case of AF, it may be that patients with advanced chronic atrial remodelling have progressed too far past the point where OSA therapy can be of

benefit. In addition, as was shown in Chapter 4, different methods for quantifying AF recurrence produce highly variable results, and this needs to be considered in future trial designs. Paroxysmal AF, by definition, is intermittent, and only continuous monitoring over a prolonged period, such as with an implantable cardiac device, can best capture AF burden in the individual patient. Rather than focusing on one treatment modality alone, a trial which focuses on effective OSA therapy targeted to the specific patient, either with CPAP or MAS, may be more successful in achieving clinically relevant OSA control in the greatest number of patients.

Overall, the studies presented in this thesis depict a number of facets in the relationship between OSA and AF, from pathophysiological mechanisms, to OSA prevalence, diagnosis and treatment in an AF cohort. Future research should focus on answering the as-yet elusive question, whether effective OSA therapy can reduce the incidence and progression of AF, and which patients are most likely to derive a benefit. This thesis has helped shape such future research by providing some preliminary evidence that MAS therapy is likely to be an effective option, and by highlighting the importance of continuous cardiac monitoring for the assessment of AF recurrence in the context of OSA therapy.

List of Figures

List of Tables

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Appendix: Patient Questionnaires

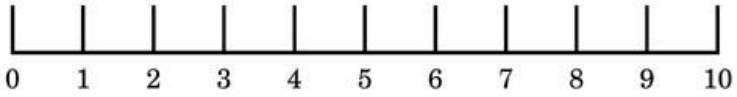
Patient-centred paired Visual Analogue Scales were used to evaluate the patient's subjective assessment of In-laboratory Polysomnography Vs a Level 3 Portable Sleep Study Device

Health
Northern Sydney
Local Health District

Patient Feedback Form

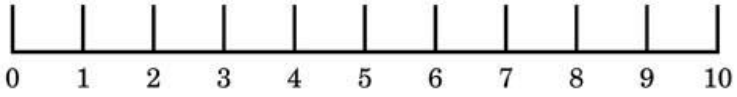
Please answer the following questions with regards to your in-hospital Sleep Study (Polysomnography):

On a scale from 1 to 10, how **comfortable** did you find the in-hospital sleep study?



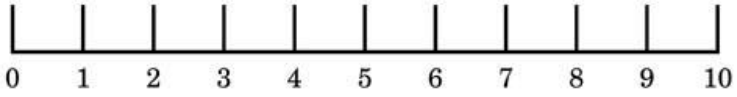
Not comfortable Neutral Very comfortable

On a scale from 1 to 10, how **convenient** did you find the in-hospital sleep study?



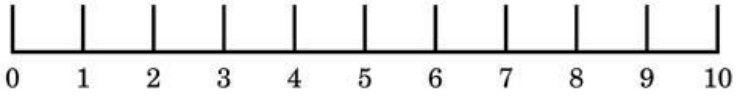
Not convenient Neutral Very convenient

On a scale from 1 to 10, how **closely** did your sleep pattern on the in-hospital study night match your normal sleep pattern at home?



Not close to normal sleep Neutral Very close to normal sleep

On a scale from 1 to 10, how **confident** were you in the results from the in-hospital sleep study?



Not confident Neutral Very confident

Please answer the following questions with regards to your at-home Sleep Study (ApneaLink):

On a scale from 1 to 10, how **comfortable** did you find the at-home sleep study?

Not comfortable Neutral Very comfortable

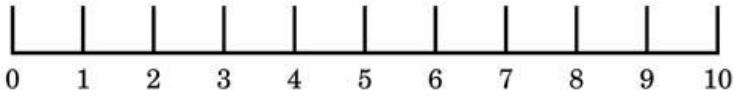
On a scale from 1 to 10, how **convenient** did you find the at-home sleep study?

Not convenient Neutral Very convenient

On a scale from 1 to 10, how **closely** did your sleep pattern on the at-home study night match your normal sleep pattern at home?

Not close to normal sleep Neutral Very close to normal sleep

On a scale from 1 to 10, how **confident** were you in the results from the at- home sleep study?



Not confident Neutral Very confident

Overall, which sleep test did you prefer?

☐ In-hospital study (Polysomnography)

☐ At-home study (ApneaLink)

☐ Neither

☐ Either

Why?

Do you have any other comments?