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Rationale, design, and endpoints of the 'DEvice-Detected CArdiac Tachyarrhythmic Events and Sleep-disordered Breathing (DEDiCATES)' study: Prospective multicenter observational study of device-detected tachyarrhythmia and sleep-disordered breathing☆

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ABSTRACT

Background: Few studies have investigated the prognostic value of cardiac implantable electronic device (CIED)-detection of sleep-disordered breathing (SDB) for risk stratification of cardiovascular events. In the Device-Detected CArdiac Tachyarrhythmic events and Sleep-disordered breathing (DEDiCATES) study, we aim to determine whether device-detected SDB events are associated with increased risk of cardiac arrhythmias or other cardiovascular outcomes.
Methods and design: Six-hundred patients (300 patients with low-voltage pacing devices and 300 with high-voltage defibrillator devices) who have dual chamber CIEDs with AP Scan™ function (Boston Scientific Inc., Marlborough, MA, USA) are planned to be enrolled in this study. AP Scan reports the average number of sleep disturbance events per hour per night in the form of a Respiratory Disturbance Index (RDI). The daily RDI values are to be used for quantitative measurement of the severity and burden of SDB. CIED-detected atrial high rate episodes (AHREs) and clinical atrial tachyarrhythmia will be assessed as the primary outcomes over a follow-up period of 2 years. Correlations between CIED-detected SDB and AHRE burdens will be analyzed. The secondary outcomes are CIED-detected or clinical ventricular arrhythmic events, stroke, heart failure hospitalization, mortality, and quality of life.
Conclusion: This study will determine the prognostic value of automated diagnostic function of CIED for SDB, which will help to improve the cardiovascular prognoses of CIED patients by enabling convenient and accurate assessments of SDB events.

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1. Introduction

Sleep-disordered breathing (SDB) is one of the most common comorbidities in patients with cardiovascular disease. SDB is frequently under-diagnosed, although it is a well-known risk factor for wide range of cardiovascular disease including arrhythmic events and mortality [1–7]. The prevalence of SDB is reported to account for up to 50% of patients with cardiac implantable electronic devices (CIEDs) [5,8,9]. The adverse impact of SDB on arrhythmogenicity and heart failure is particularly associated with reduced quality of life (QoL) and increased risk of sudden cardiac death (SCD) in patients with implantable cardioverter-defibrillator (ICD) [5,9,10]. Thus, early detection, accurate assessment, continuous monitoring of SDB, and timely intervention would improve QoL and provide survival benefits in a large proportion of patients with CIEDs. Polysomnography (PSG), although frequently used as a traditional diagnostic tool for SDB, is not always available. Moreover, PSG is difficult to repeat because it is a laboratory-based multi-parametric study and therefore requires special facility and equipment.

A recent study of CIED equipped with a trans-thoracic impedance sensor showed comparable performance in diagnostic accuracy of SDB to conventional PSG. The study also detected a good correlation in severity between CIED-detected and PSG-detected SDB [11,12]. Therefore, CIED using this sensor is expected to facilitate early detection and continuous monitoring of SDB in patients with CIEDs. Furthermore, significant improvements in the device algorithm enable us to detect subclinical arrhythmic events and to monitor the burden of arrhythmias [13–16]. To date, few studies have investigated the prognostic value of CIED-detected SDB in risk of cardiovascular events [17]. Therefore, the primary aim of this study is to determine whether device-detected SDB events are associated with increased risk of cardiac arrhythmias or other cardiovascular morbidities using a prospective multicenter registry.

2. Methods

2.1. Study design and patient population

The DEDiCATES study is designed as a prospective, multicenter, observational study. Sixteen tertiary university hospitals are participating to enroll 600 patients over an estimated recruitment period of 24 months: 300 patients with low-voltage pacing devices (pacemaker or cardiac resynchronization therapy-pacemaker) and 300 patients with high-voltage defibrillator devices (ICD or cardiac resynchronization therapy-defibrillator). Total 301 patients have been enrolled to date. The overall study design is depicted in Fig. 1. Patients who underwent implantation with CIEDs with AP Scan™ function (Boston Scientific Inc., Marlborough, MA, USA) will be eligible for the study during the first 3 ± 1 months after CIED implantation. Inclusion criteria are as follows: 1) age ≥ 19 years and 2) CHA_2DS_2VASc score ≥ 1 in males or ≥2 in females. Patients who meet any of the following criteria are excluded: 1) CIED without atrial lead, 2) persistent or permanent atrial fibrillation (AF) or atrial flutter (AFL), 3) history of catheter or surgical ablation of AF or AFL, 4) more than a moderate degree of valvular steno-insufficiency, 5) chronic obstructive pulmonary disease, 6) under current treatment for SDB, or 7) life expectancy <1 year. We plan a follow-up period of 2 years. The registry protocol was registered at clinicaltrials.gov (NCT03614377). The protocol was approved by the local institutional review boards of all participating hospitals and written informed consent will be obtained from all patients. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

2.2. CIED implantation

The right atrial lead is preferably placed at the right atrial appendage, and the right ventricular lead is placed at the right ventricular apex or septum, although other sites are allowed according to clinical situation or physician preference. CIED models possessing the AP Scan function are listed in Supplementary Table 1.

2.3. CIED programming for AP Scan and tachyarrhythmia detection

2.3.1. AP Scan algorithm

AP Scan shows trends for average numbers of respiratory disturbance events using a respiratory sensor. The respiratory sensor operates on an impedance-based algorithm. The device sends a current from the atrial (or ventricular) lead ring to the generator can and calculates changes in transthoracic impedance using the voltage resulting from injected current (Supplementary Fig. 1). AP Scan measures baseline respiratory amplitude and interval (minute ventilation signal) and interprets respiratory events with significantly reduced amplitude (below 74% of baseline) for prolonged duration (>10 s) as apnea/hypopnea events (Supplementary Fig. 2). The average number of apnea/hypopnea events per hour per night is reported daily as the Respiratory Disturbance Index (RDI). The physician needs to determine individual sleeptimes for patients by recording sleep start and end times. The algorithm subtracts 1 h from the beginning and the end of the sleeptime to define 'core sleep hours'. Apnea/hypopnea events collected during core sleep hours (a minimum of 2 h) are used to calculate RDI. The device suspends the function, if it detects excessive electrical noise or loss of lead integrity. Respiratory disturbance events lasting >60 s, considered as non-physiologic, are also rejected.

2.3.2. Measurement of severity and burden of SDB

The 'baseline severity' of SDB in CIED patients will be determined according to RDI data recorded during the first 3 ± 1 months after CIED implantation; patients with RDI ≥ 30/h for at least one night will be classified into the severe SDB group, those with 15/h ≤ maximum RDI < 30/h into the moderate SDB group, and 5/h ≤ maximum RDI < 15/h into the mild SDB group. The exact values of everyday RDI will be manually verified and summed at every scheduled or unscheduled clinic visit in each patient for precise quantitative measurement of SDB burden (Fig. 2). Device interrogation and AP Scan data from each center will be sent to a central core laboratory to monitor errors in the assessment of SDB severity and burden.

2.3.3. Programming for atrial and ventricular high rate episode detection

The cut-off rate defining an atrial high rate episode (AHRE) in the present study is programmed to 190 beats per minute (bpm) based on the 2017 EHRA consensus for device-detected subclinical atrial tachyarrhythmias [18]. At every device interrogation, data on AHRE burden will be collected as follows: total number of episodes, total duration of all AHREs, or the percentage of time spent in AHREs during the interrogation follow-up interval. In addition, numbers of AHREs with duration <1 min, 1 min ≤ duration <1 h, 1 h ≤ duration <24 h, 24 h ≤ duration <48 h, or duration ≥48 h will be obtained (Table 1). If 3 consecutive sensed ventricular events are above the ventricular tachyarrhythmia (VTA) detection rate, the ventricular high rate episode (VHRE) is recorded. The VHRE cut-off rate is programmed to 160 bpm (nominal values) for low-voltage pacing devices. In case of high-voltage defibrillator device, the cut-off rate is dependent on preset VTA monitoring or therapy zone. The setting of the VTA zone is left to the discretion of each physician.

2.4. Data collection and follow-up protocol

The attending physician at each participating center will complete a web-based case report form (http://www.ecrf.kr/predilect) with the assistance of a clinical research coordinator. Baseline clinical, electrocardiographic, echocardiographic, and device data will be collected at the time of enrollment. Detailed variables of the study are described in

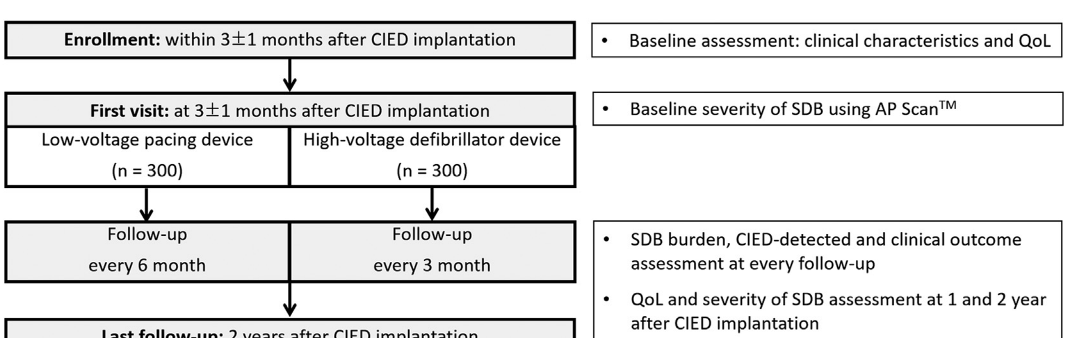

Fig. 1. Flow diagram of study enrollment and follow-up. CIED, cardiac implantable electronic device; SDB, sleep-disordered breathing; QoL, quality of life.

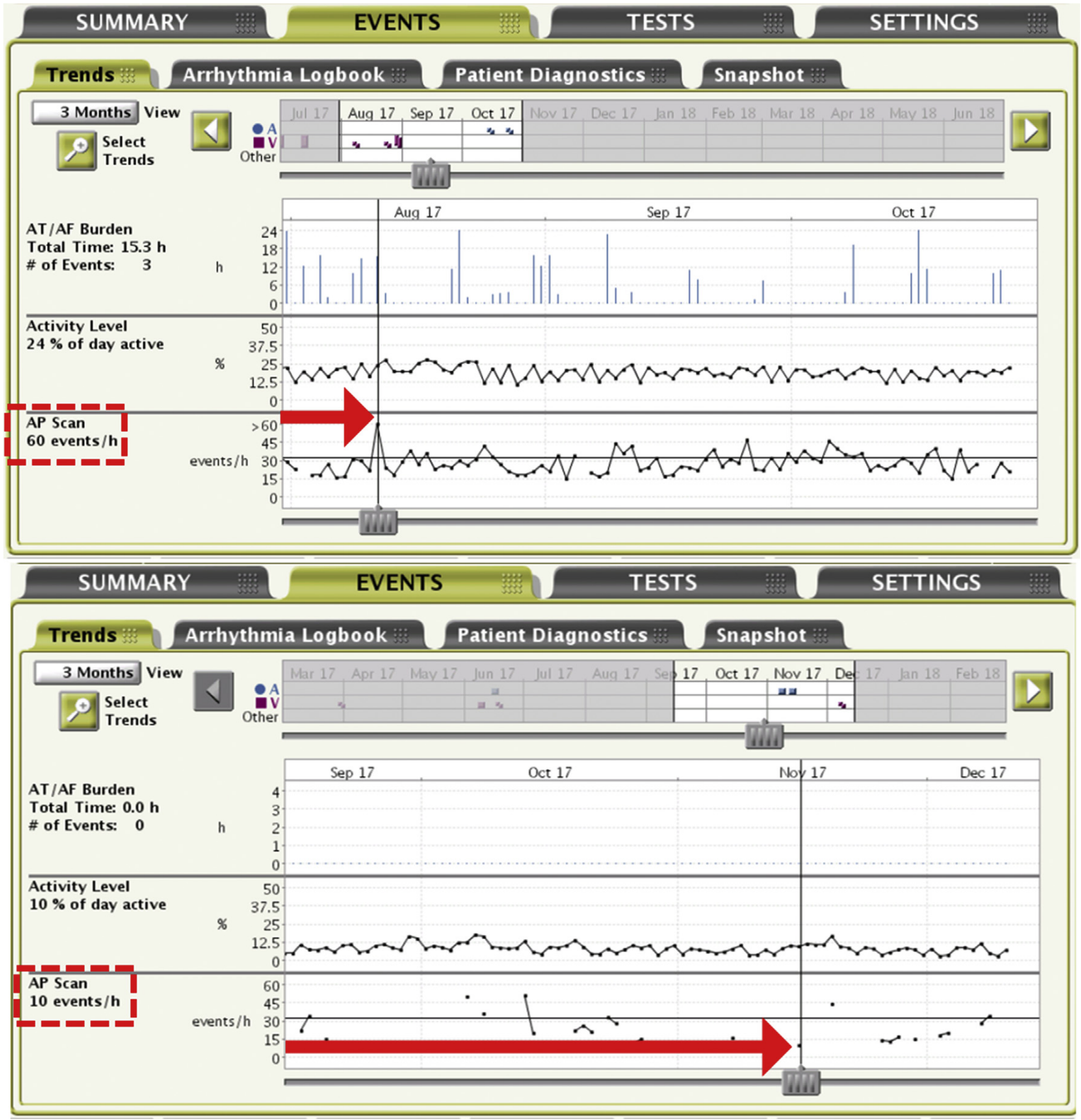

Fig. 2. Manual counting of the Respiratory Disturbance Index (RDI). Each point in the trend graph represents daily RDI value. Everyday RDI values are manually counted point by point and summed to assess the severity and burden of sleep-disordered breathing.

Supplementary Table 2. At the first clinic visit (usually 3 ± 1 months) after CIED implantation, patients will be classified based on baseline severity of device-detected SDB, as described above. Baseline QoL and risk of SDB will be assessed by questionnaires (EuroQol five dimensions and Berlin questionnaire). Patients with a low-voltage pacing device are scheduled to be followed up every 6 months, while patients with a high-voltage defibrillating device are to be followed up every 3 months after the first visit. During follow-up, CIED-detected or clinical arrhythmic events and other clinical outcomes are to be recorded, as well as the burden of device-detected SDB (Fig. 1 and Table 2). The primary outcomes are incidence of CIED-detected AHRE and clinical AF or AFL. The secondary outcomes include CIED-detected and clinical VTA events and other cardiovascular outcomes. At 12 and 24 months, QoL and risk of SDB will be assessed again by the EQ-5D and Berlin questionnaire, respectively. The details of study outcomes are shown in Table 2.

2.5. Study management and data monitoring

The registry is to be managed by a committee consisting of cardiac electrophysiologists. The committee designed the protocol and case report forms of the study. An independent monitoring team monitors data monthly, and notifies each institution about outliers or unexpected values for data verification. All device-detected and clinical events will be verified by an independent clinical event adjudication committee composed of four cardiac electrophysiologists and one general cardiologist who are not investigators in this study.

2.6. Statistical analysis

2.6.1. Outcome analysis

Descriptive data, including prevalence and severity of SDB and baseline characteristics of patients, will be analyzed before outcome analysis. Continuous variables are presented as median and interquartile range or mean ± standard deviation, whereas categorical variables are presented as number and percentage. Continuous variables will be compared between groups using Student's *t*-test. Categorical data will be compared between groups using Fisher's exact test or the Chi-square test, as appropriate. Overall outcome analysis will be performed according to baseline severity of CIED-detected SDB (no, mild, moderate, or severe SDB) in each patient. In addition, the relationships between burden of SDB and study outcomes will be also analyzed at each follow-up period. Event-free survival will be estimated by the Kaplan–Meier method and compared with the log-rank test. A Cox proportional hazards model will be used to identify predictors of each outcome. All tests are two-sided, and a p value <0.05 is considered statistically significant. IBM SPSS Statistics software version 23 (IBM Corporation, Armonk, NY, USA) will be used for statistical analysis. Interim analyses are scheduled to be performed when enrollment reaches 300 patients.

2.6.2. Sample size calculation

The prevalence of SDB in patients with CIED is estimated to be around 50% [5,8,9]. The incidence of device-detected atrial tachyarrhythmia is reported to be 35% to 50%, and major adverse cardiovascular events (MACE), which includes stroke, systemic embolism,

Table 1
Diagnostic parameters from device interrogation.

	Variables and values
AP scan	Patient sleep time, maximum and minimum RDI value, mean and median RDI, initial severity of sleep apnea, and number of days with RDI ≥30, 15 ≤ RDI <30, or RDI < 15
Atrial high rate episode	Total number of AHRE, total time in AHRE, percentage of time in AHRE, and number of episodes with duration <1 min, 1 min ≤ duration <1 h, 1 h ≤ duration <24 h, 24 h ≤ duration <48 h, duration ≥48 h
Ventricular high rate episode	Number of sustained episodes, date of first sustained episode, number and success of anti-tachycardia pacing or shock therapy
Lead integrity	Sensing amplitudes (mV), sensitivity (fixed or auto gain control, mV), impedance (ohm), pacing threshold (V at ms)

AHRE, atrial high rate episode; RDI, respiratory disturbance index.

death, or atrial fibrillation documented by surface electrocardiography, were observed in 15% of patients with CIED over 2 year follow-up [13,15]. The risk of atrial tachyarrhythmia is elevated 2 to 4 times, and the risk of MACE is 2.5 times higher, in the presence of SDB [2–4,10,19]. Based upon the results of previous research, a sample size of 596 patients will ensure that a two-sided test with α error of 0.05 has >99% power to detect 3-fold higher risk of atrial tachyarrhythmia, and 80% power to detect 2.5-fold higher risk of MACE in patients with SDB. The final sample size of 600 patients was chosen to account for a 5% drop-out rate.

3. Discussion

The prevalence of SDB ranges as high as 50% in patients with CIED [5,8,9], and the cardiovascular consequences of SDB are varied. SDB increases the risks of arrhythmia, heart failure, and sudden cardiac death [1–3]. A recent study showed that patients with an ICD and SDB had increased the risk of life-threatening ventricular arrhythmia during sleep [5]. Other studies reported a significant association between SDB and appropriate ICD therapy in congestive heart failure patients [9,10]. Moreover, SDB is well validated as a modifiable risk factor of AF [20–23]. Previous studies showed that treatment for SDB, as well as other risk factor reduction, can reduce AF recurrence [20,21,24,25]. A recent guideline for AF management states that it is reasonable to screen SDB in AF patients with risk factors, and recommends optimized SDB treatment to improve AF treatment results [23].

Recently, the accurate detection of asymptomatic AF, represented as AHREs in CIEDs, has become possible due to technical advances. The predictive impact of subclinical AF on cardiovascular events including death and stroke is now well established, as is the relationship between SDB and AF [13–15,26,27]. The Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT) study [26], including 2580 CIED patients with a history of hypertension and no previous AF, was conducted to prospectively evaluate whether subclinical AF is associated with increased risk of stroke. The study showed that AHREs are independently associated with significant increase in stroke risk (hazard ratio, 2.50; 95% confidence interval, 1.28 to 4.89; P = 0.008) [13]. A recent subanalysis of the ASSERT trial also demonstrated that AHREs >24 h are associated with higher risk of stroke than those with shorter duration (hazard ratio, 3.24; 95% confidence interval 1.51 to 6.95; P = 0.003) [28]. Therefore, we predict that investigations of the relationships between device-detected SDB and AHREs will provide important clinical information to improve the cardiovascular prognosis of patients with CIED.

Several studies have reported impacts of SDB on cardiovascular events in patients with CIED primarily focusing on ventricular arrhythmic events in patients with ICD [4,5,10,29]. However, only a limited number of studies have investigated the clinical implications of SDB in patients with pacemaker [8,17,30]. This is one of the reasons that our study is designed to include patients with low-voltage pacing devices up to half of the study sample. SDB was diagnosed by PSG in all previous studies, except for a recent one [17]. Even though PSG is a standard method to establish the presence of SDB, this test is challenging in common clinical settings. This overnight test is performed in a sleep laboratory with comprehensive recording of physiologic responses related to sleep. The requirements for special facilities and equipment, including a sleeping laboratory, electroencephalography, electrooculography, and electromyography, make PSG expensive and difficult to repeat. Due to recent technological developments, it has become feasible to detect SDB and to measure its severity using specialized diagnostic function of CIEDs, such as AP Scan [11,29,31]. This feature can make CIED a practical and inexpensive tool for SDB detection, which is especially useful for repeated assessments of the burden and severity of SDB. It is also known that the severity of SDB varies daily by up to 65% on repeated PSG [32]. Furthermore, one recent study showed that a night-by-night variability in SDB severity could lead to misclassification of SDB severity [33]. Therefore, we expect that continuous monitoring of SDB using AP Scan will yield higher accuracy to assess the severity and burden of SDB than a single PSG test.

Recent studies showed that device-detected severe sleep apnea was independently associated with higher risk of AF [17,34]. However, those studies included patients with pacemakers only and the primary endpoint was focused on AF episode alone. In terms of RDI measurement, RDIs were obtained for only one week during each 3 month follow-up period in one study [17]. In comparison, our study will include a large number of patients with defibrillators as well as pacing devices. We plan to measure various cardiovascular outcomes other than device-detected AF including quality of life. Furthermore, we are making special efforts to measure not only baseline severity but also the exact burden of SDB by manually counting all daily RDI values at every device interrogation during the entire follow-up duration. Various RDI-related values will be included for outcome analysis, such as minimal and maximal RDI, and number of days with RDI ≥ 30/h, 15/h ≤ RDI < 30/h, or 5/h ≤ RDI < 15/h. Thus, our study is designed to analyze the relationship between degree of SDB and arrhythmic events per period as well as on a per-patient basis. In this study, we arbitrarily referenced the AHI range to classify the baseline severity of SDB. The AP scan algorithm provides RDI >32 episodes/h as the cut-off value defining severe sleep apnea. However, previous studies used different thresholds to define severe sleep apnea [17,34] and there is no reference RDI to classify the non-severe sleep apnea events to date. We hope that our study can provide a guide to classify the non-severe sleep apnea and identify the impact of the severity of SDB defined by RDI ranges on cardiovascular events. To the best of our knowledge, our study will be the first to measure the burden of CIED-detected SDB in detail through an entire prolonged follow-up period. This will provide advantages over previous studies to evaluate the risk of adverse cardiovascular outcomes according to severity or burden of SDB.

Table 2
Details of follow-up outcomes.

	CIED-detected and clinical outcomes
Primary outcomes	
Atrial arrhythmia	CIED-detected atrial high rate episode Clinical atrial fibrillation or flutter
Secondary outcomes	
AF-related outcomes	Thromboembolic events, de novo heart failure or decompensation of chronic heart failure, AF progression to persistent/permanent form, ablation therapy of AF
MACE	Cardiac death, stroke, atrial fibrillation or flutter, ventricular tachyarrhythmia, and hospitalization for heart failure
Mortality	Overall and cardiovascular mortality
Ventricular arrhythmia	Clinical events and CIED-detected ventricular high rate episodes, defibrillation therapy (shock or anti-tachycardia pacing)
At 1- and 2-year after CIED implantation	
Quality of life	Assessment by EuroQol five dimensions questionnaire
Severity of SDB	Assessment by Berlin questionnaire

AF, atrial fibrillation; CIED, cardiac implantable electronic device; MACE, major adverse cardiovascular events; SDB, sleep-disordered breathing.

4. Conclusions and future perspective

This study is designed to evaluate the relationships between device-detected SDB and cardiovascular outcomes in patients with CIEDs. We expect that the prognostic value of automated diagnostic data on CIED-detected SDB will be assessed through our study. Follow-up RDI values would be useful for early detection, timely therapeutic intervention of SDB, and accurate assessment of treatment efficacy for SDB. We are planning to conduct a further interventional study to evaluate the benefits of treatment of severe SDB as assessed by AP Scan on cardiovascular outcomes in patients with CIEDs.

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Conflicts of interest

None declared.

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