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Obstructive sleep apnea and its management in patients with atrial fibrillation: An International Collaboration of Sleep Apnea Cardiovascular Trialists (INCOSACT) global survey of practicing cardiologists

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ABSTRACT

Background: Among international cardiologists it is unclear whether equipoise exists regarding the benefit of diagnosing and managing obstructive sleep apnea (OSA) to improve atrial fibrillation (AF) outcomes and whether clinical practice and equipoise are linked.

Methods: Between January 2019 and June 2020 we distributed a web-based 12-question survey regarding OSA and AF management to practicing cardiologists in 16 countries.

Results: The United States, Japan, Sweden, and Turkey accounted for two-thirds of responses. 863 cardiologists responded; half were general cardiologists, a quarter electrophysiologists. Responses regarding treating OSA with CPAP to improve AF endpoints were mixed. 33% of respondents referred AF patients for OSA screening. OSA was diagnosed in 48% of referred patients and continuous positive airway pressure (CPAP) was prescribed for 59% of them. Nearly 70% of respondents believed randomized controlled trials (RCTs) of OSA treatment in AF patients were necessary and indicated willingness to contribute to such trials.

Conclusions: There was no clinical equipoise among surveyed cardiologists; a majority expressed certainty that combined OSA and AF treatment is superior to AF treatment alone for improving AF outcomes. However, a minority of surveyed cardiologists referred AF patients for OSA testing, and while half of screened AF patients had OSA, CPAP was prescribed in little more than half of them, reflecting the view that better clinical trial evidence is needed to support this practice. Our results underscore the need for larger, multi-national prospective studies of OSA treatment and AF outcomes to inform more uniform society guideline recommendations.

1. Introduction

The International Collaboration of Sleep Apnea Cardiovascular Trialists (INCOSACT) is a consortium of sleep medicine physicians, cardiologists and researchers representing 16 countries with a common interest in generating evidence-based data to inform approaches to OSA treatment as a strategy for improving CVD outcomes [1].

Obstructive sleep apnoea (OSA) is a global health crisis intimately related to the global obesity epidemic. In the United States OSA affects 17 % of adult women and 34 % of adult men, with recent trends supporting rising incidence rates nationally [2] and internationally [3]. OSA is closely associated with features of the metabolic syndrome including insulin resistance, dyslipidemia, hypertension and central adiposity [4]. This association with the metabolic syndrome and its deleterious influence on inflammation, oxidative stress, and endothelial dysfunction likely accounts for a large portion of the association between OSA and CVD [5].

Sleep apnea is highly prevalent among patients with cardiovascular disease. Data from large prospective patient registries have revealed that sleep apnea, OSA in particular, is essentially endemic in outpatient and inpatient cardiology settings worldwide [3,6,7]. OSA has been closely associated with prevalent and incident hypertension [8], coronary artery disease [9,10], congestive heart failure [11], stroke [12] and cardiac rhythm disorders, atrial fibrillation (AF) in particular [13].

AF is the most common arrhythmia in the world, affecting at least 3 million individuals in the United States alone and over 34 million people worldwide [14]. The pathogenesis of AF is complex and incompletely understood, but is believed to involve both abnormal atrial tissue substrates as well as triggers of abnormal electrical activity, with abnormal impulses often arising from the pulmonary vein ostia [15]. OSA may predispose to the development of AF both through its acute influence on autonomic tone and intrathoracic pressures, as well as through modulating chronic changes to the underlying atrial tissue substrate [16]. Not surprisingly the prevalence of moderate or greater severity OSA is as high as 40 % in patients with AF [17,18], and similar to the prevalence of AF in patients with moderate-or-severe OSA [19].

The relationship between OSA and AF is broadly recognized by cardiovascular societies internationally, with most management guidelines acknowledging this relationship and many recommending screening for and in some cases treating OSA in patients with AF with the goal of improving AF outcomes (Table 1). However, the evidence supporting these guideline recommendations is largely based on consensus opinion (level of evidence, LOA C), driven by the strong epidemiologic association between obesity, OSA and AF and the biologic plausibility that OSA-related physiologic, biochemical and structural influences on the heart are arrhythmogenic [20–22]. There are currently no randomised clinical trial data that unequivocally support OSA treatment solely to improve AF outcomes, with one contemporary randomised trial showing no short-term improvement in AF burden in OSA patients treated with continuous positive airway pressure (CPAP) versus usual care [23]. Thus, despite a general consensus among guideline writing committees around the world that one should consider screening for and treating OSA in AF patients these recommendations lack a rigorous scientific basis. Furthermore, the opinions of cardiologists worldwide regarding the relationship between OSA and AF and the impact of those opinions of their clinical practice habits is not known.

In this INCOSACT study, we aimed to conduct a global online survey to determine the perceived importance among cardiologists of recognizing and treating OSA to improve the management of atrial fibrillation AF. A second aim was to determine whether current professional guidelines for AF management, which all recognise OSA as a risk factor for AF (and in some cases recommend OSA treatment), reflect real world beliefs and practices amongst cardiologists internationally. The survey was also used to gauge the level of interest amongst respondents for participating in randomised controlled trials that seek to clarify the evidence base for OSA treatment to improve AF outcomes. Such trials would ultimately provide crucial data that will influence future AF guideline development and AF management.

2. Materials and methods

A small team with members from both the cardiovascular and sleep specialties developed the survey based upon a consensus approach. The methods used for exploring issues of clinical equipoise were like those used in a previous survey of otolaryngology surgeons who perform upper airway surgery for OSA [24].

Survey Rationale. Our 12-question survey was divided into 3 sections with questions designed to understand:

(1) The background cardiology discipline of the respondents, how important they rate common atrial fibrillation risk factors and their experience with failure rates for the most common atrial fibrillation

[1] see supplement for complete listing.

treatments.

(2) Referral activity and factors influencing referral practices for OSA diagnosis and treatment within the context of atrial fibrillation management.

(3) The need for (a) further research linking OSA with AF and (b) clinical trials quantifying OSA treatment impact on AF outcomes and whether there is clinical equipoise for OSA treatment to mitigate adverse AF outcomes.

Survey Portal and Dissemination. Local ethics approvals or waivers were granted for each country surveyed. These were based on the survey's low risk status with no collection of data that could identify the survey respondents. The anonymized survey was implemented through a web-based portal on a secure, password protected cloud-based server, hosted in Sydney, Australia. The survey was accessible from both desktop computers and mobile telephones. The survey was designed to only capture complete responses for all 12 questions; data from respondents that began the survey but failed to finish it were not collected or counted. Consequently, incomplete responses were not saved. Survey versions were available in English, German, Japanese, Portuguese, Spanish and Turkish languages. Self-nominated country leads from within the INCOSACT membership were tasked with disseminating the online survey within their home countries with assistance from cardiologist colleagues. Introductory information and a link to the survey was provided through cardiology professional societies at scientific meetings via newsletters on scientific meeting and society websites, through group membership on the social media platform Twitter © and directly via email to staff (Japan, Australia, others). Societies and meetings involved in the survey included the American Heart Association (AHA), American College of Cardiology (ACC) including Ohio ACC, Heart Rhythm Society (HRS), Canadian Cardiovascular Society, Canadian Heart Rhythm Society, Cardiac Society of Australia and New Zealand (CSANZ), Taiwan Society of Cardiology (TSOC), the Brazilian Society of Cardiac Arrhythmias (SOBRAC) and Sociedade de Cardiologia do Estado de São Paulo (SOCESP), Brazil), the German Society of Cardiology, the Spanish Cardiology Society and Spanish Respiratory Society, the Swedish Cardiology Society and the Turkish Society of Cardiology.

Practice Guidelines. Table 1 shows the range of practice guidelines [25–31] used by surveyed countries with reference to OSA as a recognised risk factor for AF and whether it is recommended that OSA be treated as part of AF management.

3. Results

The survey was distributed to cardiologists from 16 counties (Australia, Brazil, Canada, China, France, Germany, Hong Kong, Japan, New Zealand, Singapore, Spain Sweden, Taiwan, Turkey, UK and USA). The survey was open between January 2019 and June 2020 and a total of 863 cardiologist responses were collected. Approximately-two-thirds of the total responses were from the United States (22 %), Japan (15.9 %), Sweden (13.9 %) and Turkey (14.4 %) (Fig. 1).

Q1: What area of cardiology discipline do you mostly practice in?

Nearly-one-half of respondents (48.6 %) described themselves as general cardiologist and one-quarter (25.7 %) described themselves as electrophysiologists. The remaining respondents described themselves as intervention cardiologists (11.7 %), heart failure specialists (6.8 %), cardiac imaging experts (3.1 %) and 'other' (4.1 %).

Q2: In your patients with AF that is not permanent, approximately what proportion fail the following?

Among patients with paroxysmal or persistent AF, the highest reported failure rate was for AF anti-arrhythmic drug therapies (43 %, n = 767). Cardioversion failure rates were lower at 23 %, (n = 753). First and second ablation procedure failure rates were 26.9 % (n = 725) and 17.3 % (n = 655), respectively.

Q 3: Please rate the importance of the following as risk factors for first AF or AF recurrence.

Most risk factors were rated as "extremely important" or "very important" and when combined, congestive heart failure was rated the most important risk factor amongst the 12 listed. OSA was rated third most important.

Q4: How easy is it for your AF patients to access OSA diagnostic/

Table 1
Current international guideline recommendations pertaining to obstructive sleep apnoea (OSA) and atrial fibrillation (AF).

Society *Adherent countries (bibliography reference)*	Publication Year	OSA listed as an AF risk factor?	Recommends OSA screening?	Recommends OSA treatment?
ACC / AHA / HRS (25) *USA* *Brazil*	**2014** update 2019	**Yes** Pathogenesis	**Yes, in recurrent AF** ** Statement published after completion of this survey (26) .	**No recommendation**
CCS (30) *Canada*	**2020**	**Yes** Pathogenesis Treatment failure	**Yes** For most AF patients	**Yes** To reduce recurrence rates
CSANZ (28) *Australia* *New Zealand*	**2018**	**Yes** Pathogenesis Treatment failure	**Yes** In patients with recurrent symptomatic AF	**Yes** In patients with recurrent AF
EHRA (29) (endorsed by **HRS** and **APHRS**) *Japan* *Taiwan* *Hong Kong* *China* *Singapore*	**2017**	**Yes** Potential pathogenesis	**Yes** If clinically indicated	**No recommendation**
ESC (27) *Germany* *France* *Sweden* *United Kingdom* *Turkey* *Spain*	**2020**	**Yes** Pathogenesis Treatment failure	**Yes** Prior to rhythm control strategy	**Yes** To reduce recurrence rates
Taiwan Heart Rhythm Society / Taiwan Society of Cardiology (31) *Taiwan*	**2016**	**Yes** Epidemiology	**No**	**No**

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; HRS, Heart Rhythm Society; ESC, European Society of Cardiology; CSANZ, Cardiac Society of Australian and New Zealand; EHRA, European Heart Rhythm Society; APHRS, Asia Pacific Heart Rhythm Society; CCS, Canadian Cardiovascular Society.

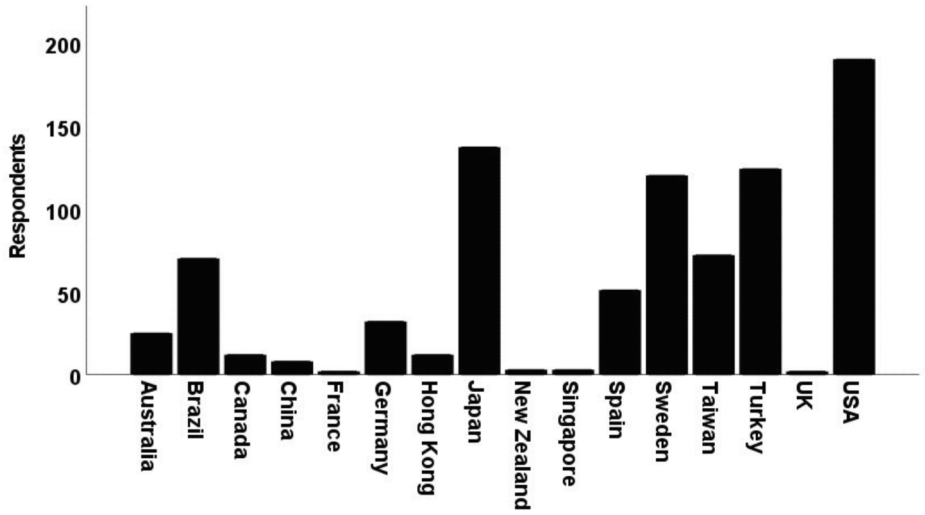

Fig. 1. Proportions of total survey responses by country of origin.

treatment services?

Access to OSA diagnostic and treatment services were deemed easy or very easy in 56.7 % of respondents. In contrast, 40.1 % found access either difficult or very difficult. In a sub-analysis broken down for countries with the largest responses, Australia, Germany, Japan, Spain, Sweden, and the USA found access mostly easy or very easy (range 52–70 %). In contrast, Brazil, Taiwan, and Turkey found access mostly difficult or very difficult (range 57–61 %).

Q 5.1: What proportion of your AF patients do you refer to OSA diagnostic/treatment services?

Q 5.2: In your patients you refer to OSA diagnostic/treatment services, what proportion initially have a Full PSG?

Q 5.3: In your patients you refer to OSA diagnostic/treatment services:

a. What Proportion are diagnosed with OSA?

b. What proportion of patients diagnosed with OSA are recommended for treatment with CPAP?

c. What proportion of patients recommended for treatment with CPAP end up using it?

Referral trends for OSA testing and treatment are shown in Table 2. Overall one third (33 %) of AF patients were referred for OSA diagnosis with less than half (41 %) of those undergoing full polysomnography. For all referred patients, nearly half (48 %) were diagnosed with OSA. However, less than two thirds (59 %) of OSA-diagnosed patients were recommended for CPAP treatment and of these, less than half (41 %) ended up using CPAP.

4. Q6: Does the proportion of patients who end up using CPAP treatment influence your decision to refer patients to OSA diagnostic/treatment services?

39 % of 801 respondents confirmed that the success of OSA treatment with CPAP was a factor in deciding whether to refer their patients for OSA diagnosis. In contrast, nearly half (~49 %) were not influenced by OSA treatment success. The remainder (12 %) were unsure.

5. Q7. In your patients diagnosed with OSA that are recommended for CPAP treatment, what proportion start CPAP: (a) prior to any AF treatment (b) after ablation treatment?

OSA treatment with CPAP prior to any AF treatment was initiated in 35 ± 28 % of patients. A similar amount (34 ± 25 %) started CPAP treatment only after attempting ablation.

Q8. Please rate overall how important you perceive the need is for further clinical research to establish the benefit of treating moderate-severe OSA with CPAP for:

(a). Preventing AF.

(b). Managing First AF.

(c). Managing Paroxysmal AF.

(d). Managing Persistent AF.

(e). Managing Permanent AF.

Nearly 80 % of respondents prioritised as extremely or very important, further research for establishing the benefit of treating moderate-severe OSA with CPAP for preventing or managing paroxysmal or a first AF episode. In contrast, less than 40 % prioritised research for OSA treatment in aiding the managing of permanent AF (Fig. 2A).

Q9. In a future randomized clinical trial that aims to assess the

Table 2
OSA diagnosis and treatment. All statistics are mean % ± SD. *p less than 0.05 comparing country mean to overall mean.

	Overall	Aust	Brazil	Germany	Japan	Spain	Sweden	Taiwan	Turkey	USA
Referred	33.0	53.6	35.9	32.4	29.5	37.2	22.7	20.3	18.5	52.0
	±29	±28*	±29	±26	±30	±25	±20*	±19*	±18*	±31*
Full PSG	41.0	61.0	57.0	31.2	34.5	42.5	36.0	39.5	34.1	45.1
	±39	±40*	±40*	±34	±37	±40	±44	±40	±35*	±36
OSA DIAG	47.7	52.3	56.1	40.1	45.6	56.7	44.9	41.5	40.0	54.4
	±31	±27	±31*	±27	±30	±27*	±33	±31	±32*	±31*
CPAP recom	59.0	66.0	63.5	59.8	55.9	71.1	53.9	44.5	41.0	75.5
	±36	±27	±33	±36	±36	±29*	±37	±32*	±37*	±32*
CPAP Used	40.7	47.1	36.8	47.0	44.9	59.5	34.5	28.7	31.8	47.4
	±29	±26	±26	±27	±33	±24*	±33*	±26*	±30*	±24*

OSA; obstructive sleep apnoea; PSG, polysomnogram; diag, diagnosis; CPAP, continuous positive airway pressure.

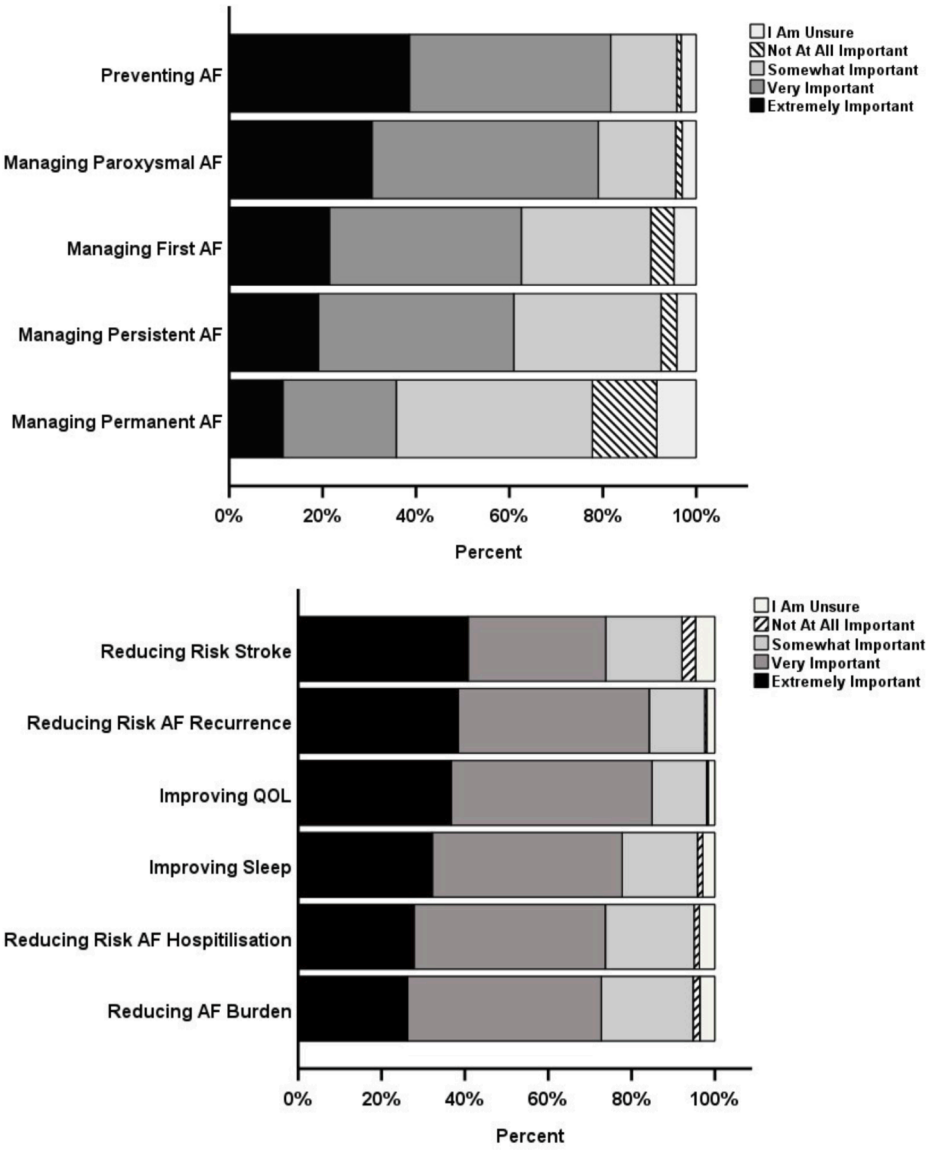

Fig. 2. Views regarding future research.A. Priority for further research to establish the benefit of CPAP therapy for preventing or managing AF in moderate severe OSA. B. Ranking of importance for studying AF outcomes in future randomised clinical trials.

impact of adding CPAP to usual therapy for AF, please rank the importance of the following outcomes.

Respondents ranked stroke reduction (40.8 %) and AF recurrence (38.5 %) as the two most extremely important AF health outcomes that needed testing in future randomised clinical trials (Fig. 2B). Reducing AF burden (26.3 %) was ranked the lowest in importance. These results were similar for general cardiologists versus EP/Arrhythmia specialists (results not shown).

Q10. Which treatment option is best for reducing the risk of each of the following outcomes in patients with AF and moderate-severe OSA?

5 = very certain, 1 = not very certain, 0 = undecided.

Please select 'Yes' or 'No' for each outcome to indicate whether you would participate in an RCT in which patients would be randomly allocated to either treatment option.

Example Outcome - Stroke:

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Survey data that determined whether clinical equipoise exists amongst cardiologists about treatment of OSA to improve AF outcomes is shown in Fig. 4. Overall, the data indicate that there is little evidence to support equipoise regarding treatment of OSA, with a vast majority of

Outcome	**AFib treatment alone** is preferable 5=very certain, 1=not very certain	Undecided	**CPAP + AFib treatment** is preferable 5=very certain, 1=not very certain	RCT Participation Yes No
Stroke	5 4 3 2 1	0	1 2 3 4 5	◯ ◯

Sample survey question designed to assess for the presence or absence of clinical equipoise regarding AF-related stroke risk and management of AF alone versus AF plus OSA.

respondents indicating with a high level of certainty that CPAP plus usual care is superior to usual care alone for reducing the risk of adverse AF outcomes.

Despite the polarized view that CPAP is best for improving/reducing risk for outcomes assessed in Fig. 3, two thirds of respondents (range 66.6 % to 72.7 %) indicated they were still willing to randomize their patients in multi-national RCT's to determine whether adding CPAP to usual care is best. Sub-analyses of data (see data supplement) showed that EP/Arrhythmia specialists felt stronger than general cardiologists that CPAP + AF treatment was preferable for reducing recurrent AF after both cardioversion and ablation.

A further analysis (Fig. 4) shows responses for the ranked importance of assessing risk reduction in stroke in a future RCT where patients are randomized to CPAP plus usual AF care versus usual AF care alone outcome (Fig. 2B), combined with the equipoise question for a stroke outcome in Fig. 3. The data indicate that respondents are mostly in favour of an RCT with a stroke outcome but already believe that CPAP will result in lower risk. Importantly, amongst respondents who rated CPAP + Usual Care at 4 or above (Fig. 4), more than 3-fold (272 respondents) were willing to randomize their own patients than were unwilling (81 respondents). Similar results were observed for all other outcomes (data not shown).

6. Discussion

Randomized controlled trial data, regarded as essential in generating evidence to support treatment recommendations, are often unsuccessful in meeting recruitment goals in a timely fashion. More specific to trials of OSA treatment with CPAP, issues with inadequate CPAP blinding, inconsistent CPAP compliance and the exclusion of symptomatic OSA patients from randomization add further difficulty in generating a clear message regarding the role of OSA treatment with CPAP to reduce cardiac risk [23]. One strategy for improving the design and deployment of these trials is to engage key stake holders in the management of these patients to assess their collective understanding of key clinical questions, current practice patterns, clinical equipoise and interest in trial participation. Accordingly, this INCOSACT survey of practicing cardiologists from across the world was divided into three distinct sections to acquire the following data: [1] The practice discipline of the respondents, how important they rate common AF risk factors and their experience with failure rates for the most common atrial fibrillation treatments. [2] Referral activity and factors influencing referral practices for OSA diagnosis and treatment within the context of atrial fibrillation management. [3] The need for further research linking OSA with AF, the need for clinical trials quantifying OSA treatment impact on AF outcomes and lastly, whether there is clinical equipoise for OSA

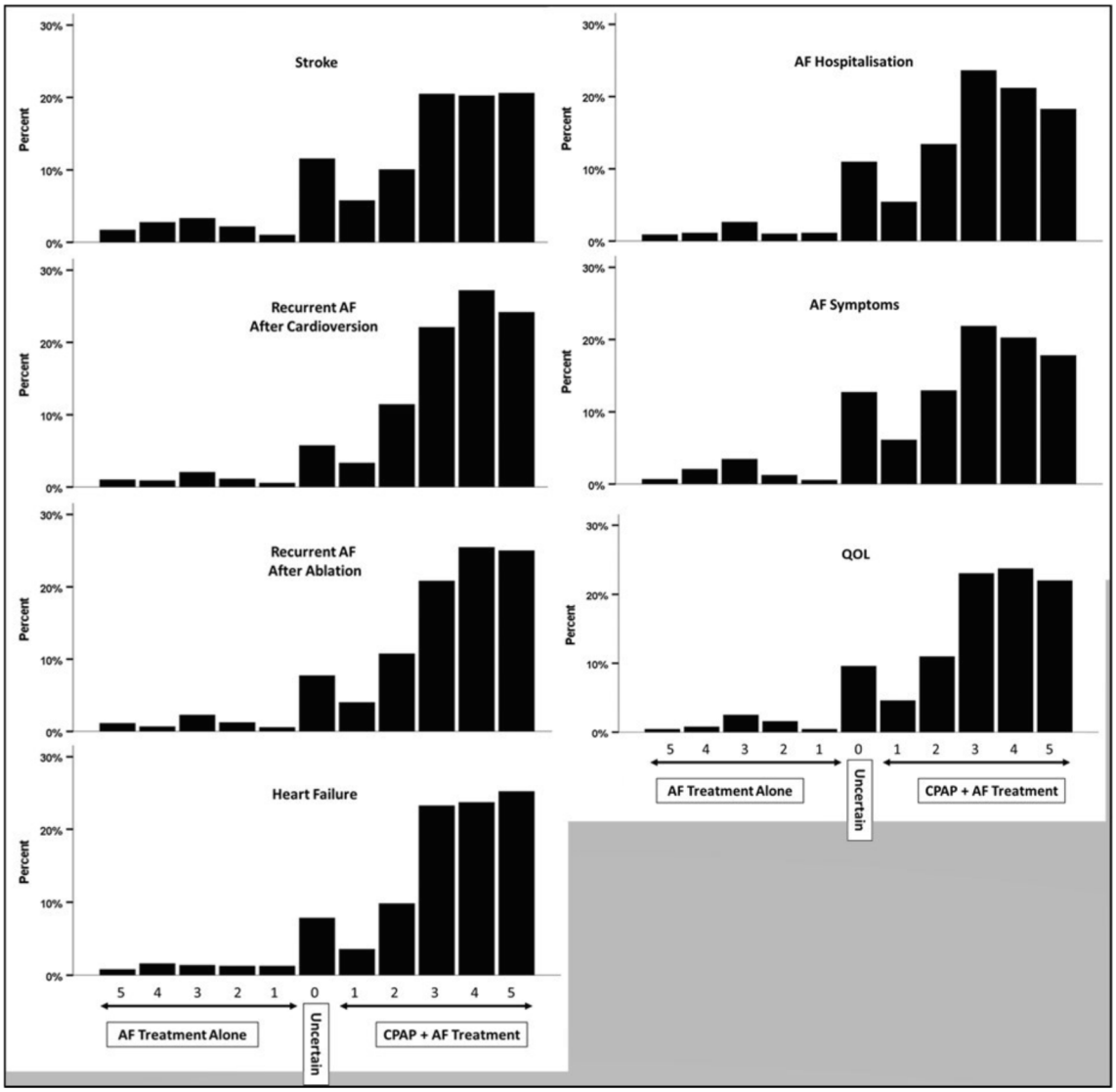

Fig. 3. Clinical Equipoise. Data compares AF Treatment Alone versus CPAP + AF Treatment as the better management strategy for AF outcomes.

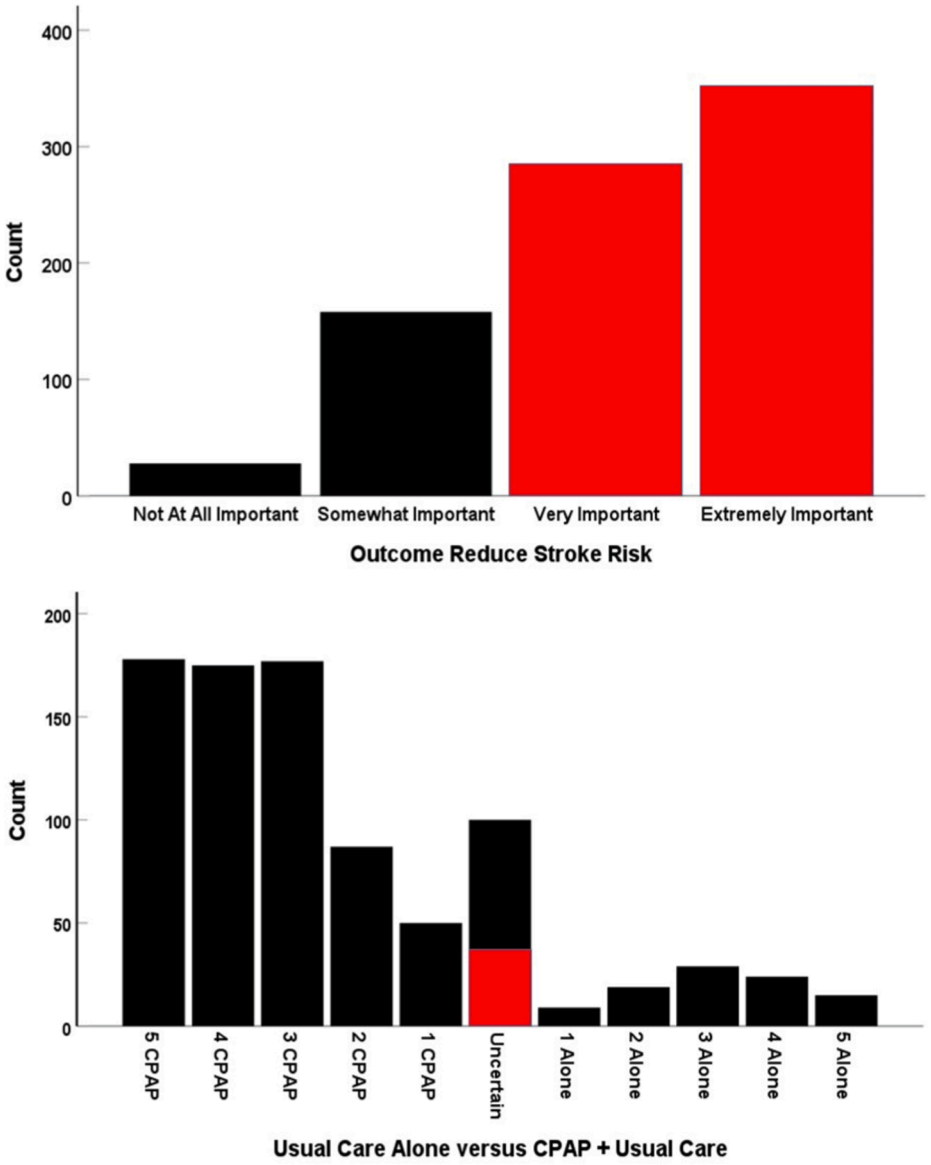

Fig. 4. Combining the responses for the stroke outcome from questions 9 and 10. Red bars indicate respondent numbers who felt it very or extremely important to conduct randomised trials with a reduction in stroke risk as an outcome (Fig. 4A) who were also in clinical equipoise (unsure, Fig. 4B). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

treatment to mitigate adverse AF outcomes.

(1). Most respondents were either general cardiologists or electrophysiologists. We detected no significant difference in the nature of the responses between general cardiologists and electrophysiologists aside from a slight preference among electrophysiologist for using CPAP prior to cardioversion and ablation procedures. Usual AF therapies failed in less than half of all patients, with greatest number of failures involving anti-arrhythmic drugs. Whereas second ablation procedures failed in less than 20 % of cases. Most of the known risk factors for AF were rated as "extremely important" or "very important" with OSA ranked third most important, suggesting that respondents generally held a core belief that OSA represents an important modifiable risk factor in patients with AF.

Our review of recently published AF management guidelines (Table 1) reveals generally uniform recommendations regarding the importance of considering OSA as a risk factor for AF and screening most patients for OSA. With the exception of the AHA/ACC/HRS, international guidelines for AF management endorse detecting and treating OSA to reduce AF risk and improve AF management. These recommendations seem to be based on the same well designed observational studies that reproducibly demonstrate OSA to be independently associated with the development of AF. However, at the same time, they acknowledge the lack of well-designed prospective randomized trials to inform these firm recommendations.

(2 & 3) In this context, our survey aimed to explore the extent to which clinicians follow practice guidelines recommending routine OSA screening in subjects with AF and OSA treatment in mitigating AF risk. In keeping with both the high prevalence of OSA in the AF population [21,32,33] and guideline recommendations, we found that respondents refer around a third of their AF patients for OSA investigation with most relying on a more limited cardio-respiratory diagnosis without polysomnography. Referral activity showed a dichotomous response with almost as many respondents finding access to OSA diagnostic services difficult as those who found it easy. This observation may be explained by regional availability of sleep laboratory space and the variable availability of home sleep apnea testing among survey responders. The data suggest that clinical suspicion of OSA identified around half of all referred patients who were confirmed to have OSA. Surprisingly, OSA

treatment was only attempted in about 60 % of diagnosed patients and for patients in whom CPAP treatment was attempted, less than half became long-term users. This high CPAP attrition rate parallels the findings in other clinical studies including those with diabetes and other cardiovascular co-morbidities [34–36]. Interestingly, this high attrition rate accounted for the decision in nearly 40 % of respondents to not refer patients for OSA investigation. The decision not to refer patients for OSA treatment may also be influenced by country-specific differences in OSA treatment expertise and access to CPAP devices and equipment. This observation underscores the importance of improving access to CPAP devices and the need to improve patient compliance through proper device selection and patient education and behavioral support. It also highlights the need to explore the benefit of other treatment alternatives such as mandibular advancement devices and hypoglossal nerve stimulation. For those respondents that do pursue OSA treatment as part of the AF management strategy, their decision to initiate treatment early (prior to other AF treatments) or late (only after attempting ablation) was equally split between respondents. This latter data suggests that clinicians initiate CPAP treatment to augment overall AF management rather than as a priority, curative step of and by itself.

The final part of our survey was designed to establish whether overall practice, with regards to detection and treatment of OSA to improve AF management, reflected the belief that there is a strong evidence base linking OSA to AF and showing that OSA treatment reduces adverse AF outcomes. Although society guidelines generally favor screening for OSA in AF patients, the practice data above contradict these recommendations. This could be explained by a lack of familiarity by survey respondents with current management guidelines, although this explanation would be presumptive and difficult to prove. Alternatively this disparity may reflect the apparent belief that the evidence base is not yet strong enough to support those guidelines. This was demonstrated by an overwhelming response favouring additional research and clinical trials to enrich the guideline evidence base for treating OSA to reduce AF risk and improve management (Q8) and reduce adverse AF outcomes (Q9). However, when presented with the question that aimed to establish whether true equipoise exists about the role of CPAP to reduce adverse AF outcomes, we were surprised that most respondents believed that CPAP added to usual AF treatment would be superior to usual treatment alone. Given the lack of strong RCT evidence supporting CPAP in this context, we would have expected respondents to be “on the fence” about whether CPAP reduces adverse AF outcomes. To explore this further, our final analysis (Fig. 4) showed that respondents felt it was extremely important to conduct RCT’s to establish the effectiveness of OSA treatment to reduce adverse AF outcomes whilst at the same time, being “very certain” that it would be effective. Furthermore, an overwhelming majority of responders expressed a willingness to participate in such trials and randomize their own patients. This suggests that clinicians largely believe that OSA treatment is an effective AF management strategy, despite their lack of consistent utilization of OSA screening and referral for CPAP treatment in AF patients diagnosed with OSA. As mentioned previously, while this may reflect country-specific barriers to OSA screening and CPAP implementation to some extent, one may also draw the conclusion that these clinicians are aware that the evidence base to support what they would like to do still needs strengthening.

Our study has several strengths. The international scope of the study is a strength given the growing prevalence of both OSA and AF globally. The survey questions were constructed using an iterative process incorporating feedback taken from representatives from each participating country. The survey questions were concise and allowed for easy translation in multiple languages. The survey itself was also relatively brief and straightforward, allowing for easy use by responders. We also feel that the web- based format of the survey, the secure nature of data acquisition and storage including no storage of IP addresses, and the lack of any need for responders to provide personal information were strengths in that they ensured data integrity by providing responders with a sense of secure anonymity.

Our study has limitations that should be acknowledged. First, despite the broad, international scope of survey distribution and the generous time allotted for responding, our response rate was relatively low. There may be several explanations for this including suboptimal visibility of the survey on society websites and concerns regarding cybersecurity in settings where the survey was distributed via email (despite the high quality of data security and assurances regarding protection of personal information) and the generally poor response rates seen in most survey studies. Variation in response rates across countries was notable, and while difficult to fully understand, appeared to relate in part to the presence of “champions” in several countries who personally engaged local and national professional societies. Since the survey in many instances was disseminated with the assistance of large cardiovascular societies our responses may have been biased by a greater proportion of cardiologists in academic versus general practice and may not be reflective of the true scope of global cardiovascular practice. We acknowledge that our survey results might have been influenced by some bias intrinsic to the survey study design, such as non– or late-response bias [37]. The motivation and interests of the responders themselves, many of whom may have a particular interest in OSA as a principal problem, may have skewed testing and treatment referral patterns in a fashion that over-estimates what we might expect from a more generalized population.

7. Conclusions

There is broad recognition of the high prevalence of OSA in AF patients and that OSA diagnosis and treatment are pursued according to published guideline recommendations. Despite this, there is a consistent opinion that stronger evidence is needed to support these recommendations. On the other hand, there is also no clear equipoise about the impact of diagnosing and treating OSA to mitigate adverse AF outcomes with most respondents agreeing that this treatment pathway is superior to AF treatment alone. Sleep apnea is generally regarded as an important modifiable risk factor for the development and perpetuation of atrial fibrillation and its failure to respond optimally to treatment appears to be a consistent message in international atrial fibrillation management guidelines. However firm suggestions regarding sleep apnea testing and management in patients with atrial fibrillation lack an evidence basis due to a paucity of credible supportive data. Our findings suggest that large, well designed, prospective randomized studies of the impact of sleep apnea screening and treatment in the atrial fibrillation population are wanted and feasible.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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References

[1] L.F. Drager, R.D. McEvoy, F. Barbe, G. Lorenzi-Filho, S. Redline, I. Initiative, Sleep Apnea and Cardiovascular Disease: Lessons From Recent Trials and Need for Team Science, Circulation. 136 (19) (2017) 1840–1850, https://doi.org/10.1161/CIRCULATIONAHA.117.029400. PubMed PMID: 29109195; PubMed Central PMCID: PMC5689452.

[2] P.E. Peppard, T. Young, J.H. Barnet, M. Palta, E.W. Hagen, K.M. Hla, Increased Prevalence of Sleep-Disordered Breathing in Adults, American Journal of Epidemiology 177 (9) (2013) 1006–1014, https://doi.org/10.1093/aje/kws342. Epub 2013/04/17 PubMed PMID: 23589584; PubMed Central PMCID: PMC3639722.

[3] C.V. Senaratna, J.L. Perret, C.J. Lodge, A.J. Lowe, B.E. Campbell, M.C. Matheson, G.S. Hamilton, S.C. Dharmage, Prevalence of obstructive sleep apnea in the general population: A systematic review, Sleep Medicine Reviews 34 (2017) 70–81, https://doi.org/10.1016/j.smrv.2016.07.002. Epub 2016/08/29 PubMed PMID: 27568340.

[4] S.Q.C. Giampá, S.F. Furlan, L.S. Freitas, T.A. Macedo, A. Lebkuchen, K.H. M. Cardozo, V.M. Carvalho, F.C. Martins, I.F.B. Azam, V. Costa-Hong, H.F. Lopes, M.L. Baptista, C.E. Rochitte, L.A. Bortolotto, G. Lorenzi-Filho, L.F. Drager, Effects of CPAP on Metabolic Syndrome in Patients With OSA, Chest 161 (5) (2022) 1370–1381, https://doi.org/10.1016/j.chest.2021.12.669. Epub 20220119 PubMed PMID: 35063452.

[5] G. Jean-Louis, F. Zizi, L.T. Clark, C.D. Brown, S.I. McFarlane, Obstructive Sleep Apnea and Cardiovascular Disease: Role of the Metabolic Syndrome and Its Components, Journal of Clinical Sleep Medicine 04 (03) (2008) 261–272. PubMed PMID: 18595441; PubMed Central PMCID: PMC2546461.

[6] J.R. Tietjens, D. Claman, E.J. Kezirian, T. De Marco, A. Mirzayan, B. Sadroonri, A. N. Goldberg, C. Long, E.P. Gerstenfeld, Y. Yeghiazarians, Obstructive Sleep Apnea in Cardiovascular Disease: A Review of the Literature and Proposed Multidisciplinary Clinical Management Strategy, JAHA 8 (1) (2019), https://doi.org/10.1161/JAHA.118.010440. Epub 2018/12/29 PubMed PMID: 30590966; PubMed Central PMCID: PMC6405725.

[7] N.M. Punjabi, The Epidemiology of Adult Obstructive Sleep Apnea, Proceedings of the American Thoracic Society 5 (2) (2008) 136–143, https://doi.org/10.1513/pats.200709-155MG. Epub 2008/02/06 PubMed PMID: 18250205; PubMed Central PMCID: PMC2645248.

[8] M. Guillot, E. Sforza, E. Achour-Crawford, D. Maudoux, M. Saint-Martin, J.-C. Barthélémy, F. Roche, Association between severe obstructive sleep apnea and incident arterial hypertension in the older people population, Sleep Medicine 14 (9) (2013) 838–842, https://doi.org/10.1016/j.sleep.2013.05.002. Epub 2013/07/09 PubMed PMID: 23831239.

[9] B. Cepeda-Valery, S. Acharjee, A. Romero-Corral, G.S. Pressman, A.S. Gami, Obstructive sleep apnea and acute coronary syndromes: etiology, risk, and management, Curr Cardiol Rep. 16 (10) (2013) 535, https://doi.org/10.1007/s11886-014-0535-y. Epub 2014/08/20 PubMed PMID: 25135347.

[10] D.J. Gottlieb, G. Yenokyan, A.B. Newman, G.T. O'Connor, N.M. Punjabi, S.F. Quan, S. Redline, H.E. Resnick, E.K. Tong, M. Diener-West, E. Shahar, Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study, Circulation. 122 (4) (2010) 352–360, https://doi.org/10.1161/CIRCULATIONAHA.109.901801. PubMed PMID: 20625114; PubMed Central PMCID: PMC3117288.

[11] A. Hetland, M. Vistnes, K.H. Haugaa, K.H. Liland, M. Olseng, T. Edvardsen, Obstructive sleep apnea versus central sleep apnea: prognosis in systolic heart failure, Cardiovasc Diagn Ther 10 (3) (2020) 396–404. PubMed PMID: 32695620; PubMed Central PMCID: PMC7369271.

[12] B. Linz, M. Hohl, L. Lang, D.W.L. Wong, A.G. Nickel, C. De La Torre, C. Sticht, K. Wirth, P. Boor, C. Maack, T. Speer, T. Jespersen, U. Schotten, P. Sanders, M. Böhm, D. Linz, Repeated exposure to transient obstructive sleep apnea-related conditions causes an atrial fibrillation substrate in a chronic rat model, Heart Rhythm. 18 (3) (2021) 455–464. PubMed PMID: 33080392.

[13] R. Acharya, S. Basnet, B. Tharu, A. Koirala, R. Dhital, P. Shrestha, et al., Obstructive Sleep Apnea: Risk Factor for Arrhythmias, Conduction Disorders, and Cardiac Arrest, Cureus. 12 (8) (2020), e9992, https://doi.org/10.7759/cureus.9992. PubMed PMID: 32855898; PubMed Central PMCID: PMC7447149.

[14] S.S. Chugh, R. Havmoeller, K. Narayanan, D. Singh, M. Rienstra, E.J. Benjamin, R. F. Gillum, Y.-H. Kim, J.H. McAnulty, Z.-J. Zheng, M.H. Forouzanfar, M. Naghavi, G. A. Mensah, M. Ezzati, C.J.L. Murray, Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study, Circulation. 129 (8) (2014) 837–847. PubMed PMID: 24345399; PubMed Central PMCID: PMC4151302.

[15] M. Haïssaguerre, P. Jaïs, D.C. Shah, A. Takahashi, M. Hocini, G. Quiniou, S. Garrigue, A. Le Mouroux, P. Le Métayer, J. Clémenty, Spontaneous Initiation of Atrial Fibrillation by Ectopic Beats Originating in the Pulmonary Veins, N Engl J Med 339 (10) (1998) 659–666. PubMed PMID: 9725923.

[16] Shantha G, Alyesh D, Ghanbari H, Yokokawa M, Saeed M, Cunnane R, et al. Antiarrhythmic drug therapy and all-cause mortality after catheter ablation of atrial fibrillation: A propensity-matched analysis. Heart Rhythm. 2019;16(9):1368-73. Epub 20190612. doi: 10.1016/j.hrthm.2019.06.007. PubMed PMID: 31201962.

[17] K. Kadhim, M.E. Middeldorp, A.D. Elliott, T. Agbaedeng, C. Gallagher, V. Malik, C. X. Wong, R.D. McEvoy, J.M. Kalman, D.H. Lau, D. Linz, P. Sanders, Prevalence and Assessment of Sleep-Disordered Breathing in Patients With Atrial Fibrillation: A Systematic Review and Meta-analysis, Canadian Journal of Cardiology 37 (11) (2021) 1846–1856. PubMed PMID: 34606918.

[18] A. Shapira-Daniels, S. Mohanty, F.M. Contreras-Valdes, H. Tieu, R.J. Thomas, A. Natale, et al., Prevalence of Undiagnosed Sleep Apnea in Patients With Atrial Fibrillation and its Impact on Therapy, JACC Clin Electrophysiol. 6 (12) (2020) 1499–1506, https://doi.org/10.1016/j.jacep.2020.05.030. PubMed PMID: 33213809.

[19] A.M. Abumuamar, P. Dorian, D. Newman, C.M. Shapiro, The prevalence of obstructive sleep apnea in patients with atrial fibrillation, Clin Cardiol. 41 (5) (2018) 601–607, https://doi.org/10.1002/clc.22933. PubMed PMID: 29745973; PubMed Central PMCID: PMC6489882.

[20] R.K. Pathak, M.E. Middeldorp, D.H. Lau, A.B. Mehta, R. Mahajan, D. Twomey, et al., Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study, J Am Coll Cardiol. 64 (21) (2014) 2222–2231, https://doi.org/10.1016/j.jacc.2014.09.028. PubMed PMID: 25456757.

[21] A.S. Gami, G. Pressman, S.M. Caples, R. Kanagala, J.J. Gard, D.E. Davison, J. F. Malouf, N.M. Ammash, P.A. Friedman, V.K. Somers, Association of atrial fibrillation and obstructive sleep apnea, Circulation. 110 (4) (2004) 364–367. PubMed PMID: 15249509.

[22] C.A. Goudis, D.G. Ketikoglou, Obstructive sleep and atrial fibrillation: Pathophysiological mechanisms and therapeutic implications, Int J Cardiol. 230 (2017) 293–300, https://doi.org/10.1016/j.ijcard.2016.12.120. PubMed PMID: 28040290.

[23] G.M. Traaen, L. Aakerøy, T.-E. Hunt, B. Øverland, C. Bendz, L.Ø. Sande, S. Aakhus, M.W. Fagerland, S. Steinshamn, O.-G. Anfinsen, R.J. Massey, K. Broch, T. Ueland, H. Akre, J.P. Loennechen, L. Gullestad, Effect of Continuous Positive Airway Pressure on Arrhythmia in Atrial Fibrillation and Sleep Apnea: A Randomized Controlled Trial, Am J Respir Crit Care Med 204 (5) (2021) 573–582. PubMed PMID: 33938787.

[24] C.J. Field, S. Robinson, S. Mackay, J.D. Harrison, N.S. Marshall, Clinical Equipoise in Sleep Surgery: Investigating Clinical Trial Targets, Otolaryngol Head Neck Surg 145 (2) (2011) 347–353. PubMed PMID: 21521883.

[25] C.T. January, L.S. Wann, J.S. Alpert, H. Calkins, J.E. Cigarroa, J.C. Cleveland, J. B. Conti, P.T. Ellinor, M.D. Ezekowitz, M.E. Field, K.T. Murray, R.L. Sacco, W. G. Stevenson, P.J. Tchou, C.M. Tracy, C.W. Yancy, 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society, Circulation. 130 (23) (2014), https://doi.org/10.1161/CIR.0000000000000041. PubMed PMID: 24682347; PubMed Central PMCID: PMC4676081.

[26] Y. Yeghiazarians, H. Jneid, J.R. Tietjens, S. Redline, D.L. Brown, N. El-Sherif, R. Mehra, B. Bozkurt, C.E. Ndumele, V.K. Somers, Obstructive Sleep Apnea and Cardiovascular Disease: A Scientific Statement From the American Heart Association, Circulation 144 (3) (2021). PubMed PMID: 34148375.

[27] Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrom-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2021;42(5):373-498. Epub 2020/08/30. doi: 10.1093/eurheartj/ehaa612. PubMed PMID: 32860505.

[28] D. Brieger, J. Amerena, J.R. Attia, B. Bajorek, K.H. Chan, C. Connell, B. Freedman, C. Ferguson, T. Hall, H.M. Haqqani, J. Hendriks, C.M. Hespe, J. Hung, J. M. Kalman, P. Sanders, J. Worthington, T. Yan, N.A. Zwar, National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Australian clinical guidelines for the diagnosis and management of atrial fibrillation 2018, Med J Aust. 209 (8) (2018) 356–362. PubMed PMID: 30067936.

[29] B. Gorenek, A. Pelliccia, E.J. Benjamin, G. Boriani, H.J. Crijns, R.I. Fogel, et al., European Heart Rhythm Association (EHRA)/European Association of Cardiovascular Prevention and Rehabilitation (EACPR) position paper on how to prevent atrial fibrillation endorsed by the Heart Rhythm Society (HRS) and Asia Pacific Heart Rhythm Society (APHRS), Eur J Prev Cardiol. 24 (1) (2017) 4–40, https://doi.org/10.1177/2047487316676037. PubMed PMID: 27815538; PubMed Central PMCID: PMC5427484.

[30] J.G. Andrade, M. Aguilar, C. Atzema, A. Bell, J.A. Cairns, C.C. Cheung, J.L. Cox, P. Dorian, D.J. Gladstone, J.S. Healey, P. Khairy, K. Leblanc, M.S. McMurtry, L. B. Mitchell, G.M. Nair, S. Nattel, R. Parkash, L. Pilote, R.K. Sandhu, J.-F. Sarrazin, M. Sharma, A.C. Skanes, M. Talajic, T.S.M. Tsang, A. Verma, S. Verma, R. Whitlock, D.G. Wyse, L. Macle, The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society Comprehensive Guidelines for the Management of Atrial Fibrillation, Canadian Journal of Cardiology 36 (12) (2020) 1847–1948. PubMed PMID: 33191198.

[31] C.-E. Chiang, T.-J. Wu, K.-C. Ueng, T.-F. Chao, K.-C. Chang, C.-C. Wang, Y.-J. Lin, W.-H. Yin, J.-Y. Kuo, W.-S. Lin, C.-T. Tsai, Y.-B. Liu, K.-T. Lee, L.-J. Lin, L.-Y. Lin, K.-L. Wang, Y.-J. Chen, M.-C. Chen, C.-C. Cheng, M.-S. Wen, W.-J. Chen, J.-

H. Chen, W.-T. Lai, C.-W. Chiou, J.-L. Lin, S.-J. Yeh, S.-A. Chen, 2016 Guidelines of the Taiwan Heart Rhythm Society and the Taiwan Society of Cardiology for the management of atrial fibrillation, Journal of the Formosan Medical Association 115 (11) (2016) 893–952. PubMed PMID: 27890386.

[32] B. Braga, D. Poyares, F. Cintra, C. Guilleminault, C. Cirenza, S. Horbach, D. Macedo, R. Silva, S. Tufik, A.A.V. De Paola, Sleep-disordered breathing and chronic atrial fibrillation, Sleep Med. 10 (2) (2009) 212–216. PubMed PMID: 18280206.

[33] Stevenson IH, Teichtahl H, Cunnington D, Ciavarella S, Gordon I, Kalman JM. Prevalence of sleep disordered breathing in paroxysmal and persistent atrial fibrillation patients with normal left ventricular function. Eur Heart J. 2008;29 (13):1662-9. Epub 2008/06/03. doi: 10.1093/eurheartj/ehn214. PubMed PMID: 18515807.

[34] Y. Peker, H. Glantz, C. Eulenburg, K. Wegscheider, J. Herlitz, E. Thunström, Effect of Positive Airway Pressure on Cardiovascular Outcomes in Coronary Artery Disease Patients with Nonsleepy Obstructive Sleep Apnea. The RICCADSA Randomized Controlled Trial, Am J Respir Crit Care Med 194 (5) (2016) 613–620, https://doi.org/10.1164/rccm.201601-0088OC. PubMed PMID: 26914592.

[35] R.D. McEvoy, N.A. Antic, E. Heeley, Y. Luo, Q. Ou, X. Zhang, O. Mediano, R. Chen, L.F. Drager, Z. Liu, G. Chen, B. Du, N. McArdle, S. Mukherjee, M. Tripathi, L. Billot, Q. Li, G. Lorenzi-Filho, F. Barbe, S. Redline, J. Wang, H. Arima, B. Neal, D.P. White, R.R. Grunstein, N. Zhong, C.S. Anderson, CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea, N Engl J Med 375 (10) (2016) 919–931. PubMed PMID: 27571048.

[36] L.M. Donovan, M. Rueschman, J. Weng, N. Basu, K.A. Dudley, J.P. Bakker, R. Wang, S.M. Bertisch, S.R. Patel, The effectiveness of an obstructive sleep apnea screening and treatment program in patients with type 2 diabetes, Diabetes Research and Clinical Practice 134 (2017) 145–152. PubMed PMID: 29054482; PubMed Central PMCID: PMC5724386.

[37] https://catalogofbias.org/biases/non-response-bias.