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Advances in screening for undiagnosed atrial fibrillation for stroke prevention and implications for patients with obstructive sleep apnoea: A literature review and research agenda

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Abstract

Atrial fibrillation (AF) is the most common type of sustained cardiac arrhythmia encountered in clinical practice, and its burden is expected to increase in most developed countries over the next few decades. Because AF can be silent, it is often not diagnosed until an AF-related complication occurs, such as stroke. AF is also associated with increased risk of heart failure, lower quality of life, and death. Anticoagulation has been shown to dramatically decrease embolic risk in the setting of atrial fibrillation, resulting in growing interest in early detection of previously undiagnosed AF. Newly developed monitoring devices have improved the detection of AF and have been recommended in guidelines for screening of AF in individuals aged 65 years and over. While screening is currently targeted to these older individuals, younger patients with obstructive sleep apnoea (OSA) are at higher risk of AF and stroke than the general population, indicating a need for targeted early detection of AF in this group. Compared to individuals without OSA, those with OSA are four times more likely to develop AF, and the risk of AF is strongly associated with OSA severity. The overall prevalence of AF among individuals with OSA remains unknown because of limitations related to study design and to the conventional methods previously used for AF detection. Recent and emerging technological advances may improve the detection of undiagnosed AF in high-risk population groups, such as those with OSA. In this clinical review, we discuss the methods of screening for AF and the applications of newer technologies for AF detection in patients with OSA. We conclude the review with a brief description of our research agenda in this area.

Keywords: atrial fibrillation; obstructive sleep apnoea; stroke; device; detection; artificial intelligence

Introduction – the burden of atrial fibrillation and obstructive sleep apnoea

Atrial fibrillation (AF) is a globally epidemic disease with increasing incidence and prevalence [1]. In 2010, the global prevalence rates of AF per 100,000 individuals were 596.2 (95% uncertainty interval [UI], 558.4–636.7) in men and 373.1 (95% UI, 347.9–402.2) in women [1]. The Rotterdam Study data suggest that the prevalence of AF will more than double between 2010 and 2060 in the European population aged ≥55 years [2]. In the US population, both the incidence and prevalence of AF are expected to double between 2010 and 2030, with the prevalence increasing from 5.2 million cases in 2010 to 12.1 million cases in 2030 [3]. Similarly, AF incidence and prevalence have been significantly increasing in Australia. Specifically, while the prevalence of AF among Australians aged ≥55 years was estimated at 5.97% among men and 4.79% among women in 2014, this is expected to rise to 6.39% and 5.64% among men and women, respectively, by the year 2034 [4]. In Australia, as well as globally, the burden of AF remains higher in elderly populations; Ball and colleagues have predicted that the number of AF cases among Australian individuals aged ≥75 years will double between 2014 and 2034, with a 2.5-fold increase among men aged ≥85 years [4].
Overall, AF is associated with a five-fold increased risk of stroke [5, 6], a 3-fold increased risk of heart failure [7], significant mortality, and lower quality of life [7, 8]. AF-related strokes tend to be more severe than non-AF-related strokes and are associated with significant mortality and morbidity. While early identification and prompt initiation of treatment for AF is associated with up to 70% reduction in stroke risk [9], under-detection of AF delays such treatment until after the first stroke in at least 20% of patients [10], as AF tends to remain silent. Recent advances in devices for AF detection have shown promise as tools for AF screening, as effectively demonstrated in the STROKESTOP study (A study of mass screening for untreated AF in a population of Swedes aged 75-76 years) [11] and the recent REHEARSE-AF trial (REmote HEArt Rhythm Sampling using the AliveCor heart monitor to screen for AF) [12].

While screening for silent AF among older individuals (over 65 years of age) has been recommended by the recent guidelines [13], previous studies have established a strong link between AF and obstructive sleep apnoea (OSA), indicating a need for targeted screening for AF in this population, even at a younger age. OSA is the most common type of sleep-disordered breathing, and has been identified as a major health risk associated with acute cardiovascular events including stroke, myocardial infarction, arrhythmias and sudden cardiac death and chronic illnesses such as hypertension and heart failure [14]. Like AF, the burden of OSA is rapidly increasing with higher incidence being observed in older population and those with cardiovascular comorbidities, such as heart failure. It is estimated that up to 30% of men and 15% of women may have OSA, with up to 90% of cases remaining undiagnosed at least partially due to difficulty accessing diagnostic services [15, 16]. The coexistence of OSA and AF represents a significant public health concern due to several common risk factors, including older age, obesity, hypertension, and metabolic diseases, all of which are rapidly increasing in the western populations. Compared to individuals without OSA, those with OSA are four times more likely to develop AF [17], and the risk of AF increases with increasing severity and is higher in individuals aged <65 years if OSA is present [18]. In a subset of patients with heart failure, the presence of OSA significantly increases the burden of arrhythmias and is associated with lower quality of life, and increased hospital readmissions whereas early detection and treatment may improve the clinical outcomes (reviewed in [19, 20]).

Further research into improved technology for early detection of these disorders is needed. In particular, there is a paucity of data on the use of contemporary devices for AF detection in this high-risk group to inform guideline development. With the increasing prevalence of overweight, obesity, and ageing population [21, 22], it is intuitive that both AF and OSA will become more prevalent in the future, creating an urgent need for simplified and effective detection of these disorders. Emerging simple, wearable devices for continuous arrhythmia detection, appear attractive as a method for unobtrusive opportunistic screening of AF in at-risk individuals and may be of great value in those with sleep apnoea.

THE ASSOCIATION BETWEEN OBSTRUCTIVE SLEEP APNOEA AND ATRIAL FIBRILLATION

Obstructive sleep apnoea in patients with atrial fibrillation

Obstructive sleep apnoea is characterised by repeated episodes of upper airway obstruction during sleep, resulting in frequent sudden drops in oxygen saturation [23]. The apnoea-hypoxia index (AHI), a measure of the frequency of obstructed breathing episodes per

hour, is used to determine the severity of OSA. According to the AHI, OSA can be classified as none/minimal (AHI < 5), mild (5 ≤ AHI < 15), moderate (15 ≤ AHI < 30), or severe (AHI ≥ 30) [24].

OSA has been shown to be highly prevalent among patients with AF. Early observational studies indicated that OSA is present in up to 49% of patients with AF [25-27] whereas more recent data suggest a higher prevalence of OSA exists in this group. In a cohort of 90 patients with AF without known cardiopulmonary diseases, 47 patients (62%) were found to have concomitant OSA (AHI > 15) [28]. In another study of 153 patients undergoing pulmonary vein isolation for medically-resistant AF, Naruse et al. [29] found that 116 patients (76%) had OSA (AHI > 5). Other studies have suggested that up to 80% of patients with AF may have OSA [30], with the differences in OSA prevalence data being primarily due to the differences in the population groups studied, and the methods (polysomnography vs questionnaire) and criteria (AHI > 5 vs AHI > 10 vs AHI > 15) used to diagnose OSA.

The concomitant presence of OSA in patients with AF has been shown to affect outcomes in patients undergoing catheter ablation. Specifically, catheter ablation for AF is more likely to fail in patients with OSA, and this risk increases with the severity of OSA [31]. In a cohort of 210 patients with drug-refractory AF (57% paroxysmal; 43% persistent), catheter ablation was 4.5 times more likely to fail in patients with high Berlin Questionnaire scores (high risk for OSA) than in patients at low risk of OSA [32]. Several other studies (Table 1) have also identified OSA as an independent risk factor for procedural failure of catheter ablation [29, 31, 33]. A 2011 meta-analysis of six studies comprising 3195 patients (958 with OSA; 3037 without OSA) concluded that OSA was associated with a 25% greater risk of AF recurrence after catheter ablation [34]. Current guidelines recommend screening and optimal treatment for OSA in high-risk patients undergoing ablation therapies for AF [35, 36]. Therapy with continuous positive airway pressure (discussed later) has been reported to significantly reduce the risk of AF recurrence after catheter ablation [37].

Table 1. Selected studies demonstrating the association between obstructive sleep apnoea (OSA) and atrial fibrillation (AF)

Study [reference] (year of publication)	**Population**	**Methods of OSA diagnosis**	**Methods of AF detection**	**Mean duration of follow-up**	**OSA-AF association**
Chilukuri et al. [32] (2009)	210 patients with refractory AF undergoing catheter ablation	Berlin Questionnaire (BQ)	12-lead ECG	25±12 months	Patients with high BQ scores (high risk of OSA) had 4.5-fold higher risk of procedural failure
Fein et al. [33] (2013)	386 patients undergoing PVI for symptomatic AF	PSG	12-lead ECG	12 months	CPAP non-use was associated with more than 2-fold higher risk of AF recurrence in OSA patients following PVI (HR, 2.15; 95% CI, 1.10 to 5.44; p = 0.02)
Naruse et al. [29] (2013)	153 patients undergoing PVI for drug-refractory AF	PSG	12-lead ECG; 24-hour Holter monitor; Portable ECG monitor	18.8±10.3 months	Untreated OSA was associated with more than two-fold increased risk of AF recurrence after ablation (HR 2.61; 95% CI 1.12–6.09; p < 0.05) compared with patients who used CPAP (HR ratio 0.41; 95% CI 0.22–0.76; p < 0.01)
Matiello et al. [31] (2010)	174 consecutive patients referred for	BQ	24-h or 48-h Holter monitor	17.0±11.5 months	After 1 year, the proportion of arrhythmia-free survival was

	circumferential pulmonary vein ablation between January 2005 and December 2007				significantly lower in patients with severe OSA (AHI ≥ 30) than in those with non-severe OSA (AHI < 30) and in those with low risk for OSA (14.3%, 30.4%, and 48.5%, respectively)
Kanagala et al. [38] (2003)	118 patients undergoing cardioversion for AF	Self-reported	Physician-documented after ECG or clinical examination	12 months	82% of patients with untreated or poorly treated OSA (n = 27) had recurrence of AF, compared with only 42% and 53% of patients with treated OSA (n = 12) or without OSA (n = 79), respectively
Neilan et al. [39] (2013)	720 patients undergoing PVI	Unspecified sleep study	ECG or prolonged cardiac monitoring.	42 months	On multivariable analysis, sleep apnoea (HR, 2.79; 95% CI, 1.97 to 3.94, p < 0.0001) and untreated sleep apnoea (HR, 1.61; 95% CI 1.35 to 1.92, P < 0.0001) were highly associated with AF recurrence

CPAP = continuous positive airway pressure; AHI = apnoea-hypoxia index; PSG = polysomnography; PVI = pulmonary vein isolation; ECG = electrocardiography; HR = hazard ratio; CI = confidence interval; SA = sleep apnoea

Atrial fibrillation in patients with obstructive sleep apnoea

There is limited data documenting the frequency of AF among patients with OSA. In a cross-sectional sleep-heart-health study of 228 patients with OSA and 338 without OSA, Mehra et al. [17] found that AF was present in 4.8% of patients with OSA, compared with 0.9% in those without OSA. After adjusting for confounding factors, subjects with OSA were four times more likely to have AF [17] compared with those without OSA. In a retrospective cohort study of 3542 adults without a known history of AF who were referred for an initial diagnostic polysomnography between 1987 and 2003 [18], OSA was significantly associated with AF, occurring in 114 of 2626 patients (4.3%) with OSA, compared with 19 of 916 patients (2.1%) without OSA. In a Western Australian longitudinal cohort of 6841 patients undergoing investigation for suspected OSA, AF occurred in 455 patients (6.6%) over the course of a mean follow-up of 11.9 years [40]. Both the presence of OSA and OSA severity were independently associated with AF diagnosis.

These studies show clearly that OSA is associated with a risk of AF and the true prevalence may have been underestimated in previous studies. In the REVEAL XT-SA study (interim results), AF occurred in 20% of patients with severe OSA (AHI ≥ 30) with an implantable loop recorder over a mean follow up of 25.1 months [41]. Importantly, these patients were compliant with CPAP, suggesting a high burden of AF in OSA even in patients who are optimally treated. There is therefore a need for improved detection of AF in this group using extended monitoring devices.

Despite the recognised association between OSA and AF, the mechanisms of increased arrhythmogenicity in OSA are not well understood. Based on animal and human studies, it has been postulated that variation in intrathoracic pressures causes changes in cardiac transmural pressure, which in turn results in left atrial stretch and an increase in the risk of AF. These observations have been demonstrated in patients with OSA, using a three-dimensional echocardiography [42] and cardiac MRI [39]. Additionally, changes in sympatho-vagal balance have been observed in OSA and shown to trigger AF; this was demonstrated in a series of animal experiments, in which AF was shown to be highly inducible in apnoeic dogs subjected to programmed stimulation during atrial refractory periods (ARP) [43]. This inducibility was associated with increased neuronal firing,

with the ensuing increase in parasympathetic and sympathetic activity being associated with the observed ARP shortening. Interestingly, AF inducibility was attenuated by ablation of the pulmonary artery ganglionated plexus, and treatment with intravenous beta blockers and atropine [43]. Other studies have also shown that the onset and duration of OSA-triggered AF can be reduced or inhibited by renal sympathetic denervation or pharmacologic inhibition of the renin-angiotensin pathway [44], although the therapeutic implications of these findings remain unclear. OSA may also induce chronic cardiac remodelling and diastolic dysfunction which may increase the risk of AF [45-48]. Systemic inflammation and oxidative stress, induced by OSA, have also been hypothesised to increase the risk of AF [49, 50]. These mechanisms, reviewed in more detail in previous publications [19, 20, 51], remain very poorly understood and further research is needed.

METHODS OF DETECTION OF ATRIAL FIBRILLATION

Limitations of current methods of detection of paroxysmal atrial fibrillation

A 12-lead electrocardiography (ECG) is the gold standard test for AF detection [36, 52], but will fail to identify paroxysmal AF (PAF) if not present during the study. Opportunistic screening for AF in clinical practice has been recommended in patients over 65 years by radial pulse palpation [36], based on evidence from the SAFE trial (A randomised controlled trial and cost-effectiveness study of systematic screening targeted and total population screening versus routine practice for the detection of atrial fibrillation in people aged 65 and over) [53]. Like a 12-lead-ECG, this method would also miss most PAF. 24-hour Holter monitors have been traditionally considered superior to a standard 12-lead ECG for the diagnosis of paroxysmal arrhythmias, but two recent landmark trials (Table 2) examining the incidence of PAF in cryptogenic stroke showed that 24-hour Holter ECGs and other conventional methods tend to miss the clear majority of PAF. The EMBRACE trial (Event Monitor Belt for Recording Atrial fibrillation after a Cerebral ischemic Event) showed that the 30-day rate of AF detection was significantly higher with an event-triggered loop recorder compared with a 24-hour Holter ECG, confirming the view that extended continuous monitoring is superior in diagnosing PAF [54]. The CRYSTAL-AF trial (CRYptogenic STroke And underLying Atrial Fibrillation) was a randomised controlled trial comparing an implantable cardiac monitor (ICM) with conventional follow-up (control) for detecting AF in patients with cryptogenic stroke [55]. Patients (40 years of age or older) with no evidence of AF during at least 24 hours of ECG monitoring underwent randomization within 90 days following an ischaemic stroke or transient ischaemic attack. The rate of AF detection was significantly higher in the ICM group compared with the control group as shown in the table. The rate of AF detection remained consistently higher in the ICM group compared with the control group, in a small group of patients who were followed up beyond 12 months. These results strongly indicate that conventional methods of AF detection (12-lead ECG, Holter monitors) are too brief, and therefore unreliable for the detection of paroxysmal AF. Furthermore, these trials show clearly that previously undiagnosed AF may be responsible for more cryptogenic strokes than previously thought, indicating a need for improved detection of undiagnosed AF for stroke prevention in high-risk groups.

Previous studies assessing the prevalence of AF among patients with obstructive sleep apnoea have relied on these traditional methods of AF detection, which are clearly not reliable for optimal detection of silent paroxysmal atrial fibrillation. There is therefore a need to develop reliable and convenient devices for early detection of AF in this group.

Table 2. Conventional methods vs implantable devices for detecting atrial fibrillation (AF) in patients with cryptogenic stroke

Study [reference]	Study design	Duration of monitoring	% AF detected in the intervention group	% AF detected in the control group
EMBRACE[a] trial [54]	Event-triggered loop recorder (n = 287) vs ECG Holter monitor (n = 285)	30 days	16.1%	3.2%
CRYSTAL-AF[b] trial [55]	Implantable cardiac monitor (n = 221) vs conventional follow-up (n = 220)	Up to 36 months	8.9%, 12.4%, and 30% at 6, 12, and 36 months, respectively	1.4%, 2.0%, and 3% at 6, 12, and 36 months, respectively

[a]EMBRACE = Event Monitor Belt for Recording Atrial fibrillation after a Cerebral ischemic Event

[b]CRYSTAL-AF = CRYptogenic STroke And underLying Atrial Fibrillation

Newer devices - Handheld intermittent ECG devices for detection of atrial fibrillation: is there a role in patients with sleep apnoea?

New technology for AF screening has evolved and represents a new era for improved detection of AF and prevention of stroke. Smartphone ECG devices such as alivecor and zenicor, consist of smartphone software applications and small handheld hardware components attached to, or near, the smartphones, allowing for automated transmission and analysis of the recorded ECG data [56, 57]. Many other devices have been invented and include the MyDiagnostick [58], the Omron HeartScan [59], iPhone 4S camera [60], and the AF-detecting BP monitors [61]. The latter detect AF based on irregularity index calculated from pulse intervals measured during the last 10 seconds of cuff deflation of the blood pressure measurement [61].

The handheld devices are effective for screening of undiagnosed AF in primary prevention [58, 62-69] and for the diagnosis of AF after stroke [70]. Table 3 shows that, at least 1% of the screened population using handheld devices, has a previously undiagnosed AF. The rate of AF detection tends to be higher with repeated intermittent recordings compared with single-time point screening, again demonstrating the superiority of extended monitoring for effective detection of PAF. Furthermore, these devices have shown superiority over the conventional methods of AF detection. In one study, intermittent handheld ECG recordings for two weeks (twice daily) was found to be more effective for detecting PAF compared with a 24-hour Holter monitor [71]. In a randomised controlled trial [12], intermittent, twice weekly ECG recording detected at least three times as many AF events as were detected with routine care over 12 months (Table 4).

Table 3. Effectiveness of intermittent handheld electrocardiography devices in detecting previously undiagnosed atrial fibrillation (AF)

Study [reference]	**Sample size, settings (geographic location)**	**Age (years)**	**Device**	**Monitoring**	**Total prevalence of AF in the population screened**	**% of new AF identified with SL-ECG[a]**
STROKESTOP[b] study [11]	7173, outpatient (Sweden)	75–76	Zenicor	Twice daily and on palpitations for 2 weeks	12.3%	3.0%
Engdahl et al. [65]	848, outpatient (Sweden)	75–76	Zenicor	Intermittently, twice daily for 2 weeks (n = 403)	14.3%	3.5%
Chan & Choy [72]	13122, outpatient (China)	>18	Alivecor	Single time-point	8.5%	0.8%
SEARCH-AF [63]	1000, outpatient (Australia)	76±7	Alivecor	Single time-point	6.7%	1.5%
Orchard et al. [62]	976, outpatient (Australia)	78±1	Alivecor	Single time-point	4.3%	0.8%
Tielman et al. [58]	676, outpatient (The Netherlands)	74±7.1	MyDiagnostick	Single time-point	8.1%	1.6%

Kaasenbrood et al. [68]	3267, outpatient (The Netherlands)	69.4±8.9	MyDiagnostick	Single time-point	3.7%	1.1%

[a]SL-ECG = Single-Lead ECG

[b]STROKESTOP = a study of mass screening for untreated AF in a population of Swedes aged 75-76 years

Handheld ECG devices allow for simple and effective diagnosis of AF. However, for effective PAF detection, repeated recordings are required, which may limit the utility of such devices in clinical practice. Furthermore, most automated ECG analysis systems currently used with handheld devices are algorithmic in nature, in that they rely on deviations from standard deflections on the ECG waveform or R-R interval variability to detect AF [58]. The REHEARSE-AF study has shown that these systems are sensitive but not sufficiently specific for AF detection, and that identification of previously undetected AF requires significant labour-intensive manual review and confirmation by a clinician [12]. Therefore, there is still an urgent need to develop more accurate and less resource-demanding automated technologies that can be incorporated into these screening devices to improve the efficiency and cost-effectiveness of AF screening.

Intermittent monitoring devices can also lead to significant bias because their sensitivities for detecting low-burden high-density AF is lower compared to high-burden low-density AF [73]. Therefore, as shown by Charitos et al [73], these devices appear to be suitable for detecting AF in patients with low temporal AF aggregation, whereas extended monitoring devices are required to detect AF in patients who are suspected to have higher AF density.

Table 4. Handheld ECG devices compared to conventional methods for the detection of previously undiagnosed atrial fibrillation (AF)

Study [reference]	Study design	Duration of monitoring	% AF detected with handheld devices	% AF detected with the control methods
REHEARSE-AF[a] [12]	iECG[b] twice weekly (n = 500) vs routine care (n = 501)	12 months	3.8%	1%
Sobocinski et al [74]	Daily 10-second ECG recording with a Zenicor device vs 24-hour Holter ECG for AF detection following cryptogenic stroke (n = 249)	30 days	6.0%	2.0%
Hendrikx et al [75]	Twice daily 30-second ECG recordings with a Zenicor device in patients undergoing evaluation for palpitations or dizziness/syncope vs 24-hour Holter ECG (n = 95)	28 days	9.5%	2.0%

[a]REHEARSE-AF = REmote HEArt Rhythm Sampling using the AliveCor heart monitor to screen for AF

[b]iECG = electrocardiography taken using a smartphone electrocardiograph

Patients with OSA tend to have higher AF density due to a higher burden of arrhythmias during the night [18, 76]. In a case-crossover study, Monahan et al. [77] showed that respiratory episodes triggered AF events. In this study, PAF was 17 times more likely to occur during respiratory disturbances than during normal nocturnal breathing, indicating that monitoring for AF using patient-operated devices would miss a large number of nocturnal PAF in patients with OSA. AF can be “opportunistically” detected in patients undergoing sleep studies using traditional sleep apnoea diagnostic methods with abilities to acquire ECG data. However, this approach requires ECG leads and electrodes to be placed across the chest (similar to the setup of a Holter monitor) and would not appropriate for screening at population level. Furthermore, full in-laboratory polysomnography studies with ECG-recording capabilities are also not widely accessible and the ability to detect AF during an overnight sleep study is currently limited by the lack of automated arrhythmia detection technology, as manual interpretation requires extensive resources and appropriate clinical training. Because of the high AF density in sleep apnoea, using handheld ECG devices for AF detection may severely underestimate the prevalence of AF in this group. Therefore, although the AF-SCREEN International Collaboration [78], and the recent clinical guidelines [13] recommend screening for AF using intermittent handheld ECG devices in individuals aged 65 years and over, this recommendation cannot yet be extended to patients with OSA for optimal detection of PAF, and further research is needed.

Emerging devices for continuous monitoring of arrhythmia and potential application in patients with sleep apnoea

Implantable devices are effective for continuous long-term detection of arrhythmias, as shown in the CRYSTAL-AF [55], PREDATE-AF (PREdicting Determinants of Atrial Fibrillation or Flutter for Therapy Elucidation in Patients at Risk for Thromboembolic Events) [79], and ASSERT trials (The Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial) [80, 81]. Data from these devices provide strong evidence that the detection of PAF or subclinical AF requires extended monitoring. However, invasive implantable loop recorders are neither feasible nor cost-effective for population-level screening. Instead, non-invasive devices for continuous monitoring of paroxysmal arrhythmias are required. Several such devices already exist on the market. ECG patch monitors are non-invasive, water-proof devices attached to the patient's skin to record ECGs continuously without interfering with the patient's daily activities. Unlike Holter monitors, these devices require no electrodes or visible lead wires. The Zio Patch (iRhythm Technologies, Inc., CA, USA) is a commonly used ECG patch monitor that can record ECG data continuously for up to 14 days [82]. The prototype ECG patch monitor NUVANT Mobile Cardiac Telemetry (Corventis, San Jose, CA, USA) can record ECG data continuously for up to 30 days [83].

Compared to implantable devices, continuous, non-invasive monitoring devices can be used for screening in a broader range of populations and may be superior to 24-hour Holter monitors [84]. These recent innovations promise a future in which simple, wearable non-invasive devices may form the basis for longer term monitoring of paroxysmal arrhythmias. Because of their ability to passively monitor for arrhythmia continuously (including during sleep), these simple, non-invasive, wearable devices may be ideally suited for opportunistic detection of AF in the patients with sleep apnoea. The early detection of AF is likely to have an impact on decisions for stroke prevention treatment, such as anticoagulation.

Furthermore, effective non-invasive and affordable wearable devices could form the cornerstone for prolonged monitoring of paroxysmal atrial fibrillation in patients who are diagnosed with ischaemic stroke, particularly those with cryptogenic stroke, in whom extended monitoring beyond the recommended 72 hours is limited by costs, staff availability, decreased compliance, and availability of high-quality ECG data [85]. Equipping such devices with a reliable automated technology for real-time AF detection would further improve the technology and reduce the costs associated with manual review of the ECG data. A recent study performed by Uphaus and colleagues showed that automated analysis of ECG data from extended ECG monitors is very feasible. In this study, the investigators compared a computer-based automated ECG analysis software algorithm with staff-based analysis of 24-hour Holter ECGs in 595 patients with ischaemic stroke or transient ischaemic attack. The authors showed that the automated software algorithm was effective in the detection of pAF with a sensitivity and specificity of 89.5% and 99.3%, respectively [86]. Of note, the diagnostic accuracy of the automated software did not differ from that of routine staff-based analysis. Although further work is needed, these results show that automation of AF detection with extended monitoring devices is possible. Future studies should explore the use of artificial intelligence systems for automated analysis of these large ECG data as such systems would be expected to be more robust due to their ability to continue learning and improving the diagnostic accuracy.

Unlike the intermittent handheld devices, extended monitoring devices also allow for improved risk stratification in patients who are found to have AF. Recent studies have suggested that quantification of newly detected AF based on its temporal persistence and burden (proportion of monitored time a patient spends in AF) may improve our understanding of the AF characteristics and assist in treatment decisions [87]. Current evidence suggests that non-paroxysmal AF is associated with higher risk of stroke and all-cause mortality than PAF [88], whereas the long-term outcomes of treating screen-detected PAF remain unknown. Therefore, improved risk stratification methods of newly detected PAF, which is only possible with extended monitoring devices, are urgently required. Future studies investigating the association between the burden/density of AF and stroke risk may improve our ability to predict the risk of stroke more accurately, taking into account the quantitative AF burden and its temporal persistence, as well as the traditional stroke risk factors.

Treatment for sleep apnoea and implications for Atrial fibrillation

Continuous positive airway pressure (CPAP) is the first-line and the recommended treatment for patients with OSA, particularly in presence of daytime sleepiness. CPAP works by splinting the airways open during sleep, thereby preventing apnoea and hypopnoea. This therapy is effective for treating the symptoms of OSA, including fatigue, daily somnolence, and snoring. CPAP can attenuate the effects of chronic OSA, including systemic inflammation, oxidative stress, and sympathetic overdrive, and may also improve the cardiopulmonary exercise capacity [89]. It has been

shown that therapy with CPAP reverses OSA-induced cardiac remodelling. In a cohort of 720 patients undergoing work up for pulmonary vein isolation, Neilan et al [39] showed that CPAP therapy (≥ 4 hours/night) was associated with lower Left ventricular mass and smaller Left atrium compared with untreated (< 4hours/night of CPAP) group. In another study, Colish et al [90] showed that treatment with CPAP for 12 months improved the measurements of cardiac structure, including left ventricular mass, right ventricular end-diastolic diameter, left and right atrial indices, and pulmonary hypertension. However, the role of CPAP for the treatment of cardiovascular diseases in patients with sleep-disordered breathing is controversial as the improvement in surrogate markers has not translated into mortality benefit and the recent studies have shown conflicting results [91].

CPAP therapy has been shown to reduce the risk of AF recurrence after pulmonary vein isolation [29, 33, 38]. In a study of 386 patients undergoing PVI, Fein et al. [33] elegantly showed that the atrial tachyarrhythmia-free survival rate was significantly higher in patients with OSA who used CPAP compared with patients with OSA who did not use CPAP (71.9% vs. 36.7%; p = 0.01). Furthermore, the arrhythmia-free survival off antiarrhythmic medications or repeat ablation was significantly higher in CPAP-treated patients with OSA compared with those with OSA who were not on CPAP treatment (65.5% vs 33.3%, p = 0.02). Interestingly, patients with OSA who used CPAP had similar event-free survival rates as patients without OSA. These observations have been consistently reported in other studies in patients undergoing catheter ablation or cardioversion for AF. A 2015 meta-analysis of 8 studies, which included 1247 patients with OSA (698 CPAP users; 549 CPAP non-users) concluded that CPAP treatment was associated with a 44% decreased risk of AF recurrence following PVI [37]. Consequently, clinical guidelines now recommend screening and treatment for OSA in appropriately selected patients with AF undergoing catheter ablation [35, 36].

In primary prevention, it remains unclear whether treatment with CPAP reduces the incidence or burden of AF. In the ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) study, there was a small tendency for CPAP to reduce the progression of AF to more permanent forms of AF in patients with OSA who were treated with CPAP [92]. However, this study had several methodological limitations and the treatment effects were too small despite reaching statistical significance. A current ongoing trial is expected to provide better understanding of the interaction between AF and sleep apnoea and will provide preliminary data on the role of CPAP in reducing the burden of AF in patients with both AF and OSA (ClinicalTrials.gov Identifier: NCT02727192). Larger randomised controlled trials will need to be performed before any evidence-based treatment recommendations can be made.

Conclusion and future direction

In this review, we have discussed the current methods for AF detection and demonstrated their significant limitations for AF detection in the general population and limitations that are more specific to patients with OSA. Smartphone-based ECG devices are more suited as event recorders and fail to detect most episodes of PAF, especially those occurring during sleep. Current automated ECG analysis is limited by low specificity for the diagnosis of PAF, which limits the applicability of this approach to population-level screening, as diagnosis confirmation relies heavily on the contribution of a physician who would review the ECG data. Current recommendations on screening for AF cannot yet be extended to patients with OSA, and further research is needed.

The clinical benefits of treating patients with low-burden paroxysmal AF are still unknown and controversies exist regarding the outcomes of treating screen-detected PAF. The simple identification of AF as a binary entity is not sufficient and the paradigm is shifting towards improved risk stratification of screen-detected AF through quantification methods. Intermittent handheld devices, recording ECG data for very brief moments can lead to significant bias and the ECG recorded with these devices cannot be used for risk stratification. Because of the likely higher AF density (higher risk of AF during sleep) among patients with AF, extended continuous monitoring devices are required for optimal detection of AF in this population group.

In our view, the ideal method of detecting AF would involve the use of simple, un-obstructive non-invasive wearable device, capable of continuous arrhythmia detection like implantable devices, without the associated procedural risks. If the device is intended for recording ECG data continuously, a very robust method of ECG data interpretation should be developed and implemented, to avoid the constant need for review by a physician. Such requirements could be met using artificial intelligence. Passive detection of AF using a trained artificial intelligence is expected to have a higher detection accuracy than traditional systems and expert cardiologists.

Finally, due to the increasing burden of both AF and OSA, it would be preferable to develop easy-to-use technologies for simultaneous detection of arrhythmia and sleep apnoea. The abilities to detect both AF and OSA concurrently using easy-to-use wearable devices would also improve the detection of these two disorders in high-risks patients, including patients with heart failure in whom both disorders are highly prevalent but underdiagnosed and undertreated. We are currently investigating the possibility of utilising artificial intelligence systems for automated detection of both AF and OSA in patients at risk of OSA. Our goal is to completely transform the traditional polysomnography into fully automated modern technologies capable of simultaneous arrhythmia and sleep apnoea detection, using simple, non-invasive, and unobtrusive wearable devices equipped with artificial intelligence. Future studies should also assess the association between the burden of AF and the risk of stroke in patients with OSA. If such association exists, a quantitative score for predicting the risk of stroke, taking into account the quantitative AF burden and density as well as the traditional stroke risk factors, would improve our ability to selectively treat patients with the greatest potential for benefiting from stroke prevention.

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