AJRCCM Articles in Press. Published on 21-June-2017 as 10.1164/rccm.201612-2497OC

Title: CONVENTIONAL POLYSOMNOGRAPHY IS NOT NECESSARY FOR THE MANAGEMENT OF MOST PATIENTS WITH SUSPECTED OBSTRUCTIVE SLEEP APNEA

Subtitle: Non-inferiority, randomized controlled trial

Authors:

Jaime Corral MD[1,2], Maria-Ángeles Sánchez-Quiroga MD[3], Carmen Carmona-Bernal PhD[4], Ángeles Sánchez-Armengol PhD[4], Alicia Sánchez-de-la-Torre MS[2,5], Joaquín Durán-Cantolla PhD[2,6], Carlos J Egea MD[2,6], Neus Salord PhD[2,7], Carmen Monasterio PhD[2,7], Joaquín Terán PhD[2,8], M Luz Alonso-Alvarez MD[2,8], Jesús Muñoz-Méndez MD[9], Eva M Arias MD[9], Marta Cabello MD[10], Josep M Montserrat PhD[2,11], Mónica De la Peña MD[2,12], José C Serrano MD[15], Ferran Barbe PhD[2,5], Juan F Masa PhD[1,2] and Spanish Sleep Network.

Collaborating group (Spanish Sleep Network): Ricardo Pereira ECS[1,2], Estefanía Garcia-Ledesma MD[1,2], Francisco J Gómez de Terreros PhD[1,2], Miguel Merchan MStat[1], Pedro Mañas[4], M Isabel Asensio-Cruz MD[4], Silvia Gómez MD[5], Anunciación Cortijo MD[5], Ainhoa Álvarez-Ruiz de Larrinaga[6], Jaime Marcos Cabrero MD[6], Mercé Gasa PhD[7], Sandra Pérez-Ramos[7], Estrella Ordax MD[8], Trinidad Díaz-Cambriles MD[9], M Ángeles Martínez-Martínez MD[10], Olga Cantalejo[10], Marta Torres PhD[11], Nuria Toledo-Pons MD[12], Ángel Ortega-González MD[13] and F Javier Barca PhD[14].

Affiliations: (1) San Pedro de Alcántara Hospital, Cáceres, Spain; (2) CIBER of Respiratory Diseases (CIBERES), ISCIII, Madrid, Spain; (3) Virgen del Puerto Hospital, Plasencia, Spain; (4) Virgen del Rocío Hospital, Sevilla, Spain; (5) Arnau de Vilanova y Santa María Hospital, Lleida, Spain; (6) OSI Araba University Hospital, Bioaraba Research Institute, Vitoria, Spain;

(7) Bellvitge Hospital, Hospitalet de Llobregat, Spain; (8) Burgos University Hospital, Burgos, Spain; (9) 12 de Octubre Hospital, Madrid, Spain; (10) Marqués de Valdecilla Hospital, Santander, Spain; (11) Clinic Hospital, Barcelona, Spain; (12) Son Espases Hospital, Mallorca, Spain; (13) Llerena-Zafra Hospital, Zafra, Spain.; and (14) Extremadura University, Cáceres, Spain

Corresponding author: Juan F Masa (fmasa@separ.es)

C/ Rafael Alberti 12, 10005 Cáceres, Spain

Telephone number: 0034927256296

Fax number: 0034927256297

Key words: sleep apnea; portable monitor; home respiratory polygraphy; cost-effectiveness

Total word count: 3,500

Sources of Funding: Sociedad Española de Neumología (SEPAR), Air Liquide (Spain), Asociación de Neumologos del Sur (Neumosur), and Sociedad Extremeña de Neumología (SEAR).

Conflict of interest: Our research team has no conflict of interest.

ClinicalTrials.gov ID: NCT01752556

This article has an online data supplement, which is accessible from this issue's table of contents online at www.atsjournals.org.

AJRCCM Articles in Press. Published on 21-June-2017 as 10.1164/rccm.201612-2497OC

Author contributions:

1. Substantial contributions to the study conception and design, acquisition of the data, or analysis and interpretation of the data: Juan F Masa PhD, M Ángeles Sánchez-Quiroga MD, Jaime Corral MD, Carmen Carmona-Bernal PhD, Ángeles Sánchez-Armengol PhD, Alicia Sánchez-de- la-Torre MS, Ferran Barbe PhD, Joaquín Durán-Cantolla PhD, Carlos J Egea MD, Neus Salord PhD, Carmen Monasterio PhD, Joaquín Terán PhD, M Luz Alonso-Martínez MD, Jesús Muñoz-Méndez MD, Eva M Arias MD, Marta Cabello MD, Josep M Montserrat PhD, Mónica De la Peña MD, José C Serrano MD

2. Drafted the article or revised the article critically for important intellectual content: Juan F Masa PhD, M Ángeles Sánchez-Quiroga MD, Jaime Corral MD, Carmen Carmona PhD, Ángeles Sánchez-Armengol PhD, Alicia Sánchez-De la Torre MS, Ferran Barbe PhD, Joaquín Durán-Cantolla PhD, Carlos J Egea MD, Neus Salord PhD, Carmen Monasterio PhD, Joaquín Terán PhD, M Luz Alonso-Martínez MD, Jesús Muñoz-Méndez MD, Marta Cabello MD, Josep M Montserrat PhD, Mónica De la Peña MD, José C Serrano MD

3. Final approval of the version to be published: Juan F Masa PhD, M Ángeles Sánchez-Quiroga MD and Jaime Corral MD

ABSTRACT

Rationale: Home respiratory polygraphy may be a simpler alternative to in-laboratory polysomnography for the management of more symptomatic obstructive sleep apnea patients, but its effectiveness has not been evaluated across a broad clinical spectrum.

Objective: To compare the long-term effectiveness (6 months) of home respiratory polygraphy and polysomnography management protocols in patients with intermediate to high sleep apnea suspicion (most patients requiring a sleep study).

Method: A multicentric, non-inferiority, randomized controlled trial with two open parallel arms and a cost-effectiveness analysis was performed in twelve tertiary hospitals in Spain. Sequentially screened patients with sleep apnea suspicion were randomized to respiratory polygraphy or polysomnography protocols. Moreover**,** both arms received standardized therapeutic decision-making, continuous positive airway pressure (CPAP) treatment or a healthy habit assessment, autoCPAP titration (for CPAP indication), health-related quality-of-life questionnaires, 24-hour blood pressure monitoring and polysomnography at the end of follow-up. The main outcome was the Epworth sleepiness scale measurement. The non-inferiority criterion was -2 points on the Epworth scale.

Results: In total, 430 patients were randomized. The respiratory polygraphy protocol was non-inferior to the polysomnography protocol based on the Epworth scale. Quality of life, blood pressure and polysomnography were similar between protocols. Respiratory polygraphy was the most cost-effective protocol, with a lower per-patient cost of 416.7€.

Conclusion: Home respiratory polygraphy management is similarly effective to polysomnography, with a substantially lower cost. Therefore, polysomnography is not necessary for the vast majority of patients with suspected sleep apnea. This finding could change established clinical practice, with a clear economic benefit.

Word count, abstract: 249

AJRCCM Articles in Press. Published on 21-June-2017 as 10.1164/rccm.201612-2497OC

INTRODUCTION

Obstructive sleep apnea (OSA) is a highly prevalent disease (1) that reduces quality of life (2) and increases cardiovascular (3,4) and traffic accident risks (5,6). The gold standard for OSA diagnosis is in-laboratory polysomnography (PSG), but it is expensive and time consuming. Less complex portable monitoring devices have been designed for rapid home diagnosis. However, the role of portable monitors in OSA management (diagnosis, treatment election and long-term effectiveness) is not fully defined.

The most frequently used type III portable monitor is an accepted (7) and cheaper (8-11) alternative for OSA diagnosis in patients with OSA suspicion who may or may not receive continuous positive airway pressure (CPAP) treatment if OSA is demonstrated. This portable monitor, also called respiratory polygraphy, includes sensors for airflow, respiratory effort, and pulse oximetry readings. However, in a large study of patients with intermediate to high clinical suspicion of OSA, the therapeutic decision making performed after diagnosis (CPAP or other treatments) by home respiratory polygraphy (HRP) was only applicable to patients with severe OSA (40% of the total sample) (12).

Other studies comparing the effectiveness of HRP and PSG protocols (diagnosis and treatment effectiveness) selected patients with a high clinical suspicion of OSA who received CPAP therapy if OSA (apnea-hypopnea index (AHI)≥15) was demonstrated (13-15) and showed similar medium-term effectiveness. However, in these studies, patients with a lower OSA suspicion or an AHI<15 (who did not receive CPAP treatment) were not included in the effectiveness analysis, resulting in an important bias related to a greater number of patients who could potentially be managed by HRP (more than twice the number reported). Neither of these studies assessed the cost-effectiveness relationship; two studies analyzed costs using other analysis methods (15,16) and demonstrated favorable findings for the HRP approach. Therefore, HRP could be a cheaper management alternative to PSG in patients with a high clinical probability of OSA who are

treated with CPAP. However, this finding may not apply to a wider clinical spectrum of patients who require a sleep study but may or may not be treated with CPAP. Moreover, the addition of the cost required to perform PSG for the management of patients without a high OSA suspicion who need a sleep study should minimize the economic advantage estimated in previous studies using HRP instead of PSG (17).

We hypothesized that the effectiveness of OSA management using HRP for the vast majority of patients who require a sleep study (who will or will not be treated with CPAP) is not inferior to management using PSG. We conducted a large, multicentric, non-inferiority, randomized controlled trial with two open parallel arms with a cost-effectiveness analysis in patients with an intermediate to high clinical probability of OSA to determine the effectiveness of HRP and PSG management protocols based on six months of follow-up using the Epworth sleepiness scale (ESS) as the primary outcome measure.

Some of the results of these studies have been previously reported in the form of abstracts (18,19).

METHODS

Participants

From May 2012 to June 2015, we sequentially screened patients between 18 and 70 years of age who were referred for pulmonary consultations because of suspected OSA at twelve tertiary hospitals in Spain (see online data supplement). Other inclusion criteria were 1) snoring or sleep apneas observed by a partner, 2) ESS ≥10 and 3) absence of clinical suspicion of any other sleep pathology that could cause daytime sleepiness (e.g., narcolepsy). The exclusion criteria were 1) psycho-physical inability to complete the questionnaires, 2) documented structural or coronary cardiopathy that was not controlled by medical treatment, 3) Cheynes-Stokes syndrome, 4) patients with uvulopalatopharyngoplasty, which can prevent effective CPAP treatment, 5) very severe

AJRCCM Articles in Press. Published on 21-June-2017 as 10.1164/rccm.201612-2497OC

nasal obstruction, which can prevent CPAP treatment, and 6) an inability to provide informed consent. The ethics committees of the twelve centers approved the study (*CEIC: Comité Etico de Investigación Clínica*). Written informed consent was obtained from all patients.

Intervention

Due to the large volume of potential patients, each center selected one, two or three days per week (depending on its work organization) to include all eligible patients on those days. We used a database to generate a simple randomization sequence. All randomized patients received instructions to maintain correct sleep hygiene (avoid the supine position; maintain regular sleep habits; not use sedatives, stimulants, alcohol or consume large meals before going to bed) and to adhere to a hypocaloric diet if they were overweight or obese. In addition, patients from both study arms followed their habitual healthcare attention with potential visits and treatments of other specialists and primary care physicians who were blinded for the allocated arm. Patients randomized to HRP or PSG protocols were treated or not with CPAP based on the results from the tests and clinical symptoms (see therapeutic decision making). The CPAP treatment groups received a home pressure titration night with an autoCPAP device (see autoCPAP titration).

HRP

Our HRP (Embla-Embletta, Natus, Pleasanton, CA, USA) measurements included oxygen saturation, airflow through nasal pressure, and thoracic and abdominal movements measured by piezoelectric bands. The patients transported the device to their homes with a prior detailed explanation and functional test device provided by a technician in the hospital setting. When the patients returned the device the following day, the raw data files were transmitted to a computer and scored manually, excluding artifact periods. PSG was performed in patients with invalid HRP tests after several repetitions, and the

subsequent cost was added to the HRP arm (see Figure E1 in the online-data supplement).

PSG in the hospital

We used standard protocols to perform PSGs and analyze the results (see online data supplement).

PSG and HRP studies with less than three recorded hours were repeated on two other occasions, and the costs were included in the overall cost calculation. For PSG, apnea was the absence of flow lasting 10 seconds or more, and hypopnea was a discernible decrease in flow lasting 10 seconds or more with oxygen desaturation (≥3%) or arousal. For HRP, the definitions were the same but without the final arousal criteria (20).

Therapeutic decision making

A sleep physician specialist at each center (always the same individual) made the therapeutic decision based on a standardized set of variables, including clinical symptoms and results from HRP or PSG, using the same website (see online data supplement). The treatment decision was guided using the Spanish Sleep Network guidelines (20). The sleep physician recommended CPAP treatment in the case of a respiratory event index (REI) ≥5 for HRP or an AHI ≥5 for PSG with significant clinical symptoms (i.e., ESS >12), potentially secondary to OSA or previous cardiovascular diseases, and a REI or an AHI ≥30, with clinical symptoms having less importance. Non-CPAP treatment included only correct sleep hygiene and a hypocaloric diet.

AutoCPAP titration

In patients (both arms) with a CPAP treatment indication, the optimal pressure for home use was obtained from a single recorded automatic-CPAP home session (S8-Autoset, Resmed, Sydney, Australia) (see online data supplement) by a researcher blinded to the study arm in the coordinating center (centralized analysis). If, after three attempts, it was

AJRCCM Articles in Press. Published on 21-June-2017 as 10.1164/rccm.201612-2497OC

impossible to determine the optimal pressure, patients received polysomnographic titration, with the extra cost.

Follow-up and outcomes

Patients were evaluated on four occasions (see online-data supplement and Table E1): a) at baseline; b) after one and three months during the follow-up period (at which points in the study, compliance and side effects in the CPAP treatment groups, or compliance with dietary and sleep hygiene measures in the groups without CPAP treatment, as well as discontinuations were registered); and c) at the end of the follow-up period (six months). At baseline and after six months, we assessed the primary outcome (ESS) and several secondary outcomes, such as health-related quality of life (HRQL), the Functional Outcomes of Sleep Questionnaire (FOSQ), SF-36, and the EuroQol 5D and Thermometer; a visual analogic wellbeing scale with respect to the condition studied (VAWS) (21,22); 24-hour blood pressure (BP) monitoring (ABPM); hourly compliance from the CPAP devices; work- or traffic-related accidents six months before and after randomization. Hospital admissions and days of admission; emergency visits and the mean incidence rate of new cardiovascular events during the follow-up period. At six months, a new PSG was performed in all patients (both arms); however, in patients treated with CPAP, PSG was conducted with the device.

Patient inclusion could be stopped when the number of patients reached the estimated sample size including dropouts, or when the two intervention arms (HRP and PSG) had at least 175 patients at the end of six months of follow-up (dropouts excluded).

Sample size calculation

Based on previous studies performed in patients treated with or without CPAP (12,21,23) we calculated the sample size for an ESS change of 3±8.1, a non-inferiority limit of -2 (23,24), an alpha error of 0.025 and a power of 90%. The estimated sample size was 175 patients in each arm and 240 in total once a dropout rate of 20% was adjusted.

Statistical analysis

Missing values for the primary and secondary outcomes (dropouts included) were addressed following a multiple imputation method with iterative multivariable regression because the missing data had a missing-at-random pattern.

Primary outcome: The a priori non-inferiority premise was -2 in the lower limit of the 95% confidence interval (CI) for the change in ESS between arms. Given that the intention-to-treat analysis could favor equivalence, we also performed a per-protocol analysis (patients who discontinued or who were missing ESS data were excluded from the analysis). We compared the change in ESS between the two arms using a 2-sided covariance analysis (ANCOVA) adjusted for the baseline value, center, age, gender, and BMI (henceforth "basic adjustment").

Secondary outcomes (inequality analysis): Intra-group changes in continuous variables from baseline to six months and the observed effects in the two arms of the study (inter-group differences) were assessed using paired t tests. When the comparison was statistically significant ($P<0.05$), paired comparisons of the groups were performed by ANCOVA, taking into account the "basic adjustment." Categorical variables were compared between baseline and six months using the x^2 test. These analyses were repeated in two subgroups of patients: a) treated or not treated with CPAP; and b) with baseline hypertension according to ABPM (23).

Cost analysis: Direct costs related to HRP or PSG procedures were analyzed. Figure E1 shows the cost imputation procedure. The cost analysis was distributed in four cost groups (see online data supplement).

Cost-effectiveness analysis: The cost difference between arms was evaluated against the difference in effectiveness based on primary outcomes (ESS) and quality-adjusted life years (QALYs) from the EuroQol questionnaire to determine the incremental cost-effectiveness ratio (ICER). We calculated the cost-effectiveness plane, where the

AJRCCM Articles in Press. Published on 21-June-2017 as 10.1164/rccm.201612-2497OC

distribution of the incremental effectiveness and costs are displayed in an x-y plot, and the cost-effectiveness acceptability curve, where the probability of preference for the HRP protocol is displayed as a function of the willingness to pay for a point in the ESS or a QALY, using a probabilistic Bayesian analysis (25). The sensitivity analysis was conducted according to percentiles of cost among centers.

Data management, imputation, statistical analyses and Bayesian cost-effectiveness analysis were performed using EXCEL 2010 (Microsoft Redmond, Washington, USA), SPSS software (IBM SPSS Statistics, Version 22.0. Armonk, NY, USA) and STATA 12 (StataCorp, College Station, Texas, USA).

RESULTS

Initially, 556 patients were selected, after which 126 were excluded, and the remaining 430 were randomized (Figure 1). No HRP test was invalid after repetitions (see Figure E1 in the online-data supplement). CPAP was indicated more frequently in the PSG arm (68%) than in the HRP arm (53%). Table 1 presents the population characteristics and sleep studies between arms. There were no significant differences between the HRP and PSG arms at baseline, nor were there differences between centers.

Main outcome

The difference in intra-group ESS improvement between the HRP arm (-4.2; 95% CI -4.8 to -3.6) and the PSG arm (-4.9; 95% CI -5.4 to -4.3) in the intention-to-treat analysis was not statistically significant (P= 0.14) (Table 2). Figure 2 shows the adjusted mean differences and 2-sided 95% CI of the change in ESS by the per-protocol and intention-to-treat analysis. In both analyses, the lower limit of the 95% CI of the mean adjusted difference (-1.50 and -1.44, respectively) was within our pre-specified non-inferiority margin (-2).

Secondary outcomes

HRQL test improvement was higher in the more specific HRQL tests for OSA (FOSQ and VAWS) and the EuroQol Thermometer (Table 2). VAWS displayed a more favorable change in the PSG arm. The ABPM parameters exhibited similar changes in the HRP and PSG arms (Table 3). The polysomnographic parameters at 6 months were similar between arms, with more favorable improvement in the percentage of deep sleep in the PSG arm.

CPAP pressure and compliance (HRP 5.1 h/day and PSG 5.3 h/day) were similar between arms (see Table E2 in the online-data supplement). The difference in work and traffic accidents between six months before and after randomization as well as the occurrence of hospital admissions, length of hospital stay, emergency visits and the cardiovascular event incidence rate per 100 patients/year six months after randomization were similar between arms (see Table E2 in the online-data supplement).

Cost-effectiveness analysis

The cost per patient in the PSG arm (736€) was more than double the cost of HRP (320€) (see Table E3 in the online-data supplement), mainly due to the lower cost of the HRP test (see Figure E2 in the online-data supplement). The average difference in effectiveness between the HRP and PSG protocols was -0.74 for ESS and -0.004 for QALY analysis (see Table E3 in the online-data supplement). The probabilistic Bayesian analysis (Figure 3 and see Figure E3 in the online-data supplement) indicated that HRP management was preferred because the estimated probability that HRP would be cheaper than PSG was higher (100%) than the estimated probability that PSG would be more effective than HRP (93% for ESS and 84% for QALY). Because the effectiveness (ESS and QALYs) was similar between arms, the HRP protocol is preferable due to its lower cost. The sensitivity analysis at the same level of effectiveness showed a minimum savings of 292.7€ and a maximum savings of 571.1€ (see Table E4 and additional results section in the online-data supplement for more details). Figure 3 shows the sensitivity

AJRCCM Articles in Press. Published on 21-June-2017 as 10.1164/rccm.201612-2497OC

analysis based on a probabilistic Bayesian approach at the same level of effectiveness for the 10th, 50th and 90th cost percentiles among centers.

Subgroup analysis

Analysis of the primary and secondary variables between the HRP and PSG arms in the subgroups of patients who received or did not receive CPAP treatment showed no significant differences except in the percentage of deep sleep in patients without CPAP treatment in the PSG arm (see Tables E5-7 in the online-data supplement).

In the subgroup of patients with hypertension, BP improved significantly in both arms, without significant differences in the inter-group adjusted comparison (see Table E8 in the online-data supplement).

DISCUSSION

To the best of our knowledge, this study is the first to compare the long-term effectiveness of HRP and PSG management protocols in a real and large population of patients with an intermediate to high OSA suspicion who were treated with or without CPAP. The principal findings are as follows: a) the effectiveness of the HRP protocol assessed by ESS is not inferior to that of the PSG protocol; b) the effectiveness assessed by HRQL, ABPM and PSG is similar between protocols; and c) the cost-effectiveness relationship is favorable to the HRP arm.

Over two decades, the diagnostic efficacy of HRP versus PSG has been evaluated in several studies with divergent methodology and results (9,11,26-28). HRP underestimates the AHI because 1) the denominator, HRP recorded time, is higher than the PSG sleep time; and 2) HRP cannot identify hypopnea with associated arousal without desaturation, which can be assessed using PSG. Although the last disadvantage would appear to be of limited importance (29), the average difference between REI and AHI according to HRP and PSG, respectively, was close to 10, even when the HRP recording time was reduced

to eliminate periods with movement suggesting wakefulness (8). However, most studies have determined a cut-off point to confirm an OSA diagnosis (8-11,26-28), and some studies have also identified a cut-off point to exclude OSA (8,9,26,28) at half the cost of the PSG (8,30). However, in clinical practice, diagnosis is followed by therapeutic decision making (CPAP or other treatments) based on the results of HRP and PSG. Using HRP, accurate therapeutic decisions can be made (in agreement with the PSG results) only for patients with severe OSA (REI ≥30) (12).

Previous studies did not include a follow-up period to evaluate the long-term effectiveness and considered PSG to be the gold standard (i.e., disagreements between HRP and PSG were considered incorrect for HRP). Three randomized controlled studies assessed the effectiveness of CPAP treatment after a diagnosis of OSA using PSG or HRP (13-15). Patients were selected to receive CPAP treatment if relevant OSA (AHI ≥15) was confirmed (high clinical probability of OSA). The two protocols (HRP and PSG) showed similar improvements in REI and AHI, quality of life, clinical symptoms, CPAP adherence and cost advantages (14-16), but cost-effectiveness was not analyzed. Because these studies only included patients with a high clinical probability of OSA who were treated with CPAP (approximately 40% of the patients needing sleep studies), the results could not provide conclusive effectiveness and cost data (20) for a population with a wider clinical spectrum of disease who might or might not be treated with CPAP and potentially managed by HRP.

Compared with the three previous studies using HRP, the present study mainly adds a wider clinical spectrum of disease (patients treated with or without CPAP), a long-term cost-effectiveness analysis for this wider population, a PSG at the end of the study and ABPM results showing that PSG is not necessary for the vast majority of patients with a suspicion of OSA who are candidates for a sleep study.

AJRCCM Articles in Press. Published on 21-June-2017 as 10.1164/rccm.201612-2497OC

Given that the criteria to define intermediate or high clinical OSA probability are not strictly characterized or widely accepted, our selection criteria of patients with intermediate to high clinical OSA probability may partially overlap with the criteria to define high clinical OSA probability in some previous studies using HRP (13-15). However, in our study, the AHI was approximately 40% lower (24 in the present study and 39-45 in previous studies) and the dispersion measure was approximately double the measure reported in previous studies. Additionally, the percentage of patients without a CPAP indication was 40% in our study compared with 7% (13) 27% (14) and 2% (15) from previous studies. These findings confirm our wider spectrum of OSA severity.

Other studies have compared the short- (31) and medium-term (32) effectiveness of simpler portable monitoring (type IV) (7) with PSG. The results were similar to previous studies using HRP, but only patients with a high OSA suspicion and CPAP treatment indication were included in the analysis.

Because of the AHI underestimation with HRP, we indicated CPAP in 15% fewer patients using HRP compared with PSG. However, this was not associated with important consequences because improvements in the primary and secondary outcomes were similar between the arms in the subgroup of patients not treated with CPAP (with the exception of a smaller deep-sleep percentage with the HRP protocol). Thus, refining the HRP protocol (i.e., increasing the predisposition to indicate CPAP in “borderline” cases or using an REI cut-off point from HRP superior to an AHI cut-off point from PSG) may avoid this worsening. However, the absence of greater improvement in the remaining outcomes suggested that the PSG protocol indicated 15% more CPAP treatments without significant benefits and with a higher cost. In other words, the fact that borderline patients located at the fringes of HRP underestimation in comparison with PSG (10 points of AHI on average) (8) has no real benefit in deciding upon CPAP versus no CPAP, increasing the role of HRP.

As mentioned previously, our patients had a wide range of OSA severities and no uniform treatment; consequently, moderate intragroup improvement was observed in both arms. In both arms, the intragroup improvement was higher in the subgroup of patients treated with CPAP, although only moderate improvement was observed for BP (see Table E7 in the online-data supplement). Some studies have shown early improvement (i.e., first three months) in BP in OSA patients treated with CPAP, depending on the baseline BP (33). Accordingly, in the subgroup of patients with baseline hypertension, based on ABPM criteria, the intragroup improvement in BP was significant in both arms (see Table E9 in the online-data supplement).

Several studies have estimated the cost effectiveness of HRP compared with PSG based on simulated models of hypothetical cohorts of patients that include diagnosis, CPAP titration and CPAP adherence, with conflicting results (34,35). In the present analysis, we applied a more solid, methodological cost calculation approach based on the following criteria: a) our study was conducted using a real and large cohort of patients; b) only direct costs were included; and c) no assumptions of cost calculations were incorporated.

Adequate professional qualifications are recommended in most clinical practice guidelines. Accordingly, we included only hospitals with a great deal of experience in HRP OSA management, which was also supported by a study performed in our environment showing better agreement in therapeutic decision making using HRP in comparison with PSG among more expert professionals (30).

Our study has some limitations: 1) the randomization group was necessarily open to researchers because therapeutic decisions were based on the HRP or PSG results; it was also open to patients, although the performance of different diagnostic tests appeared to have a minor impact on the patients; 2) the methodology included some variable decision nodes in certain intra- and inter-observers in terms of therapeutic decisions, as well as the use of autotitration to determine the visual CPAP level. The variability in therapeutic

AJRCCM Articles in Press. Published on 21-June-2017 as 10.1164/rccm.201612-2497OC

decisions was minimized, in part by using the Spanish Sleep Network guidelines criteria and inter-observer variability to determine the visual CPAP level with a centralized assessment; 3) we focused our cost evaluation on direct costs related to the HRP or PSG procedures (test and repetition cost, patient cost and CPAP cost), excluding other potential direct costs, such as hospital admission, emergency visits and work/traffic accidents, because these events may either be caused by OSA or not and are not strictly related to HRP or PSG management. In any case, as the occurrence of these events was similar in both arms, their inclusion should not cause differences in costs; and 4) we specifically selected a single OSA treatment as an alternative to CPAP treatment as it was hygienic-dietary measures to avoid contamination between the arms when applying other potential therapies (i.e. mandibular advance device). Therefore, patients in both study arms without OSA (RDI/AHI<5) at baseline (16% in the HPR and 9% in the PSG ones) had the same treatment (hygienic-dietary measures). However, patients from both study arms followed their habitual healthcare attention with other specialists and primary care physicians (if necessary) who were blinded for the allocated arm. Non-substantial changes in pharmacological treatment sleepiness-related were produced during the follow-up. Since we did not include patients with sleepiness not potentially caused (totally or partially) by OSA, most of them improved in their sleepiness and the PSG performed at 6 months revealed that the majority presented a mild OSA in both study arms.

In conclusion, the HRP management protocol is not inferior to PSG and presents substantially lower costs. Therefore, PSG is not necessary for the vast majority of patients with suspicion of OSA. This finding could change established clinical practice, with a clear economic benefit.

ACKNOWLEDGMENTS:

We are indebted to Verónica Rodríguez and Vanessa Iglesias for their assistance in the translation of the manuscript and to Asunción Martín, Elena Sandoval, Soledad Guillen, Trinidad Amigo, Pablo Mejias, Jose L. Cabrero and Carmen Lorenzana for technical assistance in the sleep laboratory.

AJRCCM Articles in Press. Published on 21-June-2017 as 10.1164/rccm.201612-2497OC

REFERENCES

1. Durán J, Esnaola S, Rubio R, Iztueta A. Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr. Am J Respir Crit Care Med 2001;163:685-689.
2. Ballester E, Badia JR, Hernández L, Carrasco E, de Pablo J, Fornas C, Rodriguez-Roisin R, Montserrat JM. Evidence of the effectiveness of continuous positive airway pressure in the treatment of sleep apnea/hypopnea syndrome. Am J Respir Crit Care Med 1999;159:495–501.
3. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet 2005;365:1046-1053.
4. Barbé F, Durán-Cantolla J, Sánchez-de-la-Torre M, Martínez-Alonso M, Carmona C, Barceló A, Chiner E, Masa JF, Gonzalez M, Marín JM, Garcia-Rio F, Diaz de Atauri J, Terán J, Mayos M, de la Peña M, Monasterio C, del Campo F, Montserrat JM, Spanish Sleep And Breathing Network. Effect of continuous positive airway pressure on the incidence of hypertension and cardiovascular events in nonsleepy patients with obstructive sleep apnea: a randomized controlled trial. JAMA 2012;307:2161-2168.
5. Terán-Santos J, Jiménez-Gómez A, Cordero-Guevara J. The association between sleep apnea and the risk of traffic accidents. Cooperative Group Burgos-Santander. N Engl J Med 1999;340:847-851.
6. Masa JF, Rubio M, Findley LJ. Habitually sleepy drivers have a high frequency of automobile crashes associated with respiratory disorders during sleep. Am J Respir Crit Care Med 2000;162:1407–1412.
7. Collop NA, Anderson WM, Boehlecke B, Claman D, Goldberg R, Gottlieb DJ, Hudgel D, Sateia M, Schwab R, Portable Monitoring Task Force of the American Academy of

Sleep Medicine. 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;3:737–747.

8. Masa JF, Corral J, Pereira R, Duran-Cantolla J, Cabello M, Hernández-Blasco L, Monasterio C, Alonso A, Chiner E, Rubio M, Garcia-Ledesma E, Cacelo L, Carpizo R, Sacristan L, Salord N, Carrera M, Sancho-Chust JN, Embid C, Vázquez-Polo FJ, Negrín MA, Montserrat JM. Effectiveness of home respiratory polygraphy for the diagnosis of sleep apnoea and hypopnoea syndrome. Thorax 2011;66:567–573.

9. Whittle AT, Finch SP, Mortimore IL, MacKay TW, Douglas NJ. Use of home sleep studies for diagnosis of the sleep apnoea/hypopnoea syndrome. Thorax 1997;52:1068-1073.

10. Parra O, García-Esclasans N, Montserrat JM, García Eroles L, Ruíz J, López JA, Guerra JM, Sopeña JJ. Should patients with sleep apnoea/hypopnoea syndrome be diagnosed and managed on the basis of home sleep studies? Eur Respir J 1997;10:1720–1724.

11. Alonso Alvarez Mde L, Terán Santos J, Cordero Guevara J, González Martínez M, Rodríguez Pascual L, Viejo Bañuelos JL, Marañón Cabello A. [Reliability of home respiratory polygraphy for the diagnosis of sleep apnea-hypopnea syndrome: analysis of costs]. Arch Bronconeumol 2008;44:22–28. doi: 10.1016/S1579-2129(08)60005-1.

12. Masa JF, Corral J, Pereira R, Duran-Cantolla J, Cabello M, Hernández-Blasco L, Monasterio C, Alonso A, Chiner E, Zamorano J, Aizpuru F, Montserrat JM, Spanish Sleep Network. Therapeutic decision-making for sleep apnea and hypopnea syndrome using home respiratory polygraphy: a large multicentric study. Am J Respir Crit Care Med 2011;184:964–971.

13. Kuna ST, Gurubhagavatula I, Maislin G, Hin S, Hartwig KC, McCloskey S, Hachadoorian R, Hurley S, Gupta R, Staley B, Atwood CW. Noninferiority of functional

AJRCCM Articles in Press. Published on 21-June-2017 as 10.1164/rccm.201612-2497OC

outcome in ambulatory management of obstructive sleep apnea. Am J Respir Crit Care Med 2011;183:1238-1244.

14. Rosen CL, Auckley D, Benca R, Foldvary-Schaefer N, Iber C, Kapur V, Rueschman M, Zee P, Redline S. A multisite randomized trial of portable sleep studies and positive airway pressure autotitration versus laboratory-based polysomnography for the diagnosis and treatment of obstructive sleep apnea: the HomePAP study. Sleep 2012 ;35:757-767.

15. Andreu AL, Chiner E, Sancho-Chust JN, Pastor E, Llombart M, Gomez-Merino E, Senent C, Barbé F. Effect of an ambulatory diagnostic and treatment programme in patients with sleep apnoea. Eur Respir J 2012;39:305-312.

16. Kim RD, Kapur VK, Redline-Bruch J, Rueschman M, Auckley DH, Benca RM, Foldvary-Schafer NR, Iber C, Zee PC, Rosen CL, Redline S, Ramsey SD. An economic evaluation of home versus laboratory-based diagnosis of obstructive sleep apnea. Sleep 2015;38:1027-1037.

17. Masa JF, Corral J, Sanchez de Cos J, Duran-Cantolla J, Cabello M, Hernández-Blasco L, Monasterio C, Alonso A, Chiner E, Aizpuru F, Vázquez-Polo FJ, Zamorano J, Montserrat JM. Collaborating group: Garcia-Ledesma E, Pereira R, Cancelo L, Martinez A, Sacristan L, Salord N, Carrera M, Sancho-Chust JN, Negrín MA, Embid C. Effectiveness of three sleep apnea management alternatives. Sleep 2013;36:1799–1807.

18. Masa JF, Sánchez-Quiroga MA, Corral J, Carmona-Bernal C, Sánchez-Armengol A, Sánchez-de-la-Torre A, Barbe F, Durán-Cantolla J, Egea CJ, Salord N, Monasterio C, Terán J, Alonso-Martínez ML, Muñoz-Méndez J, Arias EM, Cabello M, Montserrat JM, De la Peña M, Serrano JC, Spanish Sleep Network. Conventional polysomnography is not necessary in obstructive sleep apnea syndrome management. 2017 ATS International Conference. Washington, DC; 2017.

19. Sanchez-Quiroga MA, Masa-Jiménez JF, Barbé-Illa F, Cabello Najera M, Salord-Oleo N, Duran-Cantolla J, Capote-Gil F, Muñoz-Méndez J, Terán-Santos J, Montserrat JM. De la Peña-Bravo M, Serrano JC. Efficacy and cost-effectiveness of home respiratory polygraphy. Eur Respir J 2016;48:OA4797.

20. Lloberes P, Durán-Cantolla J, Martínez-García MÁ, Marín JM, Ferrer A, Corral J, Masa JF, Parra O, Alonso-Álvarez ML, Terán-Santos J. Diagnosis and treatment of sleep apnea-hypopnea syndrome. Arch Bronconeumol [Engl], 2011 Ed 2011;47:143–156.

21. Masa JF, Jiménez A, Durán J, Capote F, Monasterio C, Mayos M, Terán J, Hernández L, Barbé F, Maimó A, Rubio M, Montserrat JM. Alternative methods of titrating continuous positive airway pressure: a large multicenter study. Am J Respir Crit Care Med 2004;170:1218-1224.

22. Spanish Group of Breathing Sleep Disorders, Masa JF, Jiménez A, Durán J, Carmona C, Monasterio C, Mayos M, Terán J, Barbé F, Rubio M, Failde I, Mota M, Montserrat JM. Visual analogical well-being scale for sleep apnea patients: validity and responsiveness: a test for clinical practice. Sleep Breath 2011;15:549-559.

23. Antic NA, Buchan C, Esterman A, Hensley M, Naughton MT, Rowland S, Williamson B, Windler S, Eckermann S, McEvoy RD. A randomized controlled trial of nurse-led care for symptomatic moderate-severe obstructive sleep apnea. Am J Respir Crit Care Med 2009;179:501-508.

24. Chai-Coetzer CL, Antic NA, Rowland LS, Reed RL, Esterman A, Catcheside PG, Eckermann S, Vowles N, Williams H, Dunn S, McEvoy RD. Primary care vs specialist sleep center management of obstructive sleep apnea and daytime sleepiness and quality of life: a randomized trial. JAMA 2013;309:997-1004.

25. Fenwick E, O'Brien BJ, Briggs A. Cost-effectiveness acceptability curves—facts, fallacies and frequently asked questions. Health Econ 2004;13:405–415.

AJRCCM Articles in Press. Published on 21-June-2017 as 10.1164/rccm.201612-2497OC

26. García-Díaz E, Quintana-Gallego E, Ruiz A, Carmona-Bernal C, Sánchez-Armengol A, Botebol-Benhamou G, Capote F. Respiratory polygraphy with actigraphy in the diagnosis of sleep apnea-hypopnea syndrome. Chest 2007;131:725–732.

27. Ayappa I, Norman RG, Seelall V, Rapoport DM. Validation of a self-applied unattended monitor for sleep disordered breathing. J Clin Sleep Med 2008;4:26–37.

28. Reichert JA, Bloch DA, Cundiff E, Votteri BA. Comparison of the NovaSom QSG, a new sleep apnea home-diagnostic system, and polysomnography. Sleep Med 2003;4:213–218.

29. Masa JF, Corral J, Gomez de Terreros J, Duran-Cantolla J, Cabello M, Hernández-Blasco L, Monasterio C, Alonso A, Chiner E, Aizpuru F, Zamorano J, Cano R, Montserrat JM. Collaborating group: Garcia-Ledesma E, Pereira R, Cancelo L, Martinez A, Sacristan L, Salord N, Carrera M, Sancho-Chust JN, Embid C. Significance of including a surrogate arousal for sleep apnea-hypopnea syndrome diagnosis by respiratory polygraphy. Sleep 2013;36:249–257.

30. Guerrero A, Embid C, Isetta V, Farre R, Duran-Cantolla J, Parra O, Barbé F, Montserrat JM, Masa JF. Management of sleep apnea without high pretest probability or with comorbidities by three nights of portable sleep monitoring. Sleep 2014;37:1363-1373.

31. Berry RB, Hill G, Thompson L, McLaurin V. Portable monitoring and autotitration versus polysomnography for the diagnosis and treatment of sleep apnea. Sleep 2008;31:1423-1431.

32. Mulgrew AT, Fox N, Ayas NT, Ryan CF. Diagnosis and initial management of obstructive sleep apnea without polysomnography: a randomized validation study.Ann Intern Med 2007;146:157-166.

33. Durán-Cantolla J, Aizpuru F, Montserrat JM, Ballester E, Terán-Santos J, Aguirregomoscorta JI, Gonzalez M, Lloberes P, Masa JF, De La Peña M, Carrizo S,

Mayos M, Barbé F, Spanish Sleep and Breathing Group. Continuous positive airway pressure as treatment for systemic hypertension in people with obstructive sleep apnoea: randomised controlled trial. BMJ 2010;341:c5991.

34. Deutsch PA, Simmons MS, Wallace JM. Cost-effectiveness of split-night polysomnography and home studies in the evaluation of obstructive sleep apnea syndrome. J Clin Sleep Med 2006;2:145–153.

35. Pietzsch JB, Garner A, Cipriano LE, Linehan JH. An integrated health-economic analysis of diagnostic and therapeutic strategies in the treatment of moderate-to-severe obstructive sleep apnea. Sleep 2011;34:695-709.

AJRCCM Articles in Press. Published on 21-June-2017 as 10.1164/rccm.201612-2497OC

CAPTIONS

Figure 1: Flow chart of the study protocol. Abbreviations: ITT = intention to treat; HRP = home respiratory polygraphy; and PSG = polysomnography.

Figure 2: Adjusted mean and 95% confidence interval of ESS change by per-protocol and intention-to-treat analysis. Because the premise of non-inferiority was -2 in the lower bound of the 95% confidential interval, HRP was not inferior to PSG management. Abbreviations: ESS = Epworth sleepiness scale; HRP = home respiratory polygraphy; PSG = polysomnography.

Figure 3: Panel A: Cost-effectiveness plane. The probabilistic Bayesian analysis indicated that HRP management was preferred. Although PSG management is slightly more effective, it is much more expensive. Panel B: Cost-effectiveness plane according to the original values and incremental cost percentiles (P10, P50 and P90) based on sensitivity analysis using a probabilistic Bayesian approach. Abbreviations: HRP = home respiratory polygraphy; PSG = polysomnography; and ESS = Epworth sleepiness scale.

Table 1: Anthropometric characteristics, alcohol and smoking habits, and comorbidities.

	Randomized	HRP	PSG
	N=430	N=218	N=212
Gender, male, %	70.5%	69.7%	71.2%
Age, years, median (IQR)	50 (16)	51 (15.3)	50 (18)
BMI, kg/m2, median (IQR)	30.7 (7.3)	30.2 (7.7)	31.1 (7.2)
Neck circumference, cm, median (IQR)	41 (6)	41 (4.8)	41 (6)
Active drinker, %	21.6%	22	21.2
Alcohol, gr, median (IQR)	20 (20)	15 (20)	24 (22.5)
Active smoker, %	24,1%	24,8	18,9
Pack years, mean (SD)	26.2 (17.5)	25.1 (17.7)	27.6 (17.6)
Hypertension, %	30.2	31.2	29.2
Diabetes, %	9.3	10,6	8
Dyslipidemia, %	25.6	26.6	24.5
Ischemic heart disease, %	4	5	2,8
Arrhythmia, %	2.1	3.2	0.9
Stroke, %	1.9	1.4	2.4
Neoplasias, %	1.4	1.4	1,4
Anxiety, %	10.5	11.9	9
Depression, %	11.2	11.5	10.8
ESS, median (IQR)	13 (5)	13 (6)	13 (5)
Habitual unrefreshing sleep, %	62.5	62	63.2
Habitual snorer, %	94.2	94.6	93.9
Habitually observed apneas, %	59.1	57.8	60.4
Traffic/work accidents, %	8.6	10.1	7.5
Recorded time, min, median (IQR)		440.3 (60)	430 (40.1)
Valid or total sleep times, min, median (IQR)		420 (67.7)	354.5 (91.9)
%light sleep, median (IQR)			63.5 (23.9)
%deep sleep, median (IQR)			18.9 (15.8)
%REM sleep, median (IQR)			15.4 (9.4)
Arousal index, median (IQR)			32.2 (31.9)
REI/AHI, median (IQR)		20.9 (33.4)	28.5 (43.3)
Mild or no OSA (REI/AHI=0-14.9), %		41.2	25.0
Moderate OSA (REI/AHI=15-29.9), %		23.9	25.9
Severe OSA (REI/AHI≥30), %		34.9	49.1
DI, median (IQR)		16.7 (38.6)	18.2 (41.6)
%TST<90, median (IQR)		9.8 (34.7)	5.4 (28)

Abbreviations: BMI = body mass index; ESS = Epworth sleepiness scale; REI = respiratory event index; AHI = apnea-hypopnea index; OSA= obstructive sleep apnea; DI = desaturation index (≥3% oxygen saturation drop); and %TST<90 = percentage of the TST below 90% oxygen saturation.

AJRCCM Articles in Press. Published on 21-June-2017 as 10.1164/rccm.201612-2497OC

Table 2: Baseline measurements and changes with treatment related to the primary and secondary outcomes of HRQL and BMI.

	Baseline, median (IQR)		Intra-group differences, mean (SD)		P value of inter-group differences	
	HRP	PSG	HRP	PSG	Unadjusted	Adjusted
ESS	13 (6)	13 (5)	**-4.2 (5.4)‡**	**-4.9 (5.3)‡**	0.14	--
FOSQ	94 (27)	93 (28)	**6.7 (16.7)‡**	**6.5 (18.1)‡**	0.919	--
EuroQol 5D	0.79 (0.32)	0.79 (0.3)	0.01 (0.17)	**0.03 (0.16)***	0.311	--
EuroQol Thermometer	70 (30)	70 (30)	**3.1 (19.1)***	**5.1 (17.4)‡**	0.263	--
SF 36-Physical	46.7 (15.3)	45.5 (14.6)	1.2 (9.2)	**2.6 (9.1)‡**	0.101	--
SF 36-Mental	46.8 (18)	45.7 (17.5)	**2.5 (12.2)†**	1.4 (11.7)	0.334	--
VAWS	58.3 (32.4)	57.1 (31.3)	**4.4 (22.8)†**	**9.1 (23.4)‡**	**0.035**	**0.043**
BMI, kg/m^2	30.2 (7.7)	31.1 (7.2)	0.04 (1.76)	0 (1.7)	0.797	--

Abbreviations: HRQL: health-related quality of life; ESS = Epworth sleepiness scale; FOSQ = Functional Outcomes of Sleep Questionnaire; SF 36 = Medical Outcome Survey Short Form 36; VAWS = visual analogical well-being scale; and BMI = body mass index.
P values of intra-group differences (six months - baseline): *=<0.05; †=<0.01; and ‡=<0.001
P values of inter-group differences unadjusted or adjusted by basic adjustment (baseline values of the variable analyzed, center, age, gender and BMI).

Table 3: Baseline measurements and changes with treatment related to 24-hour blood pressure monitoring.

	Baseline, median (IQR)		Intra-group differences, mean (SD)		P value of inter-group differences	
	HRP	PSG	HRP	PSG	Unadjusted	Adjusted
24-h BP, mmHg	90 (11)	91 (12)	-0.2 (6.6)	0 (8.1)	0.241	--
Daytime BP, mmHg	93 (12)	94 (12)	-0.3 (7.8)	-0.3 (8.7)	0.405	--
Nocturnal BP, mmHg	83 (14)	83 (13)	-0.4 (9.6)	-0.4 (10.2)	0.387	--
24-h systolic BP, mmHg	119 (16)	120 (16)	0.4 (9.9)	0.3 (11)	0.65	--
Daytime systolic BP, mmHg	123 (16.3)	124 (15.8)	0.6 (11)	-0.3 (10.9)	0.656	--
Nocturnal systolic BP, mmHg	111 (18.3)	112 (18)	0.4 (11.9)	0.3 (13.6)	0.791	--
24-h diastolic BP, mmHg	74.5 (10)	76 (10)	-0.6 (5.9)	-0.8 (6.5)	0.089	--
Daytime diastolic BP, mmHg	78 (11.3)	78.5 (10.8)	**-1 (6.2)***	-0.6 (7.1)	0.298	--
Nocturnal diastolic BP, mmHg	68.5 (12)	70 (11)	0.3 (8.4)	-0.1 (8)	0.145	--

Abbreviations: BP = blood pressure
P values of intra-group differences (two months - baseline): *=<0.05.
P values of inter-group differences unadjusted or adjusted by basic adjustment (baseline values of the variable analyzed, center, age, gender and BMI).

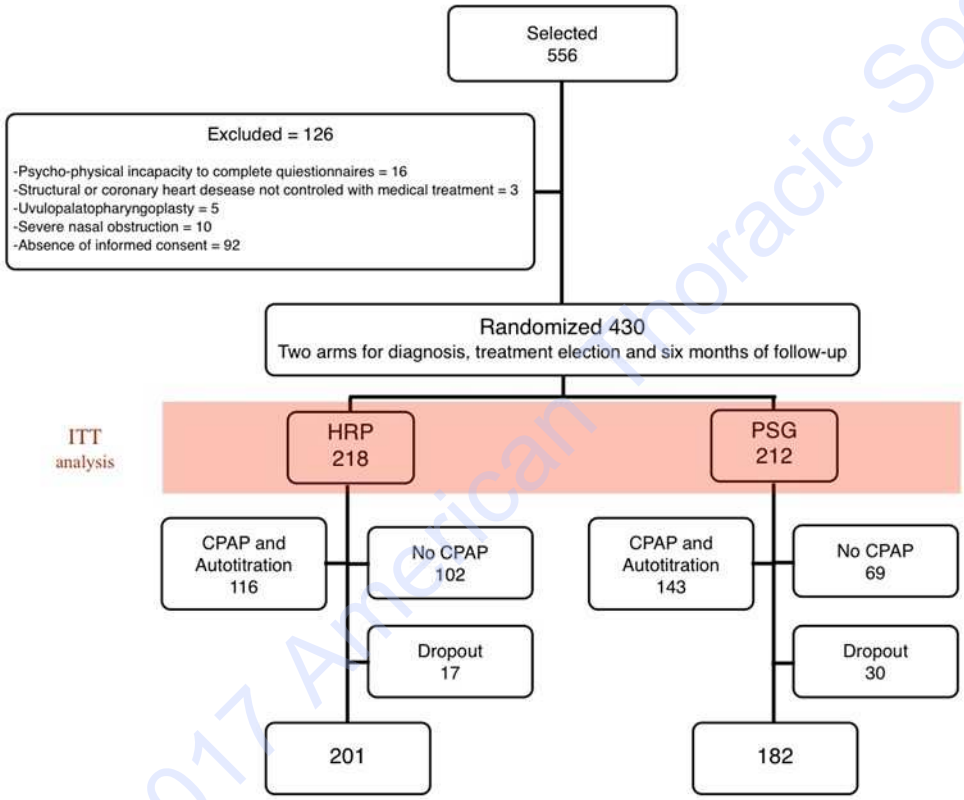
AJRCCM Articles in Press. Published on 21-June-2017 as 10.1164/rccm.201612-2497OC

Table 4: Polysomnographic outcomes at six months and differences between groups.

	At six months, median (IQR)		HRP-PSG differences, mean (SD)	P value of inter-group differences	
	HRP	PSG		Unadjusted	Adjusted
Recorded time, min	426 (31.5)	427.5 (38.8)	-2.9 (61.5)	0.484	--
Valid or total sleep times, min	345.7 (114.3)	351.5 (118.6)	-9.3 (181.1)	0.454	--
% light sleep	60.9 (21.8)	60 (21)	2.9 (28.6)	0.14	--
% deep sleep	19.6 (17.1)	20.8 (15.3)	-2.8 (19.2)	**0.031**	**0.023**
% REM sleep	17.9 (9.7)	17.5 (9.6)	0.2 (11.6)	0.775	--
Arousal index	17 (16.9)	17 (16.2)	1.3 (18.4)	0.292	--
AHI	6.9 (14.2)	6.8 (13.6)	1.4 (18.9)	0.286	--
DI	4.7 (9.4)	4.5 (10.1)	1.4 (15.7)	0.197	--
Mean $SatO_2$	94 (3.2)	94 (3)	-0.1 (10.3)	0.901	--
%TST<90	0.4 (9.6)	0.5 (11.3)	1.2 (29.6)	0.566	--

AHI = apnea-hypopnea index; DI = desaturation index; and %TST<90 = percentage of the TST below 90% of oxygen saturation.
P values of inter-group differences unadjusted or adjusted by basic adjustment (baseline values of the variable analyzed, center, age, gender and BMI).

Figure 1



AJRCCM Articles in Press. Published on 21-June-2017 as 10.1164/rccm.201612-2497OC

Figure 2

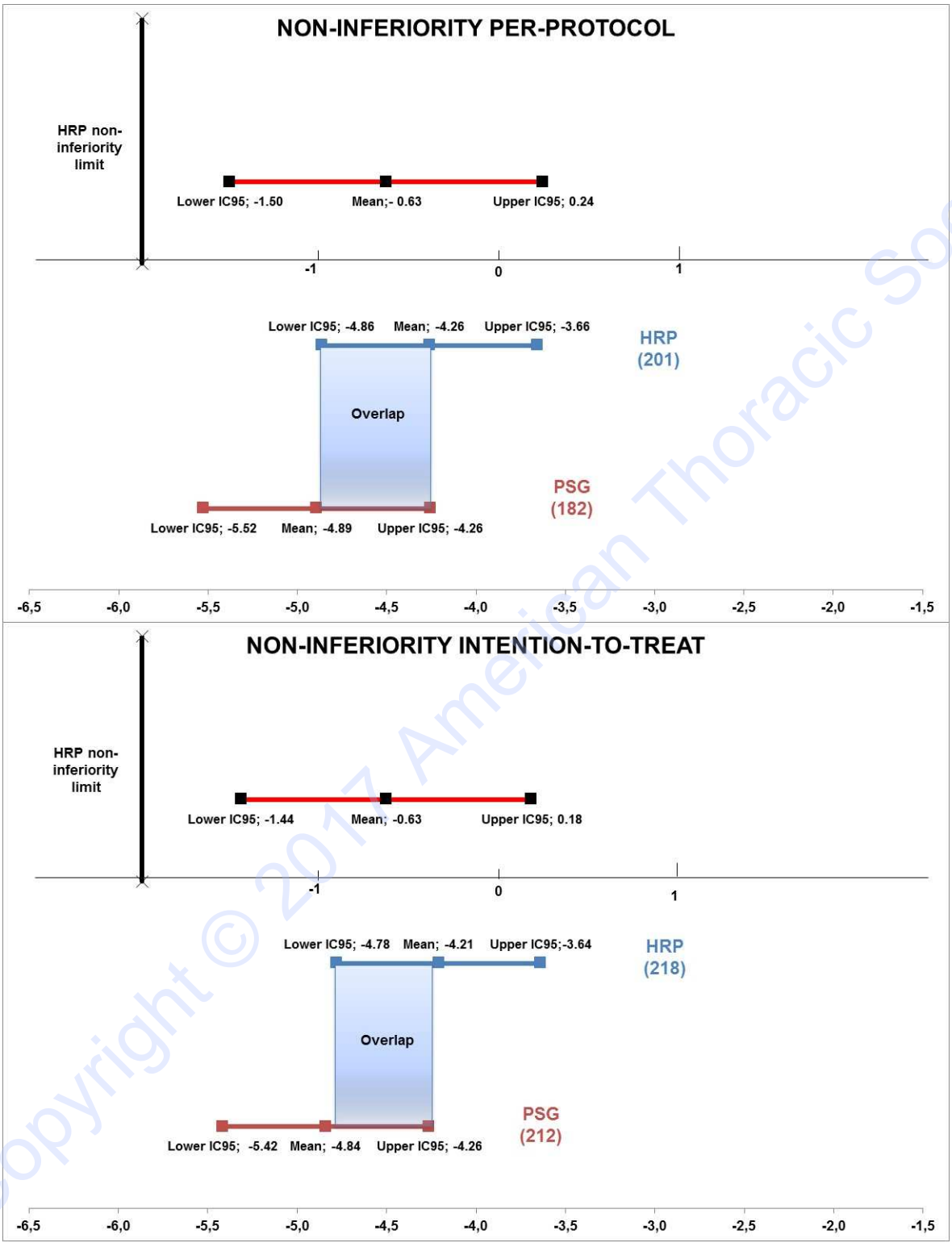
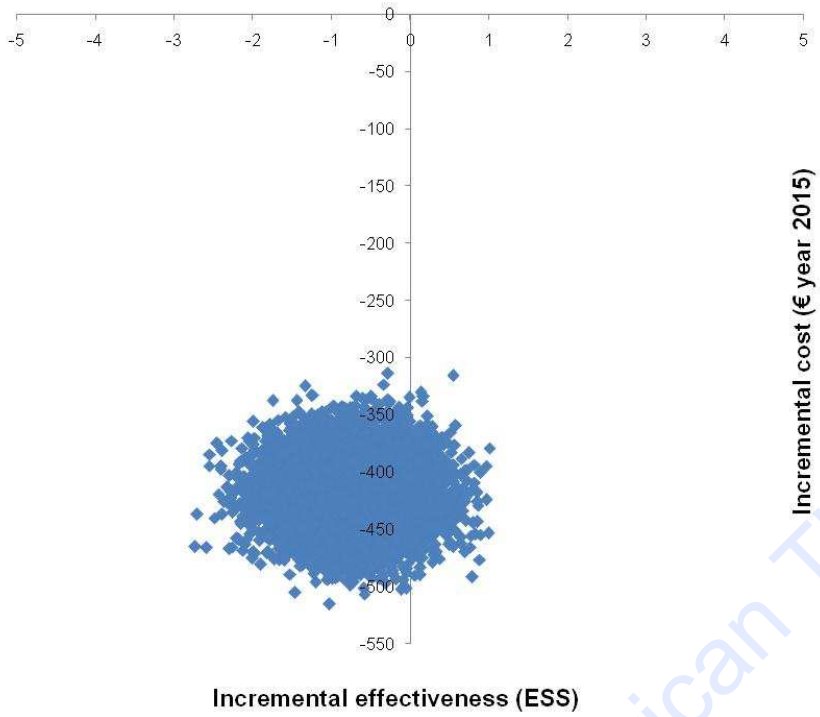


Figure 3

Panel A



Panel B