



**HAL**  
open science

## **Implantable cardiac devices in sleep apnoea diagnosis: A systematic review and meta-analysis**

Raoua Ben Messaoud, Charles Khouri, Jean-Louis Pepin, Jean Luc Cracowski, Renaud Tamisier, Fabian Barbieri, Marie Joyeux-Faure, Pascal Defaye

### **► To cite this version:**

Raoua Ben Messaoud, Charles Khouri, Jean-Louis Pepin, Jean Luc Cracowski, Renaud Tamisier, et al.. Implantable cardiac devices in sleep apnoea diagnosis: A systematic review and meta-analysis. International Journal of Cardiology, 2021, 10.1016/j.ijcard.2021.12.014 . hal-03498005

**HAL Id: hal-03498005**

**<https://hal.science/hal-03498005v1>**

Submitted on 22 Jul 2024

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

**Title Page:**

**Implantable cardiac devices in sleep apnoea diagnosis: a systematic review and meta-analysis**

**Short title: Sleep apnoea diagnosis with implanted cardiac devices**

Raoua Ben Messaoud<sup>\*a</sup>, Charles Khouri<sup>\*a,b</sup>, Jean Louis Pépin<sup>a,c</sup>, Jean Luc Cracowski<sup>a,b</sup>, Renaud Tamisier<sup>a,c</sup>, Fabian Barbieri<sup>d</sup>, Anna Heidbreder<sup>e</sup>, Marie Joyeux-Faure<sup>a,c\$</sup> and Pascal Defaye<sup>f\$</sup>

a-HP2 Laboratory, Inserm U1300, Grenoble Alpes University, Grenoble, France

b-Regional Pharmacovigilance Center, Grenoble Alpes University Hospital, Grenoble, France

c-EFCR Laboratory, Thorax and Vessels division, Grenoble Alpes University Hospital, Grenoble, France

d-University Hospital for Internal Medicine III (Cardiology and Angiology), Medical University Innsbruck, Austria

e-Sleep Disorders Clinic, Department of Neurology, Medical University Innsbruck, Austria

f-Arrhythmia Unit, Cardiology Department, Grenoble Alpes University Hospital, Grenoble, France

**e-mail addresses :**

Raoua Ben Messaoud : ext-rbenmessaoud@chu-grenoble.fr : : "This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation"

Charles Khouri : ckhour@chu-grenoble.fr : : "This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation"

Jean Louis Pépin : JPepin@chu-grenoble.fr : : "This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation"

Jean Luc Cracowski : JLCracowski@chu-grenoble.fr : : "This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation"

Renaud Tamisier : RTamisier@chu-grenoble.fr : : "This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation"

Fabian Barbieri : fabian.barbieri@i-med.ac.at: : "This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation"

Anna Heidbreder : anna.heidbreder@i-med.ac.at: : "This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation"

Marie Joyeux-Faure : MJoyeuxfaure@chu-grenoble.fr: : "This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation"

Pascal Defaye : PDefaye@chu-grenoble.fr: : "This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation"

\*Co-first authors § Co-last authors

### **Address for correspondence:**

Jean-Louis Pépin and Charles Khouri

Laboratoire EFCR, CHU de Grenoble, CS 10217 38043 Grenoble – France

Phone: (33+) 4.76.76.55.16 / Fax: (33+) 4.76.76.55.86

E-mail: jpepin@chu-grenoble.fr

Word counts: 244 (Abstract); 3103 (Text)

### **Funding**

This work was supported by the French National Research Agency in the framework of the "Investissements d'avenir" program (ANR-15-IDEX-02) and the "e-health and integrated care and trajectories medicine and MIAI artificial intelligence" Chairs of excellence from the Grenoble Alpes University Foundation. This work was partially supported by MIAI @ Grenoble Alpes, (ANR-19-P3IA-0003).

### **Disclosure**

None of the authors has a relationship with industry or other conflicts of interest to declare concerning this work.

1 **Implantable cardiac devices in sleep apnoea diagnosis: a systematic review and meta-**  
2 **analysis**

3

4 **Short title: Sleep apnoea diagnosis with implanted cardiac devices**

5

6 Word counts: 244 (Abstract); 3103 (Text)

7

8 **Abbreviations:**

9 AF: Atrial Fibrillation

10 AHI: Apnoea-Hypopnoea Index

11 AIC: Akaike Information Criterion

12 AUC: Area Under the ROC Curve

13 AVB: Atrioventricular Block

14 BMI: Body Mass Index

15 CAI: Central Apnoea Index

16 CI: Confidence Interval

17 CPAP: Continuous Positive Airway Pressure

18 CRT-D: Cardiac Resynchronization Therapy Defibrillator

19 CRT-P: Cardiac Resynchronization Therapy Pacemaker

20 CSA: Central Sleep Apnoea

21 HF: Heart Failure

22 ICD: Implantable Cardioverter Defibrillator

23 OSA: Obstructive Sleep Apnoea

24 PG: Polygraphy

25 PM: Pacemaker

26 PSG: Polysomnography

- 1 RDI: Respiratory Disturbance Index
- 2 ROC: Receiver Operating Characteristic
- 3 SAS: Sleep Apnoea Syndrome
- 4 SND: Sinus Node Dysfunction

## 1 **Abstract**

## 2 **Background**

3 A particularly high burden of sleep apnoea is reported in patients treated with cardiac  
4 implants such as pacemakers and defibrillators. Sleep apnoea diagnosis remains a complex  
5 procedure mainly based on sleep and respiratory indices captured by polysomnography (PSG)  
6 or respiratory polygraphy (PG).

## 7 **Aim**

8 We aimed to evaluate the performance of implantable cardiac devices for sleep apnoea  
9 diagnosis compared to reference methods.

## 10 **Method**

11 Systematic structured literature searches were performed in PubMed, Embase and  
12 Cochrane Library was performed to identify relevant studies. Quantitative  
13 characteristics of the studies were summarized and a qualitative synthesis was  
14 performed by a randomized bivariate meta-analysis and completed by pre-specified  
15 sensitivity analyses for different implant types and brands.

## 16 **Results**

17 16 studies involving 999 patients met inclusion criteria and were included in the meta-  
18 analysis. The majority of patients were men, of mean age of  $64 \pm 4.6$  years. Sensitivity of  
19 cardiac implants for sleep apnoea diagnosis ranged from 60 to 100%, specificity from 50 to  
20 100% with a prevalence of sleep apnoea varying from 22 to 91%.

21 For an apnoea-hypopnoea index threshold  $\geq 30$  events/hour during polysomnography  
22 (corresponding to severe sleep apnoea), the overall performance of the implants was relevant  
23 with a sensitivity of 78% and a specificity of 79%.

24 Subgroup analyses on implant type and brand provided no additional information owing to  
25 the small number of studies.

1 **Conclusion**

2 The respiratory disturbance index provided by cardiac implants is clinically relevant and  
3 might improve access to sleep apnoea diagnosis in at-risk cardiovascular populations.

4

5 PROSPERO Registration number: CRD42020181656

6

7 **Keywords:** sleep apnoea syndrome, diagnosis, pacemaker, implantable cardiac defibrillator,  
8 polysomnography

9

10

## 1. Introduction

Obstructive sleep apnoea (OSA) [1] is a chronic condition nowadays considered as a major societal health problem due to its multi-organ implications that pose a disabling burden for affected individuals and on health systems. OSA affects nearly one billion people worldwide [2]. Individuals with cardiovascular [3, 4] and/or metabolic diseases [5, 6] comprise populations with high OSA prevalence. More than 60% of individuals with OSA exhibit obesity and co-morbidities including hypertension, arrhythmias, stroke, coronary heart disease, heart failure [7] and metabolic dysfunction [8]. These multimorbid OSA populations are frequently minimally symptomatic reporting few sleep apnoea-related complaints and patients are sometimes referred to sleep laboratories to identify treatable sleep-related cardio-metabolic risk factors.

Polysomnography (PSG), and respiratory polygraphy (PG), are the standard techniques for OSA diagnosis. However, in-laboratory PSG is onerous, associated with unacceptably long waiting lists and the manual scoring of sleep stages, micro-arousals, and respiratory events is challenging. Consequently they are unsuitable for the widespread use required to address the growing sleep apnoea epidemic [9], particularly in the context of the COVID-19 pandemic [10].

There is strong agreement among experts on the need to develop advanced diagnostic approaches that incorporate novel technologies providing valid surrogates for PSG. A particularly high burden of sleep apnoea has been reported in patients with cardiac implants [11]. prevalence of OSA varies with the indication for an ICD. In patients implanted for severe heart failure, sinus node dysfunction, atrial fibrillation or atrioventricular block [12, 13], the prevalence of OSA was up to 59%; however, OSA was estimated to be 32% in those with bradyarrhythmia. [12, 14].



In cardiac implant devices, sleep apnoea diagnosis depends on minute sensors measuring ventilation by means of transthoracic impedance. Thoracic impedance is determined by the proportion of air to fluids between two measurement locations. Implantable pacemakers measure transthoracic impedance between leads implanted in the endocardium and in the pectoral aggregate. Thoracic impedance rises with inspiratory effort and falls during expiration. From these measurements indices of sleep-related breathing disorders can be automatically derived [15-18].

Remote monitoring, which is nowadays standard practice for cardiac implants, allows clinical personnel to readily consult sleep apnoea severity indices stored in the device via a secured website [19]. According to the available literature, the sleep apnoea diagnosis performance of cardiac implants seems promising but overall interpretation is flawed by heterogeneity in the populations studied, use of different thresholds for sleep apnoea diagnosis, and the brand-specific development of proprietary algorithms that have different levels of performance.

In this context, the main objective of this systematic review and meta-analysis was to assess the performance of cardiac implant algorithms compared to PSG or respiratory PG.

## **2. Methods**

The protocol of this systematic review and meta-analysis followed the current recommendations of the PRISMA statement [20] and the Cochrane handbook [21]. The review and meta-analysis were prospectively registered on 5<sup>th</sup> July 2020 in the PROSPERO database ([https:// www.crd.york.ac.uk](https://www.crd.york.ac.uk))(Registration number: CRD42020181656).

### **2.1. Search strategy and resources**

The systematic comprehensive search for relevant studies used the bibliographic database Ovid MEDLINE(R) (Pubmed and EMBASE) and covered the period from their

inception up to September 2020. Studies potentially eligible for inclusion were initially sought by one author (RBM) using the following controlled vocabulary (MeSH) and text-words: sleep apnoea/apnea, pacemakers (PMs), Implantable Cardiac Defibrillator (ICD), implantable cardiac devices, PSG, respiratory PG, diagnosis. Further details of the literature search strategy are reported in the supplement.

We also searched of the reference lists of all studies registered between 2015 and 2020, and abstracts of major respiratory conferences including the annual pneumology and sleep congresses of the American Thoracic Society (ATS), the Associated Professional Sleep Societies (APSS), the European Respiratory Society (ERS), the European Sleep Research Society (ESRS), “la Société Française de Recherche et Médecine du Sommeil (SFRMS)”, and “la Société de Pneumologie de Langue Française (SPLF)”.

Two authors (RBM and MJF) screened all titles and abstracts and downloaded full-text publications of potentially relevant references. We selected only English language articles without restrictions on year of publication. As the main objective of our review was to assess the accuracy of cardiac devices (pacemakers (PMs) and defibrillators) for sleep apnoea diagnosis, we focused on two parameters, the sensitivity and specificity of cardiac device diagnosis compared to a reference method, PSG or respiratory PG. The availability of these parameters was thus mandatory for a study to be included in the meta-analysis. Thus, in all the included studies patients had to be implanted with a cardiac device and have undergone an overnight sleep test (PSG, PG). Selected studies were validated for inclusion independently by two other authors (JLP and PD). Any disagreement concerning the inclusion or not of a study was resolved by consensus and with input from a third author (RT).

This meta analysis was based on previously published studies, so new ethical approval or new patient consent were not required.

## **2.2. Data extraction**

For studies included in the final selection, the study characteristics and outcome data were extracted to a form designed to capture all essential and specific characteristics needed to assess the study's quality and the diagnostic accuracy of the surrogate for PSG. The extracted data included: identifiers (authors, year, and country), design (number of centres, interval between cardiac implantation and overnight PSG), patient characteristics (e.g. inclusion/exclusion criteria, age, sex, Body Mass Index (BMI), comorbidities), characteristics of the implantable cardiac device (e.g. type, brand, and name) and details on diagnostic accuracy (sensitivity, specificity and additional values). When necessary, the corresponding authors of published studies were contacted to request unpublished data sets, subgroup results or clarification of the study methods.

### **2.3. Quality assessment**

We assessed the risk of bias for each included study using the Quality Assessment of Diagnostic Accuracy Studies tool (QUADAS-2) [22] (see the online supplemental data).

### **2.4. Statistical analysis**

We performed a bivariate random effect meta-analysis to evaluate 0. Then, summary Receiver Operating Characteristic (ROC) curves were calculated based on the logit sensitivity and specificity.

Cardiac implant performances were reported at different apnoea–hypopnoea index (AHI) severity thresholds in different studies, therefore we estimated diagnostic accuracy parameters and the summary ROC curves using several different AHI severity thresholds ( $\geq 5$ ,  $\geq 15$  and  $\geq 30$  events/hour). When several cardiac implant thresholds were tested in a same study, we used the results from the authors' main analysis. To facilitate the interpretation of diagnostic accuracy estimates, we calculated the number of cases missed and the number of cases wrongly diagnosed in a hypothetical cohort of 1000 patients with cardiac

implants based on pooled sensitivity and specificity values from the meta-analysis. We calculated these values for an expected prevalence of sleep apnoea in the population of 20%, 40%, or 60%.

We assessed the heterogeneity of study estimates by examining Forest plots of sensitivity and specificity across studies and overlap of 95% CIs.

Subgroup analyses and meta-regressions were performed examining cardiac implant diagnostic performances for an AHI severity of  $\geq 30$  events/hour. We initially examined diagnostic accuracy parameters according to the type of cardiac implant (Cardiac Resynchronization Therapy Defibrillator (CRT-D), Cardiac Resynchronization Therapy Pacemaker (CRT-P), ICD, PM). For four studies we contacted the corresponding authors for subgroup results according to cardiac implant type and obtained the results for 2 studies [16, 23]. We also analyzed the different types of cardiac implants by brand (Boston Scientific, ELA Medical, Sorin/LivaNova, Medtronic) to assess brand-related diagnostic accuracy. Moreover, for the largest group (implants commercialized by Boston Scientific), we calculated sensitivities, specificities, and summary ROC curves for several cutoff values used for the diagnosis of severe sleep apnoea (AHI>30). We identified the best threshold value using the “metadiag” package developed by Steinhauser et al.[24]. To select the best model, we compared the Akaike Information Criterion (AIC) among a series of models with different specifications (i.e., common random versus different random intercepts, common versus different random slopes) and selected the one with the smallest AIC using the same strategy as presented by Steinhauser et al.[24].

We conducted univariate meta-regressions to explore whether the following characteristics: age, BMI, sex, atrial fibrillation (AF) and sleep apnoea prevalence, might influence the cardiac implant performance. All covariates with a P-value  $\leq 0.2$  were included in the multivariate model.

We explored the link between the quality and sensitivity analyses by removing studies considered at highest risk of bias across key domains (selection, verification).

Finally, we assessed publication bias by visually examining the Diagnostic Odds Ratio funnel plot for asymmetry.

All statistical analyses were performed with R (version 3.6.2) and mada, lme4, meta and diagmeta work packages.

### **3. Results**

#### **3.1. Overview of eligible studies**

From a total of 859 screened references from diverse sources, after applying the inclusion/exclusion criteria, 16 studies were found to be appropriate for a full-text review and were included in the qualitative and quantitative analyses (meta-analysis) (e-Figure 1).

#### **3.2. Study population**

Tables 1 and e-Table 1 summarize the properties of the selected studies [15-18, 23, 25-35] including the diagnostic data, the type of implant and the brand. Additional details about the included studies are reported in Supplemental e-Table 2. From an initial sample of 999 patients, we analyzed 750 complete sets of patient data (75%). All the participants had undergone one night of PSG/PG post-implantation at different time schedules. The delay between overnight PSG and device implantation varied from one day to 6 months. Incomplete datasets were due to missing Respiratory Disturbance Indices (RDI) owing to technical problems, invalid PSG data or loss to follow-up (death, patient withdrawal from study, hospitalization etc.).

The predominant brands were Boston Scientific, ELA Medical and Sorin/LivaNova. In 13 studies, patients had implanted pacemakers. We found 4 studies with CRT-P/D and 4 with ICD.

#### **3.3. Performance of cardiac implants**

The results of the bivariate random effect meta-analyses for the three most usual AHI thresholds ( $\geq 5$ ,  $\geq 15$  and  $\geq 30$  events/hour) are given in Table 3. Using these thresholds, the mean positive likelihood ratios were 3.74, 3.1 and 3.98, respectively. The summary ROC curves are presented for each threshold ( $\geq 5$ ,  $\geq 15$  and  $\geq 30$ , events/h) in Figure 2A, B and C respectively; and the Forest plots of the univariate analyses in Supplementary e-Figure 2.

The prevalence of sleep apnoea ranged from 22% to 91% according to the study (median, 75%; interquartile range, 62%-79%). We then calculated the post-test probabilities, missed cases, and wrongly diagnosed cases in a hypothetical cohort of 1000 patients using the results of the bivariate meta-analysis for pre-test probabilities of 20, 40 and 60% (e-Table 3).

### **3.4. Heterogeneity**

Visual examination of the Forest plots of the univariate meta-analyses (e-Figure 2) did not confirm a wide variation of study estimates. However, the prediction interval from the summary ROC curves (Figure 1) reflected substantial heterogeneity between studies.

### **3.5. Risk of bias and applicability**

The results of the Risk of bias assessment are shown in e-Figure 3 and Supplementary e-Table 4. None of the studies raised applicability concerns. We determined that there was a low risk of bias in 14 studies and 2 studies had a high risk of bias. Our results were unchanged after exclusion of the articles with a high risk of bias (e-Table 5).

### **3.6. Subgroup analyses**

For the majority manufacturer (Boston Scientific), we compared the performances of pacemakers using severe sleep apnoea thresholds obtained by different methods (AHI threshold of  $\geq 30$  by PSG or PG). Among the 7 available studies, the optimal threshold value for pacemakers was 33.14, yielding a sensitivity of 78% (59-90%) and a specificity of 71% (56-84%). Subgroup analyses for implant type and manufacturer (e-Table 6) did not provide additional information owing to the small number of studies in each subgroup.

### **3.7. Meta-regression analysis**

Including the main covariates (age, sex, BMI, AF or Sleep Apnoea Syndrome (SAS) prevalence) failed to give significant results in univariate meta-regression analysis (e-Table 7).

### **3.8. Publication bias**

No publication bias was suggested on visually inspecting the funnel plots for severe SAS. However, the funnel plot for AHI>15 suggests a potential publication bias (Figure 2).

## **4. Discussion**

To the best of our knowledge, this is the first meta-analysis to investigate whether there is agreement between respiratory disturbance indices (RDIs) derived from impedance sensors embedded in cardiac implants and the AHI provided by PSG or respiratory PG recordings. For an AHI threshold  $\geq 30$  events/hour, defining severe sleep apnoea, the sensitivity of cardiac implants for sleep apnoea diagnosis was 78% and the specificity was 79% with an area under the ROC curve of 0.84. At this threshold and with a SAS prevalence of 60%, the mean positive likelihood ratio was 3.98 giving post-test probability of obtaining a true-positive diagnosis of 84%.

The prevalence of Obstructive (OSA) and central sleep apnoea (CSA) reaches 50% in patients with the most common cardiovascular diseases [4, 36]. Pre-existing OSA is a strong predictor of incident coronary heart disease, HF [37] or AF [38] and then sleep apnoea appears as a strong modulator of the long-term trajectories of these diseases. As an example, occult OSA increases the recurrence of AF after ablation [39], therefore the European Society of Cardiology guidelines for atrial fibrillation recommend that AF patients should be screened for symptoms of OSA. However, most AF or cardiac failure patients are not somnolent and only minimally symptomatic for OSA[40] and strategies on how to implement OSA testing in routine daily cardiology practice are not well established [41].

While individual studies included in this systematic review reported on rather small and heterogeneous groups of patients, the current meta-analysis has provided a clearer picture of the clinical relevance of cardiac implants as diagnostic tools for sleep apnoea.

The diagnostic performance of cardiac implants reported here compares favorably with PSG or respiratory PG, and RDIs derived from cardiac implants significantly transformed the pre-test probability to a clinically relevant high post-test probability [42] of 84%, a true-positive diagnosis of severe sleep apnoea for a SAS prevalence of 60%.

A sleep apnoea diagnosis strategy supported by cardiac implant RDIs might provide several benefits for patients and improve the efficacy and productivity of healthcare providers.

Firstly, the diagnostic tool incorporated in cardiac implants can be directly consulted by cardiologists during their routine clinical practice. No action is required on the part of the patients, and moreover, telecardiology with remote monitoring and trained manpower already exists, avoiding unattainable investments for implementing a new diagnostic pathway [43]. The main limitation is that cardiologists show limited interest in this “apnoea” functionality with little or no integration into their routine practice. Screening for sleep apnoea through cardiac implants would provide a first triage, preventing patients with extremely low RDIs being referred for PSG and prioritizing patients with RDIs in the severe range for immediate diagnosis and management.

The “gold standard” for sleep apnoea diagnosis remains a subject of debate although laboratory polysomnography is consistently reported as the method of reference by international guidelines. However, assessment in a single night has been brought into question as it can lead to misdiagnosis, particularly for cardiology patients with frequent fluctuations in their clinical status. Implantable devices allowing assessments to be repeated across several nights and during both stable and unstable episodes might be more reliable than a single measurement in unfamiliar surroundings.



During the severe phases of the health crisis, most sleep centers have reported near-cessation of activities and growing waiting lists [44]. However, for cardiovascular diseases, during the COVID-19 pandemic, remote monitoring via cardiac implants has provided easy detection of arrhythmic events and acute decompensation issues without the need for in-person visits [45]. So, appropriate triage taking advantage of cardiac implant data might facilitate the flow of patients by prioritizing valid indications for in-laboratory testing.

Secondly, a substantial number of sleep apnoea patients show considerable night-to-night variability in RDI resulting in high rates of OSA diagnostic misclassification when only a single night of testing is used [46]. If, as suggested, sleep apnoea partly drives AF,[47] then a more accurate assessment of the severity of sleep apnoea may help improve the efficacy of rhythm control strategies [12, 48]. If sleep apnoea severity is variable, then daily monitoring through cardiac implants would provide a more complete picture of a patient's sleep apnoea over time. The evaluation of each patient could be improved using parameters calculated by remote monitoring platforms from the ICD measurements such as intrathoracic fluids as well as RDI, heart rate variability, and activity parameters.

Moreover, it has been shown that cardiac resynchronization therapy (CRT) reduces sleep apnoea severity [49,50]. The improvement is essentially explained by a reduction in central events. The presence of associated central sleep apnoea might be an additional item to consider when choosing a CRT device able to monitor sleep apnoea severity.

Another important benefit would be the potential of using exacerbations in sleep apnoea severity to detect acute cardiac events such as decompensated HF or the onset of AF[51-53]. An elevation in central apnoea index has been reported as being consistently associated with the progression of HF and acute HF exacerbation [54, 55] as well as being a marker of AF[56]. A rise in RDI detected by cardiac implants would nicely complement

existing remote monitoring tools designed to detect exacerbations, and thus reduce heart failure readmissions [57].

Certainly, the best strategy for improving sleep apnoea diagnosis is not solely based on technological advances but also by reshaping and digitalizing the diagnostic pathway [58].

Such approaches have been reported as promising, particularly the setting-up of virtual sleep laboratories/clinics allowing easy access to diagnosis and remote digital care in cardiologic populations [59]. One of the main advantages of implantable devices is that one can readily obtain repeated nightly measurements giving trajectories of sleep apnoea severity to assess responses to different treatment interventions including CPAP and to characterize daily CV risk (AF, CHF decompensation etc.) [48].

#### **4.1. Limitations**

The studies included were heterogeneous in terms of the populations, cardiac implant brands and metrics. This restricted comparisons between the algorithms used by different brands and sensitivity analyses in different contexts and patient subgroups. Also, a clear distinction between central and obstructive events contributing to the RDI is currently not available. This limits the interpretation of the findings of our meta-analysis and their application to clinical decisions because obstructive sleep apnoea entails treatment by Continuous Positive Airway Pressure (CPAP), whereas CSA requires the intensification of interventions to improve cardiac function or rhythm control. Future studies should certainly address these issues in more depth.

#### **5. Conclusion**

Patients with implantable cardiac devices represent only a small proportion of all individuals potentially requiring sleep apnoea testing. The diagnostic technique evaluated in this

metaanalysis is only available to a part of this large population in urgent need of simplified solutions for sleep apnoea diagnosis.

Based on our findings, we can confirm that the respiratory disturbance index provided by cardiac implants is clinically relevant and might improve access to sleep apnoea diagnosis in at-risk cardiovascular populations.

This article has an online data supplement.

### **Acknowledgement**

The authors would like to thank Alison Foote (Grenoble Alpes University Hospital, France) for editing the manuscript.

### **Funding**

This work was supported by the French National Research Agency in the framework of the "Investissements d'avenir" program (ANR-15-IDEX-02) and the "e-health and integrated care and trajectories medicine and MIAI artificial intelligence" Chairs of excellence from the Grenoble Alpes University Foundation. This work was partially supported by MIAI @ Grenoble Alpes, (ANR-19-P3IA-0003).

### **Disclosure**

None of the authors has a relationship with industry or other conflicts of interest to declare concerning this work.

### **Ethics committee approval**

Ethics committee approval is not applicable as this was not a clinical trial. All participants in the included studies had provided informed consent for the use of their anonymized data for research purposes.

## References

- [1]. Levy P, Kohler M, McNicholas WT, et al. Obstructive sleep apnoea syndrome. *Nat Rev Dis Primers*. 2015;1:15015.
- [2]. Benjafield AV, Ayas NT, Eastwood PR, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *The Lancet Respiratory Medicine*. 2019;7(8):687-98.
- [3]. Pepin JL, Borel AL, Tamisier R, Baguet JP, Levy P, Dauvilliers Y. Hypertension and sleep: overview of a tight relationship. *Sleep Med Rev*. 2014;18(6):509-19.
- [4]. Drager LF, McEvoy RD, Barbe F, Lorenzi-Filho G, Redline S, Initiative I. Sleep Apnea and Cardiovascular Disease: Lessons From Recent Trials and Need for Team Science. *Circulation*. 2017;136(19):1840-50.
- [5]. Ryan S, Cummins EP, Farre R, et al. Understanding the pathophysiological mechanisms of cardiometabolic complications in obstructive sleep apnoea: towards personalised treatment approaches. *Eur Respir J*. 2020;56(2).
- [6]. Ryan S, Arnaud C, Fitzpatrick SF, Gaucher J, Tamisier R, Pepin JL. Adipose tissue as a key player in obstructive sleep apnoea. *Eur Respir Rev*. 2019;28(152).
- [7]. Linz D, Hohl M, Ukena C, et al. Obstructive respiratory events and premature atrial contractions after cardioversion. *Eur Respir J*. 2015;45(5):1332-40.
- [8]. Kent BD, Grote L, Ryan S, et al. Diabetes mellitus prevalence and control in sleep-disordered breathing: the European Sleep Apnea Cohort (ESADA) study. *Chest*. 2014;146(4):982-90.
- [9]. Lyons MM, Bhatt NY, Pack AI, Magalang UJ. Global burden of sleep-disordered breathing and its implications. *Respirology*. 2020;25(7):690-702.

- [10]. Patel SR, Donovan LM. The COVID-19 Pandemic Presents an Opportunity to Reassess the Value of Polysomnography. *American journal of respiratory and critical care medicine*. 2020;202(3):309-10.
- [11]. Fox H, Bitter T, Gutleben KJ, Horstkotte D, Oldenburg O. Cardiac or Other Implantable Electronic Devices and Sleep-disordered Breathing - Implications for Diagnosis and Therapy. *Arrhythmia & electrophysiology review*. 2014;3(2):116-9.
- [12]. Garrigue S, Pépin JL, Defaye P, et al. High prevalence of sleep apnea syndrome in patients with long-term pacing: the European Multicenter Polysomnographic Study. *Circulation*. 2007;115(13):1703-9.
- [13]. Moubarak G, Bouzeman A, de Geyer d'Orth T, Bouleti C, Beuzelin C, Cazeau S. Variability in obstructive sleep apnea: Analysis of pacemaker-detected respiratory disturbances. *Heart rhythm*. 2017;14(3):359-64.
- [14]. Fietze I, Röttig J, Quispe-Bravo S, et al. Sleep apnea syndrome in patients with cardiac pacemaker. *Respiration; international review of thoracic diseases*. 2000;67(3):268-71.
- [15]. Scharf C, Cho YK, Bloch KE, et al. Diagnosis of sleep-related breathing disorders by visual analysis of transthoracic impedance signals in pacemakers. *Circulation*. 2004;110(17):2562-7.
- [16]. Defaye P, Mendelson M, Tamisier R, et al. Validation of an apnea and hypopnea detection algorithm implemented in implantable cardioverter defibrillators. The AIRLESS study. *Scientific reports*. 2019;9(1):9597.
- [17]. D'Onofrio A, La Rovere MT, Emdin M, et al. Implantable cardioverter-defibrillator-computed respiratory disturbance index accurately identifies severe sleep apnea: The DASAP-HF study. *Heart rhythm*. 2018;15(2):211-7.

- [18]. Defaye P, de la Cruz I, Martí-Almor J, et al. A pacemaker transthoracic impedance sensor with an advanced algorithm to identify severe sleep apnea: the DREAM European study. *Heart rhythm*. 2014;11(5):842-8.
- [19]. Health Quality O. Remote Monitoring of Implantable Cardioverter-Defibrillators, Cardiac Resynchronization Therapy and Permanent Pacemakers: A Health Technology Assessment. *Ont Health Technol Assess Ser*. 2018;18(7):1-199.
- [20]. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
- [21]. Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. *Cochrane Database Syst Rev*. 2019;10:ED000142.
- [22]. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med*. 2011;155(8):529-36.
- [23]. Barbieri F, Dichtl W, Heidbreder A, et al. Sleep apnea detection by a cardiac resynchronization device integrated thoracic impedance sensor: A validation study against the gold standard polysomnography. *PloS one*. 2018;13(4):e0195573.
- [24]. Steinhauser S, Schumacher M, Rucker G. Modelling multiple thresholds in meta-analysis of diagnostic test accuracy studies. *BMC Med Res Methodol*. 2016;16(1):97.
- [25]. Aimé E, Rovida M, Contardi D, et al. Long-term screening for sleep apnoea in paced patients: preliminary assessment of a novel patient management flowchart by using automatic pacemaker indexes and sleep lab polygraphy. *Heart, lung & circulation*. 2014;23(10):943-50.
- [26]. Chen R, Chen K, Dai Y, Zhang S. Utility of transthoracic impedance and novel algorithm for sleep apnea screening in pacemaker patient. *Sleep & breathing = Schlaf & Atmung*. 2019;23(3):741-6.

- [27]. Defaye P, Pépin JL, Poezevara Y, et al. Automatic recognition of abnormal respiratory events during sleep by a pacemaker transthoracic impedance sensor. *Journal of cardiovascular electrophysiology*. 2004;15(9):1034-40.
- [28]. Dias M, Gonçalves I, Amann B, et al. Utility of new-generation pacemakers in sleep apnea screening. *Sleep medicine*. 2017;37:27-31.
- [29]. Gonçalves IS, Agostinho JR, Silva G, et al. Accuracy and utility of a pacemaker respiratory monitoring algorithm for the detection of obstructive sleep apnea in patients with atrial fibrillation. *Sleep medicine*. 2019;61:88-94.
- [30]. Ribeiro S, Bonito L, Guimaraes MJ, et al. Importance of cardiac implantable electronic devices in the diagnosis of Sleep Apnea Syndrome. *Rev Port Cardiol*. 2019;38(6):451-5.
- [31]. Shalaby A, Atwood C, Hansen C, et al. Feasibility of automated detection of advanced sleep disordered breathing utilizing an implantable pacemaker ventilation sensor. *Pacing and clinical electrophysiology : PACE*. 2006;29(10):1036-43.
- [32]. Taguchi Y, Matsushita K, Ishikawa T, et al. Successful screening of sleep-disordered breathing using a pacemaker-based algorithm in Japan. *Journal of cardiology*. 2019;73(5):394-400.
- [33]. Della Rocca DG, Albanese M, Placidi F, et al. Feasibility of automated detection of sleep apnea using implantable pacemakers and defibrillators: a comparison with simultaneous polysomnography recording. *Journal of interventional cardiac electrophysiology : an international journal of arrhythmias and pacing*. 2019;56(3):327-33.
- [34]. Lima Da Silva G., Guimaraes T., Francisco A.R.G., et al. Added value of Pacemaker respiratory monitoring algorithm versus conventional polisomnography in the diagnosis of obstructive sleep apnoea. *Eur Heart J*. 2016.

- [35]. Simon Pearce S., Cowie M.R. SR, Polkey M., A. V. Validity of an algorithm in implantable devices for the diagnosis of sleepdisordered breathing in heart failure. *Eur Heart J*. 2016;72-3.
- [36]. Gottlieb DJ, Punjabi NM. Diagnosis and Management of Obstructive Sleep Apnea: A Review. *JAMA*. 2020;323(14):1389-400.
- [37]. Gottlieb DJ, Yenokyan G, Newman AB, et al. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. *Circulation*. 2010;122(4):352-60.
- [38]. Gami AS, Hodge DO, Herges RM, et al. Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation. *J Am Coll Cardiol*. 2007;49(5):565-71.
- [39]. Farrehi PM, O'Brien LM, Bas HD, et al. Occult obstructive sleep apnea and clinical outcomes of radiofrequency catheter ablation in patients with atrial fibrillation. *J Interv Card Electrophysiol*. 2015;43(3):279-86.
- [40]. Kadhim K, Lau DH, Sanders P, Linz D. Sleep apnea in atrial fibrillation - Highly prevalent, highly relevant, but most patients are not somnolent! *Int J Cardiol Heart Vasc*. 2020;26:100463.
- [41]. Desteghe L, Hendriks JML, McEvoy RD, et al. The why, when and how to test for obstructive sleep apnea in patients with atrial fibrillation. *Clin Res Cardiol*. 2018;107(8):617-31.
- [42]. Collop NA, Anderson WM, Boehlecke B, et al. Clinical guidelines for the use of unattended portable monitors in the diagnosis of obstructive sleep apnea in adult patients. Portable Monitoring Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med*. 2007;3(7):737-47.



- [43]. Parthiban N, Esterman A, Mahajan R, et al. Remote Monitoring of Implantable Cardioverter-Defibrillators: A Systematic Review and Meta-Analysis of Clinical Outcomes. *J Am Coll Cardiol*. 2015;65(24):2591-600.
- [44]. Johnson KG, Sullivan SS, Nti A, Rastegar V, Gurubhagavatula I. The impact of the COVID-19 pandemic on sleep medicine practices. *J Clin Sleep Med*. 2020.
- [45]. Piro A, Magnocavallo M, Della Rocca DG, et al. Management of cardiac implantable electronic device follow-up in COVID-19 pandemic: Lessons learned during Italian lockdown. *J Cardiovasc Electrophysiol*. 2020.
- [46]. Roeder M, Bradicich M, Schwarz EI, et al. Night-to-night variability of respiratory events in obstructive sleep apnoea: a systematic review and meta-analysis. *Thorax*. 2020.
- [47]. Mazza A, Bendini MG, De Cristofaro R, Lovecchio M, Valsecchi S, Boriani G. Pacemaker-detected severe sleep apnea predicts new-onset atrial fibrillation. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology*. 2017;19(12):1937-43.
- [48]. Linz D, Brooks AG, Elliott AD, et al. Variability of Sleep Apnea Severity and Risk of Atrial Fibrillation: The VARIOS-AF Study. *JACC Clinical electrophysiology*. 2019;5(6):692-701.
- [49]. Mascia G, Paoletti Perini A, Cartei S, et al. Sleep-disordered breathing and effectiveness of cardiac resynchronization therapy in heart failure patients: gender differences? *Sleep Med*. 2019;64:106-11.
- [50]. Lamba J, Simpson CS, Redfearn DP, Michael KA, Fitzpatrick M, Baranchuk A. Cardiac resynchronization therapy for the treatment of sleep apnoea: a meta-analysis. *Europace*. 2011;13(8):1174-9.

- [51]. Schmickl CN, Heckman E, Owens RL, Thomas RJ. The Respiratory Signature: A Novel Concept to Leverage Continuous Positive Airway Pressure Therapy as an Early Warning System for Exacerbations of Common Diseases such as Heart Failure. *J Clin Sleep Med*. 2019;15(6):923-7.
- [52]. Light M, Orr JE, Malhotra A, Owens RL. Continuous positive airway pressure device detects atrial fibrillation induced central sleep apnoea. *Lancet* 2018;392(10142):160.
- [53]. Prigent A, Serandour AL, Luraine R, Poineuf JS, Bosseau C, Pepin JL. Interrelated atrial fibrillation and leaks triggering and maintaining central sleep apnoea and periodic breathing in a CPAP-treated patient. *Respirol Case Rep*. 2020;8(8):e00666.
- [54]. Khayat R, Jarjoura D, Porter K, et al. Sleep disordered breathing and post-discharge mortality in patients with acute heart failure. *Eur Heart J*. 2015;36(23):1463-9.
- [55]. Tremel F, Pepin JL, Veale D, et al. High prevalence and persistence of sleep apnoea in patients referred for acute left ventricular failure and medically treated over 2 months. *Eur Heart J*. 1999;20(16):1201-9.
- [56]. Linz D, Baumert M, Desteghe L, et al. Nightly sleep apnea severity in patients with atrial fibrillation: Potential applications of long-term sleep apnea monitoring. *Int J Cardiol Heart Vasc*. 2019;24:100424.
- [57]. Emani S. Remote Monitoring to Reduce Heart Failure Readmissions. *Curr Heart Fail Rep*. 2017;14(1):40-7.
- [58]. Pepin JL, Baillieul S, Tamisier R. Reshaping Sleep Apnea Care: Time for Value-based Strategies. *Ann Am Thorac Soc*. 2019;16(12):1501-3.
- [59]. Verhaert DVM, Betz K, Gawalko M, et al. A VIRTUAL Sleep Apnoea management pathway For the work-up of Atrial fibrillation patients in a digital Remote Infrastructure: VIRTUAL-SAFARI. *Europace*. 2021.

## Figure legends

### **Figure 1. Summary ROC curve of the bivariate model with study estimates**

The solid line is the summary ROC curve; the red line is the 95% CI around the summary point, the broken line is the prediction interval.

### **Figure 2. Funnel plot of studies assessing the performances of pacemakers for moderate to severe and severe SAS diagnosis, using the Diagnostic Odds Ratio**

Funnel plots for AHI>5 but <15 are not shown due to the small number of studies (n=2)

**Graphical Abstract:** An overview on sleep apnoea diagnosis with cardiac devices versus the reference test (Polysomnography or Polygraphy) and the principal meta-analysis results

## Tables

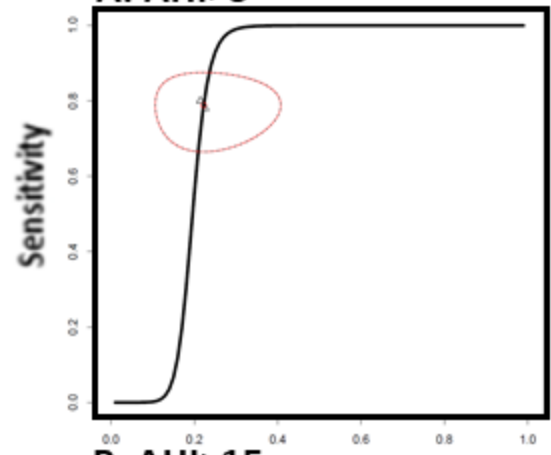
### **Table 1. Characteristics of included studies**

### **Table 2. Results of the bivariate meta-analysis for the 3 selected apnoea-hypopnoea cut-offs**

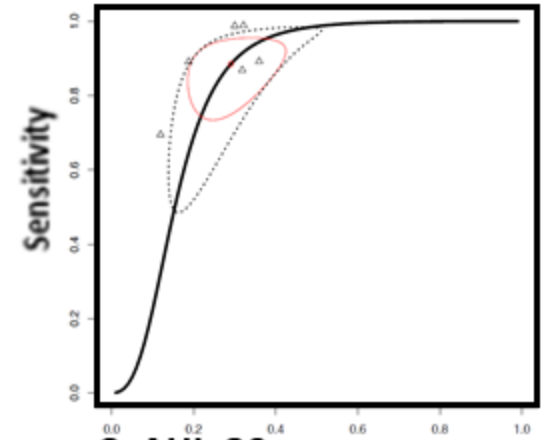
## Online Data Supplement

Including e-Figure1 to e-Figure 4 and e-Tables 1 to 7.

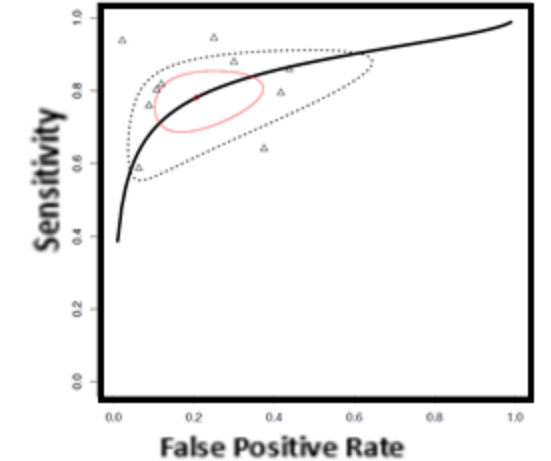
**A. AHI>5**



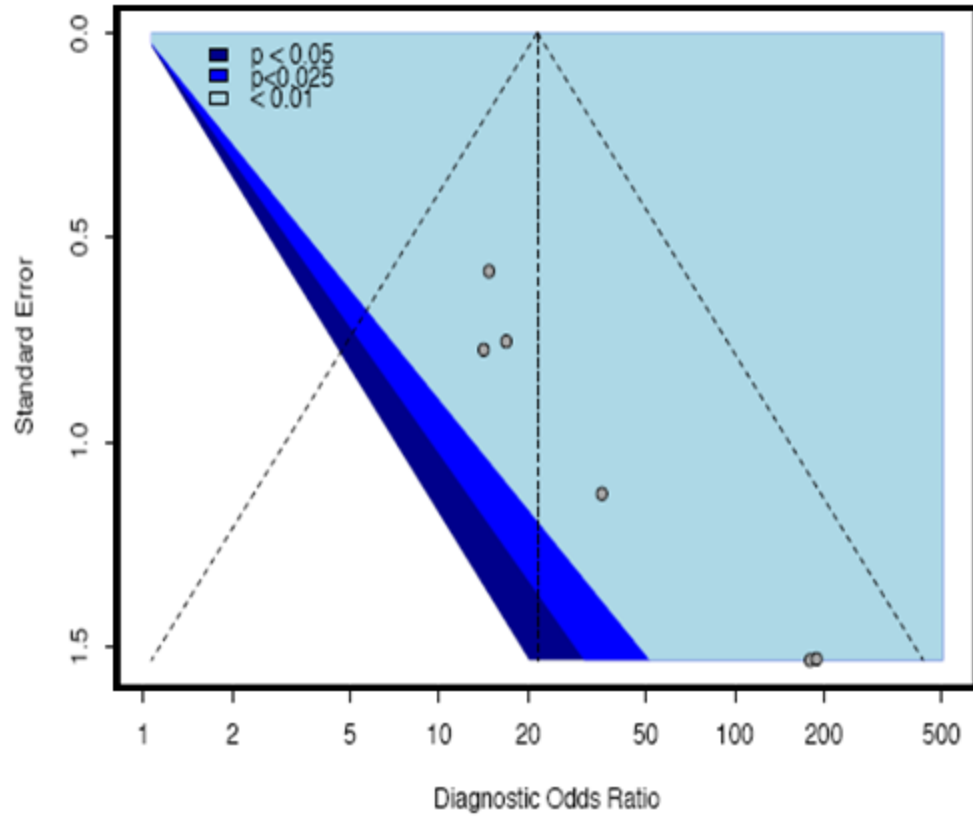
**B. AHI>15**



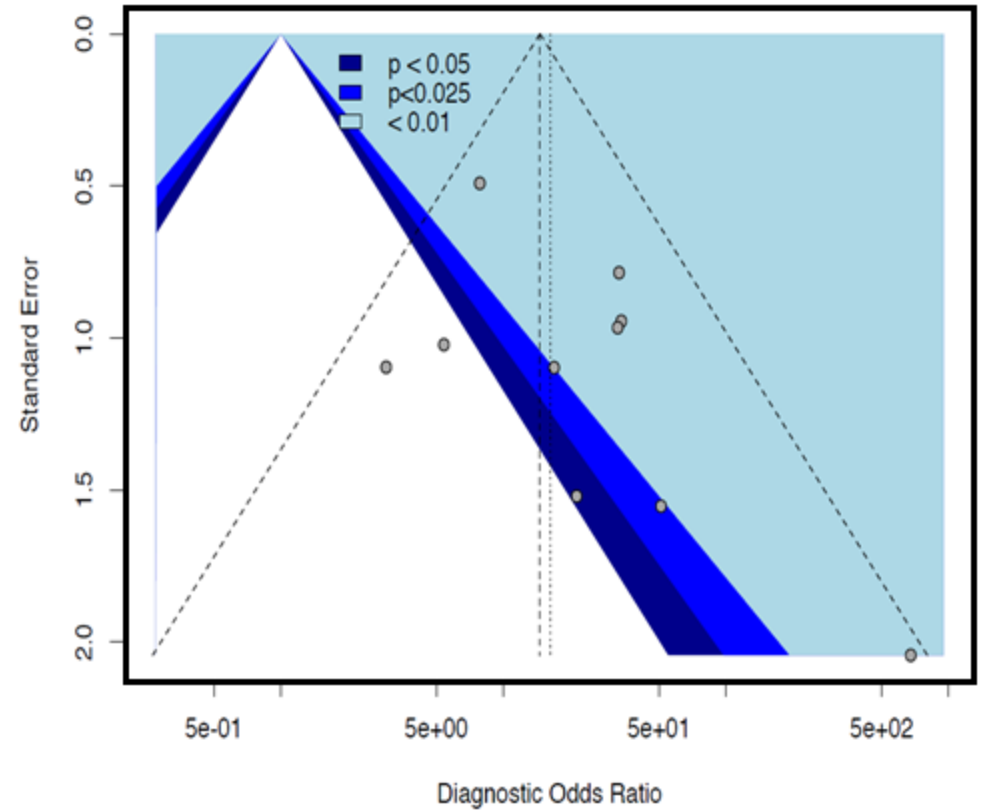
**C. AHI>30**



**B. AHI>15**



**C. AHI>30**



Study (Author, year)	Country (number of centers)	Implant type	Included patients	Valid data	Age (years)	BMI (kg/m <sup>2</sup> )	Sexe M/F	AF	SAS
Aimé et al, 2014 (23)	Italy (1)	26 PM Talent, ELA Medical	61	26	71.4	22.6	13/13	NS	22
Barbieri et al, 2018 (21)	Austria (1)	18 CRT-D / 23 CRT-P, Boston Scientific	41	21	75.0	25.7	31/10	24	16
Chen et al, 2018 (24)	China (1)	55 PM Vitalio J237 or J27, Boston Scientific	64	55	66.5	24.5	40/24	27	42
					68.6	23.4	40/24	27	42
D'Onofrio et al, 2017 (16)	Italy (13)	87 CRT-D / 86 ICD, Boston Scientific	265	173	68.0	27.0	139/34	31	38
Defaye et al, 2004 (25)	France, UK, Belgium	42 PM Talent, ELA Medical	46	42	70.5	26.0	30/12	NS	26
Defaye et al, 2014 (17)	France-Spain	40 PM Reply TM 200, Sorin CRM	40	31	73.8	27.7	27/13	14	28
Defaye et al, 2019 (15)	France (3)	9 CRT-D / 16 ICD Boston Scientific	70	25	59.9	25.9	24/1	12	8
Della Roca DG et al, 2019	Italy (7)	12 PM 19 ICD Boston Scientific	31	29	70	29	20/11	NS	NS
Dias et al, 2017 (26)	Portugal (1)	54 PM Reply TM 200, LivaNova	60	54	77.0	27.0	31/23	NS	40
Gonçalves et al, 2019 (27)	Portugal (1)	81 PM Reply TM 200, kora TM 100 and Kora TM 250 Microport	81	81	73.0	NS	47/34	36	50
Lima Da Silva G et al, 2016		24 PM Reply TM 200 LivaNova	24	24	75	NS	NS	NS	NS
Pearse S.S et al, 2016		60 PM Boston Scientific	60	50	69	NS	43/17	NS	NS
Ribeiro et al, 2019 (28)	Spain (1)	23 PM Reply 200 kora TM 100 Livanova / 5 CRT-D / 1 ICD, Boston Scientific	29	29	76.1	26.8	21/8	8	22
						27.0	21/8	8	22
Scharf et al, 2004 (14)	Switzerland (2)	22 PM Kappa 400, Medtronic	22	22	65.5	28.0	14/8	NS	17
Shalaby et al, 2006 (29)	Germany-PA (3)	54 PM Pulsar Max Pulsar Max II Insignia Plus, Boston Scientific	60	54	62.0	33.0	45/15	2	40
					67.0	29.0	45/15	11	40

Taguchi et al, 2019 (30)	Japan (1)	34 PM Reply TM 200, Kora 250, Sorin/LivaNoVa	45	34	71.2	23.4	18/16	14	31
--------------------------	-----------	---	----	----	------	------	-------	----	----

AF, Atrial Fibrillation; BMI, Body Mass Index, CRT-D, Cardiac Resynchronization Therapy Defibrillator; CRT-P, Cardiac Resynchronization Therapy pacemaker; F, Female; ICD, Implantable Cardiac Defibrillator; M, Male; NS, Non-Specified; PM, pacemaker; SAS, Sleep Apnea Syndrome.

Table 2. Results of the bivariate meta-analysis for the 3 selected apnea-hypopnea cut-offs

<b>AHI cutoff</b>	<b>Number of studies</b>	<b>Sensitivity (95% CI)</b>	<b>Specificity (95% CI)</b>	<b>Area under the ROC curve</b>	<b>Positive Likelihood Ratio (95% CI)</b>	<b>Negative Likelihood Ratio (95% CI)</b>
<b>5</b>	2	0.79 (0.69-0.86)	0.78 (0.63-0.87)	0.80	3.74 (2.09- 6.38)	0.28 (0.17- 0.41)
<b>15</b>	6	0.89 (0.77-0.95)	0.71 (0.60- 0.80)	0.82	3.10 (2.26- 4.25)	0.17 (0.08- 0.31)
<b>30</b>	10	0.78 (0.71-0.84)	0.79 (0.66-0.88)	0.84	3.98 (2.34- 6.57)	0.28 (0.21- 0.37)

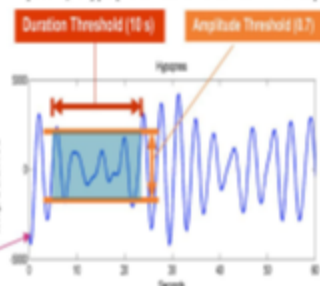
AURC, Area under the ROC curve; CI, Confidence Interval



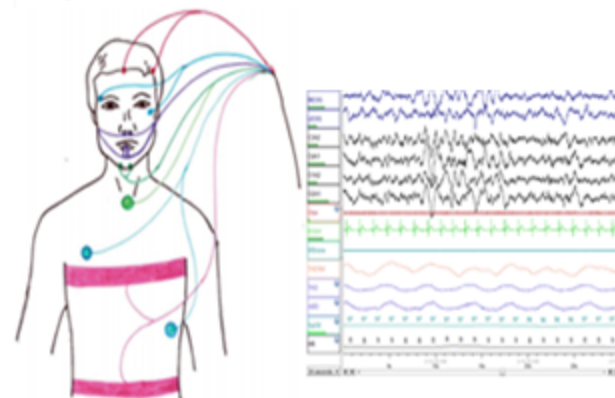
## Implantable cardiac devices



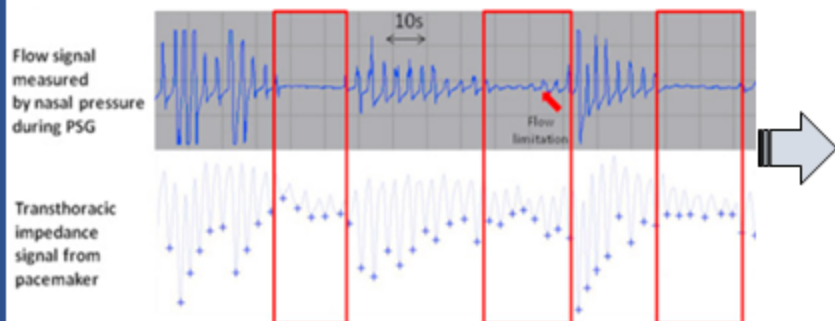
### Apnea / Hypopnea Event Detection Example



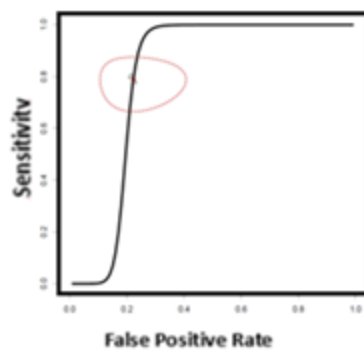
## Polysomnography (PSG)



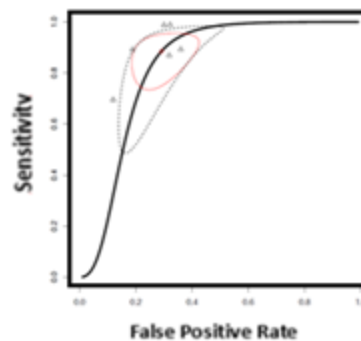
## Comparison of a one night PSG and The cardiac device events for different AHI thresholds



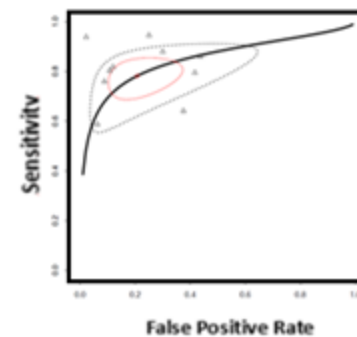
### A. AHI>5



### B. AHI>15



### C. AHI>30



A high global performance for each threshold