Intensive *versus* standard follow-up to improve continuous positive airway pressure compliance

Izolde Bouloukaki, Katerina Giannadaki, Charalampos Mermigkis,
Nikolaos Tzanakis, Eleni Mauroudi, Violeta Moniaki, Stylianos Michelakis,
Nikolaos M. Siafakas and Sophia E. Schiza

Affiliation:
Sleep Disorders Center, Dept of Thoracic Medicine, University of Crete, Heraklion, Crete, Greece.

Correspondence:
Izolde Bouloukaki, Sleep Disorders Center, Dept of Thoracic Medicine, University of Crete, 71110 Heraklion, Crete, Greece. E-mail: izolthi@gmail.com

ABSTRACT   We aimed to compare the effect of intensive *versus* standard interventions on continuous positive airway pressure (CPAP) adherence 2 years after CPAP initiation, as well as on sleepiness, quality of life, depression, hospitalisation and death rate due to cardiovascular disease (CVD).

3100 patients with newly diagnosed sleep apnoea were randomised into the standard group, with usual follow-up care, or the intensive group, with additional visits, telephone calls and education. Subjective daytime sleepiness (Epworth Sleepiness Scale; ESS), quality of life (36-item Short Form Health Survey; SF-36) and the patient's level of depression (Beck Depression Inventory; BDI) were recorded before and 2 years after CPAP initiation, together with CVD hospitalisations and death rate.

2 years after CPAP initiation, the intensive group used CPAP significantly more than the standard group (6.9 *versus* 5.2 h per night; p<0.001). ESS, SF-36 and BDI scores were also significantly better in the intensive group. Furthermore, the standard group had significantly more deaths and hospitalisations due to CVD.

CPAP usage can be improved by both intensive and standard patient support. However, the patients who received intensive CPAP support had significantly better ESS, BDI and SF-36 scores, and lower cardiovascular morbidity and mortality, suggesting that an intensive programme could be worthwhile.

@ERSpublications
Intensive CPAP support improves sleepiness, quality of life, depression, hospitalisation and death rate http://ow.ly/xHejr

Introduction

Obstructive sleep apnoea–hypopnoea syndrome (OSAHS) is a common chronic disorder that often requires lifelong care [1]. Estimates of disease prevalence are in the range of 4–7%, with certain subgroups of the population being at higher risk [2]. OSAHS is associated with neurocognitive and cardiovascular morbidities, public health consequences (driving, accidents at work and home) and a reduced quality of life [3]. Given the important implications of untreated OSAHS, as well as the increased all-cause mortality observed in patients with severe OSAHS [4, 5], the need for effective treatment is paramount.

Continuous positive airway pressure (CPAP) is a well-established, effective and evidence-based treatment for moderate-to-severe OSAHS [6], which significantly ameliorates the symptoms of the syndrome as well as its cardiovascular consequences. However, CPAP acceptance and adherence in daily clinical practice is often problematic. It is estimated that a significant number of patients, ranging from 29% to 83% in various studies, are nonadherent, defined as a mean CPAP usage of <4 h per night [7, 8]. Most studies of CPAP adherence have been performed in North America, England, France, Germany, China or Australia. However, there is a paucity of data regarding patterns of use in other ethnic groups, such as Greek people [9–11] a typical Mediterranean population, and the question of whether race plays a role in CPAP adherence remains to be determined. Furthermore, in Greece, many patients do not consider OSAHS as a health problem and have a poor perception of the associated risks.

Since OSAHS is a chronic disease, CPAP could be a lifelong treatment; therefore, good compliance is essential in order to maximise the beneficial effects of this therapy. Several studies have emphasised the need to identify patients who are at the greatest risk for nonadherence, with a view to developing techniques for improving overall adherence [8, 12–16]. CPAP adherence might be improved by an intensive follow-up programme, including family support, management of the side-effects of CPAP therapy and behavioural therapy, where problems can be addressed through a multidisciplinary team approach. However, there is a shortage of data from long-term randomised clinical trials to support the efficacy of an intensive *versus* standard follow-up programme in terms of CPAP use. Therefore, the aim of our study was to compare the effects of two interventions, intensive and standard, on CPAP adherence and treatment outcomes, such as sleepiness, mood, quality of life, hospitalisation and death rate due to cardiovascular disease (CVD), as well as withdrawal of therapy, 2 years after CPAP initiation.

Methods

Patients

We conducted a prospective, randomised, controlled, parallel-group trial of standard *versus* intensive support for newly diagnosed OSAHS patients undergoign CPAP therapy. Between June 2007 and June 2011, 5110 consecutive patients aged between 18 and 65 years, who were admitted to the Sleep Disorders Center (Dept of Thoracic Medicine, University of Crete, Heraklion, Crete, Greece) for evaluation of suspected sleep disordered breathing, were considered as potential recruits for this study. The inclusion criteria were: 1) newly diagnosed OSAHS by polysomnography according to standard criteria, 2) moderate-to-severe OSAHS, 3) no history of previous CPAP therapy, and 4) an above-elementary school education. The exclusion criteria were: refusal to participate, refusal of CPAP therapy, central sleep apnoea syndromes, obesity hypoventilation syndrome, restrictive pulmonary and restrictive chest wall diseases, severe congestive heart failure, a history of life-threatening arrhythmias, severe cardiomyopathy, long-term oxygen therapy, family or personal history of mental illness, drug or alcohol abuse, severe cognitive impairment, concurrent oncological diseases, and a history of narcolepsy or restless legs syndrome.

On the basis of the above criteria, we excluded 2010 patients (fig. 1). Of the excluded patients 19 refused to participate, eight had central sleep apnoea syndromes, 350 had no OSAHS, 1121 had mild OSAHS without symptoms requiring conservative therapy or mandibular advancement devices, 56 had restrictive pulmonary and restrictive chest wall diseases, 122 had obesity hypoventilation syndrome, 21 had a history of life-threatening arrhythmias, 22 had a personal history of mental illness, 38 had severe cognitive impairment, 31 had concurrent oncological diseases, nine had a history of narcolepsy, 20 had restless legs syndrome, 35 had severe congestive heart failure, 12 had severe cardiomyopathy, 44 were on long-term oxygen therapy, 71 had a history of previous CPAP therapy, and 31 had lower than elementary school education. Eligible patients (n=3100) were randomly assigned in a 1:1 ratio to receive either the standard intervention (n=1550), of usual follow-up care, or the intensive intervention (n=1550), with augmented follow-up care based on additional appointments at the CPAP clinic, telephone calls and education. Randomisation was performed using a computer-generated list of random numbers. Patients were blinded to the group to which they were allocated and were followed for a minimum of 2 years. All subjects provided written informed consent and ethical approval was provided by the University Hospital Ethics Committee (University of Crete, Heraklion, Crete, Greece).
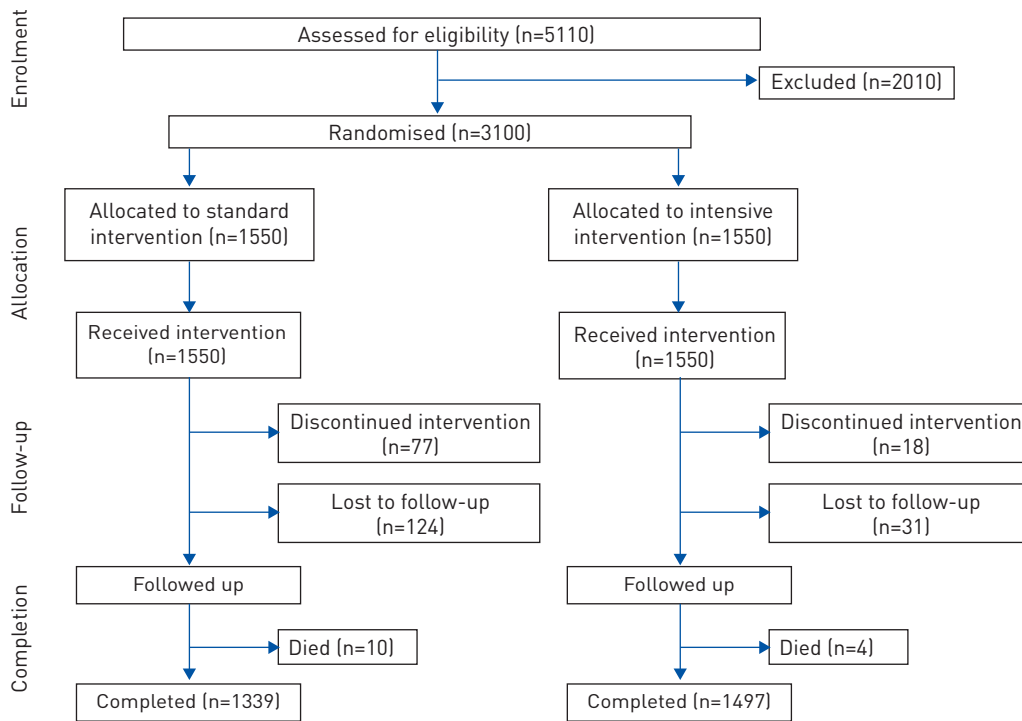
FIGURE 1 Study flow diagram.

Data collection

All patients underwent a detailed evaluation that included age, body mass index (BMI), medical history focused on sleep-related symptoms, associated conditions and comorbidities, smoking history and alcohol intake. Subjective daytime sleepiness, reflected by the Epworth Sleepiness Scale (ESS), quality of life recorded using the 36-item Short Form Health Survey (SF-36), and the patient's level of depression obtained from the Beck Depression Inventory (BDI) were recorded in both groups before and 2 years after initiation of CPAP.

The ESS is currently the most widely used subjective test of daytime sleepiness in clinical practice [17].

The SF-36 is a reliable and validated tool for the assessment of general (physical and mental) health and quality of life [18–20]. The 36-item questionnaire encompasses eight domains: physical functioning, social functioning, mental health, role limitations due to physical problems, role limitations due to emotional problems, vitality (energy and fatigue), bodily pain, and general health perceptions. Each domain is scored separately from 0 (worst) to 100 (best).

The BDI 21-item questionnaire is a widely used and well-validated self-reported inventory of depressive symptoms [21–23]. The BDI measures the severity of depressive symptoms over the preceding week. For each item, the respondent chooses one or more options rated from 0 (absence of symptoms) to 3 (the most severe level). Total scores range from 0 to 63 and represent the sum of the highest levels endorsed on each item. Scores below 10 are considered normal.

Sleep study and CPAP treatment
Polysomnography

All patients underwent a single-night full diagnostic polysomnography (PSG) study (Alice 5 Diagnostic Sleep System; Philips Respironics, Andover, MA, USA) according to standard techniques, with monitoring of the electroencephalogram (EEG), electro-oculogram, electromyogram, flow (by oronasal thermistor and nasal air pressure transducer), thoracic and abdominal respiratory effort (by respiratory induction plethysmography), oximetry, and body position. Snoring was recorded by a microphone placed on the anterior neck. Polysomnographic recordings were manually interpreted over 30-s periods, by skilled staff, in accordance with the American Academy of Sleep Medicine (AASM) 2007 guidelines [24]. The scorer was always the same person, who was blinded to the origin of the data. The determination of sleep stages and arousals was performed, according to the AASM 2007 criteria, using EEG montages including frontal, central and occipital leads. The definition of apnoea and hypopnoea followed the AASM standard criteria [24].

The apnoea–hypopnoea index (AHI), calculated as the number of apnoea and hypopnoea events per hour of sleep, was used to diagnose OSAHS and assess its severity. OSAHS was considered mild if the AHI was $\geqslant 5$ events·h^{-1} but <15 events·h^{-1}, as moderate if AHI was $\geqslant 15$ events·h^{-1} but <30 events·h^{-1}, and as severe if AHI was $\geqslant 30$ events·h^{-1}.

CPAP titration

CPAP treatment was offered to every patient with moderate-to-severe OSAHS, irrespective of symptoms. CPAP titration PSG was performed within 1 week of the first diagnostic PSG in order to determine the optimal CPAP level. Patients were wired up for full PSG, and CPAP was then manually titrated to the correct therapeutic pressure to abolish all "visible" nocturnal OSAHS events. All the patients received education prior to the CPAP titration night and completed a questionnaire at the end of the first night, reporting their quality of sleep and any side-effects under CPAP titration.

Interventions

All study groups received individual counselling during scheduled clinic appointments, at their initial sleep clinic consultation, and after the completion of the PSG studies. During these appointments, they received one-on-one counselling by a sleep physician regarding the results of their PSG studies, basic information on OSAHS, its known effects on comorbid conditions, proper sleep hygiene, adjunctive/conservative methods to improve sleep, and the importance of treatment adherence. All patients took home a brochure describing the need for and benefits of CPAP therapy and attended a CPAP clinic, where they were given specific counselling on the proper use and maintenance of CPAP, and underwent personalised, formal mask fitting by a specialised nurse. The sleep technicians and nurses were highly trained in sleep medicine and CPAP equipment, with an average of 10 years of experience in sleep disorders and CPAP therapy. The total time for the appointment in the CPAP clinic was 15 min per patient. The patient was encouraged to bring his/her family to these appointments.

In the standard group, once CPAP was started, patients were reviewed in the outpatient sleep clinic after 1 month and at 3-monthly intervals during the first year, and every 6 months thereafter. During these appointments, a clinical assessment was made and patients were further encouraged to use the device. In addition, the patients had the opportunity to discuss other health issues related to the condition, such as weight reduction and smoking cessation. At each visit, the compliance data were downloaded from the CPAP device and reviewed by the CPAP clinic nurse together with the patient. Any concerns or questions, such as pressure sores, persistent air leakage, claustrophobia, nasal congestion and other side-effects resulting from the nasal mask interface that might lead to suboptimal compliance were addressed immediately by the CPAP clinic nurse. Changes in the CPAP settings, nose/face mask, or circuit were made after consultation with the responsible sleep physician, if necessary. If nasal complaints were significant, either a topical steroid spray or anticholinergic nasal spray was prescribed. If these failed, a heated humidifier was then made available. In addition, a 24-h treatment consultation telephone line to the sleep nurses was open for the patients. This format adhered to the standardised approach according to our CPAP clinic's procedures. To avoid data bias, all participating sleep nurses were instructed not to personally influence the patients' CPAP adherence beyond the planned interventions. Each follow-up visit lasted 15–30 min. If there were doubts about a patient's compliance or willingness to continue with the programme, the referring physician made personal contact with the patient, by telephone or through direct in-person interviews, in order to resolve barriers to adequate compliance. Each patient always saw the same sleep physician during the follow-up period of the study. Additionally, we recorded any hospitalisation due to CVD, in particular fatal and nonfatal cardiovascular events. Fatal events were defined as death from myocardial infarction, heart failure or stroke. Nonfatal events included the occurrence of nonfatal myocardial infarction, stroke, transient ischaemic attack (TIA), arrhythmia and acute coronary insufficiency requiring coronary artery bypass surgery or percutaneous transluminal coronary angiography, or both. The randomised patients who abandoned the trial were followed by telephone calls in order to evaluate cardiovascular morbidity and mortality.

In the intensive group, all of the features described above for the standard group were included in the follow-up, plus additional visits involving patients' partners or family, home visits, telephone calls and education in an effort to resolve problems encountered with CPAP. During this follow-up care, the patient's partner or family were required to accompany the patient. All patients in this group attended a 15 min video education session covering a series of topics about OSAHS and CPAP, presented by a sleep physician. This education session included basic information regarding OSAHS, its sequelae, treatment options and the benefits of adherence to therapy, similar to the information provided during the initial counselling sessions. This was followed by a 10–15 min lecture from the sleep clinic's registered nurses in order to reinforce the key concepts of the education session and the benefits of adherence. All patients were

instructed to keep a sleep diary for the first month of treatment. During the first week of CPAP set-up, patients were contacted by the nurse, on the second and seventh day, *via* telephone in order to discuss any concerns they might have regarding air pressure, mask fitting, leaks and other issues as they arose. If there were doubts about a patient's adherence, the nurse performed a home visit to check the CPAP device and remind them to use it. On this visit, the patient was given repeat instructions about how to turn the machine on and off, and about the placement of the interface. Furthermore, during the first month of treatment, patients were reviewed by the sleep specialist, on the 15th and 30th day of treatment.

Patients were advised to bring their CPAP device and interface at every visit to the clinic. The importance of good adherence was emphasised, encouraging the patients to use the CPAP device throughout sleep every day, and to make every effort to put it back on after night-time awakenings. In addition, patients were invited to discuss misconceptions about sleep apnoea and barriers to use, share their experience on the use of CPAP, concerns, fears and beliefs, as well as the perceptions of their partner and family, in order to increase patients' positive expectations regarding CPAP benefits and to shift the balance of patients' focus from the barriers to the benefits of treatment. They were invited to put on their interface during the clinic visit, a procedure that was always supervised by the sleep physician.

CPAP adherence

CPAP usage data included mask type (nasal or full face), number of nights on CPAP, average use per night (hours), air leakage and air pressure delivered. The chronological data (measured by a real-time clock and uploaded to a computer using specialised software) were obtained from the CPAP machine at each follow-up appointment. The self-reported number of nights per week and hours per night CPAP was being used, as recorded in the sleep diary, were compared with the data obtained from the CPAP machine during the first month. Regular CPAP compliance was defined as using the therapy for an average of 4 h per night on at least 70% of the nights [25].

Cost evaluation

The estimated costs of each intervention were calculated and compared between groups. The estimated costs of hospital visits, home visits, telephone calls and education were obtained from the Financial Department of the Sleep Disorders Center (Dept of Thoracic Medicine, University of Crete, Heraklion, Crete, Greece). This cost was compared with the benefit of the decreased hospitalisation and death rate due to CVD, with its associated costs. The annual total cost of medical care for CVD equals €512 157 000, based on the national annual medical care cost for CVD for the year 2006, as presented in the European Cardiovascular Disease Statistics 2008 [26]. According to the Hellas Health I study [27] the incidence of CVD in 2006 was 5.8% of the adult general population. If the aforementioned data are used with the total number in the general population, then the annual cost of medical care for CVD is equal to €815.5 per patient.

Statistical analysis

Data were normally distributed. Numerical variables are presented as mean ± SD. Intention-to-treat analysis was carried out, in which all patients receiving the allocated interventions were included in the analysis. All tests were two-tailed and p-values <0.05 were assumed to represent statistical significance. Differences between groups were examined using the independent-samples t-test for continuous variables and the Chi-squared test for categorical data. Objective compliance, assessed from the data obtained from the CPAP machine during the first month, was correlated with subjective compliance from the sleep diary using Pearson's correlation analysis. The Kaplan–Meier method of survival analysis was applied for the calculation of survival rates, and log-rank analysis was used to detect differences between groups. Clinically relevant variables were entered into a Cox proportional hazard model analysis to determine the variables independently associated with mortality in the two study groups. The following variables were finally selected to enter into the Cox proportional hazard model: age, BMI, sex, smoking habits, arterial hypertension, diabetes mellitus, previous coronary heart disease, arrhythmia, previous stroke or TIA, AHI, improvement in questionnaire scores, and the type of intervention (standard or intensive). Cox analysis was repeated for two subgroups of patients, according to treatment adherence (group 1: <6 h of CPAP use per night, group 2: >6 h of CPAP use per night; on nights when CPAP was used) and risk of cardiovascular mortality was compared between the groups. Although regular CPAP compliance was defined as using the therapy for an average of 4 h a night on at least 70% of the nights, a cut-off of >6 h was used, because studies indicate that >6 h per night results in normal levels of objectively measured and self-reported daytime sleepiness, as well as significantly improved memory, daily functioning and improved survival rates [28, 29]. The results were expressed as hazard ratios (HR) and 95% confidence intervals, and a p-value <0.05 was considered statistically significant. Data were analysed using PAWP 17.0 software (SPSS Inc., Chicago, IL, USA).

TABLE 1 Baseline characteristics of patients in the standard and intensive follow-up groups

	Standard group	Intensive group	p-value
Subjects n	1550	1550	
Demographics			
Age years	55.6 ± 10.2	55.1 ± 10.7	0.42
Males %	77.0	73.1	0.52
BMI $kg \cdot m^{-2}$	38.1 ± 9.2	37.5 ± 14.8	0.23
Diagnostic PSG			
AHI $events \cdot h^{-1}$	53.3 ± 25.7	52.0 ± 22.8	0.23
ODI $events \cdot h^{-1}$	51.4 ± 28.2	49.5 ± 30.2	0.17
Mean Sa_{O_2} %	90.8 ± 5.4	90.2 ± 6.2	0.51
Minimum Sa_{O_2} %	76.4 ± 9.1	76.3 ± 9.8	0.72
After CPAP titration			
AHI $events \cdot h^{-1}$	2.7 ± 1.6	2.9 ± 1.6	0.07
ODI $events \cdot h^{-1}$	2.6 ± 1.2	2.6 ± 1.8	0.07
Mean Sa_{O_2} %	95.9 ± 1.2	95.8 ± 6.6	0.66
Lowest Sa_{O_2} %	91.4 ± 13.7	90.7 ± 7.5	0.72
Questionnaire scores			
ESS	11.5 ± 5.8	12.7 ± 5.4	0.07
BDI	15.5 ± 8.0	15.1 ± 7.0	0.07
SF-36 physical component	75.6 ± 6.9	74.9 ± 8.5	0.06
SF-36 mental health component	79.3 ± 8.4	78.5 ± 7.6	0.08

Data are presented as mean $\pm$ SD, unless otherwise stated. BMI: body mass index; PSG: polysomnography; AHI: apnoea–hypopnoea index; ODI: oxygen desaturation index; Sa_{O_2}: arterial oxygen saturation; CPAP: continuous positive airway pressure; ESS: Epworth Sleepiness Scale; BDI: Beck Depression Inventory; SF-36: 36-item Short Form Health Survey.

Results

Patients

As shown in table 1, there were no significant differences in demographic and sleep characteristics between the study groups at baseline. Trends toward significance were observed in the baseline questionnaire scores, although differences were neither clinically nor statistically significant. 155 of the 3100 patients, 124 receiving standard support and 31 intensive support, were lost to follow-up: 77 (4.9%) patients in the standard group and 18 (1.1%) in the intensive group had stopped using CPAP, and 10 patients in the standard group and four in the intensive support group died after randomisation (fig. 1). All 3100 patients were included in the final analysis. BMI, neck and waist circumference did not change significantly during the study.

Compliance with CPAP therapy for OSA patients

In the standard group, during the first month of treatment, the objective mean $\pm$ SD measured time of use was 6.4 ± 1.1 h per night, compared with the self-reported time of use, which was 7.2 ± 1.2 h per night; there was a significant correlation between the two (r=0.76, p<0.001). In the intensive group, the objective measured mean time of use was 7.6 ± 1.2 h per night, compared with a self-reported time of use of 8.0 ± 1.3 h per night; the correlation between the two was even stronger in this group (r=0.959, p<0.001).

The use of CPAP over the first 24 months of therapy is shown in table 2. During the 2 years of CPAP therapy, patients who received the intensive support used CPAP significantly more than the standard group (6.9 versus 5.2 h per night, respectively; p<0.001). Furthermore, there was a difference in the percentage of days CPAP was used (88.1 versus 75.1%; p<0.001) between the intensive and standard groups. Most patients in the intensive group who continued on CPAP treatment (92.8%) had an objective daily use ⩾4 h.

During the study period, 667 (23.5%) patients required a heated humidifier: 335 (21.6%) patients in the standard group and 302 (19.5%) patients in the intensive group.

Questionnaires

ESS, BDI and SF-36 scores at baseline and after the 24-month follow-up period are shown in table 3. Both groups showed significant improvements in ESS, BDI and SF-36 scores compared with baseline. However, the patients who received intensive CPAP support had significantly lower symptom scores at 24 months in the BDI questionnaires than the patients receiving standard support. Furthermore, in the intensive group,

TABLE 2 Comparison of continuous positive airway pressure (CPAP) use between standard and intensive groups after 24 months follow-up

	Standard	Intensive	p-value
% days CPAP used a week	75.1 ± 23.9	88.1 ± 8.2	<0.001
Days CPAP used a week	5.2 ± 2.3	6.2 ± 3.9	<0.001
Hours per night, on nights CPAP was used[#]	5.2 ± 2.2	6.9 ± 1.8	<0.001
Regular use of CPAP %	79.8	92.8	<0.001

Data are presented as mean$\pm$SD, unless otherwise indicated. [#]: Calculated by dividing the total hours of CPAP use by the number of days on which CPAP was used.

there was a significantly higher score for overall quality of life as evaluated by the total SF-36 score, reflected as an improvement among all domains of the SF-36 questionnaire, after 24 months follow-up. When baseline excessive daytime sleepiness assessed by ESS was compared at 24-month follow-up, it was observed that daytime sleepiness showed a greater improvement in the intensive group.

Hospitalisation rate, cardiovascular morbidity and mortality

During the follow-up period, the hospitalisation rate due to CVD was 4.8% overall (a total of 137 patients with new cardiovascular events were identified). In the standard group, there were 96 (6.2%) hospitalisations for cardiovascular events (11 arrhythmia, nine unstable angina, 11 nonfatal stroke, 15 pulmonary oedema due to heart failure, 36 nonfatal myocardial infarction and 14 TIA) and 62 (4.0%) cardiovascular deaths. In the intensive group, there were 45 (2.9%) hospitalisations for cardiovascular events (three unstable angina, six arrhythmia, 21 nonfatal myocardial infarction, four TIA, five pulmonary oedema due to heart failure, six nonfatal stroke) and 28 (1.8%) cardiovascular deaths. The standard group had more deaths due to CVD (62 (4.0%) *versus* 28 (1.8%), respectively; p<0.001) and significantly greater cardiovascular morbidity (96 (6.2%) hospitalisations *versus* 45 (2.9%), respectively; p<0.001) compared with the intensive group. Figure 2 illustrates the Kaplan–Meier survival analysis for cardiovascular death in the standard and intensive groups. Table 4 shows the Cox regression analysis results. It can be seen that standard intervention approach, older age, increased BMI and current smoking are associated with poorer survival, whereas intensive intervention, hours of CPAP use and SF-36 physical and mental component score improvements were associated with better survival. Additionally, significant differences in cardiovascular mortality were observed between patients with <6 h use of CPAP per night and those with >6 h CPAP use.

Subgroup analysis

The best predictors of cardiovascular mortality for the two subgroups were as follows.

1) <6 h of CPAP use per night. CVD mortality for patients with <6 h of CPAP use per night was predicted by the presence of older age (HR (95% CI) 1.066 (1.03–1.10); p<0.001) and also significantly by BMI (HR

TABLE 3 Comparison of questionnaire scores between the standard and intensive groups at baseline and at the end of the 24-month follow-up period

	Standard group				Intensive group				p-value[#]
	Baseline	24 months	Difference (improvement)	p-value	Baseline	24 months	Difference (improvement)	p-value	
ESS	11.5 ± 5.8	7.2 ± 4.3	4.3 ± 6.1	<0.001	12.7 ± 5.4	4.2 ± 1.6	8.1 ± 6.0	<0.001	<0.001
BDI	15.5 ± 8.0	11.1 ± 6.8	3.7 ± 8.2	0.04	15.1 ± 7.0	7.8 ± 5.9	7.0 ± 7.8	<0.001	<0.001
SF-36 physical component	75.6 ± 6.9	81.7 ± 18.2	5.9 ± 11.4	0.006	74.9 ± 8.5	86.3 ± 6.2	11.6 ± 7.7	<0.001	<0.001
SF-36 mental health component	79.3 ± 8.4	88.6 ± 9.8	8.9 ± 6.9	0.007	78.5 ± 7.6	92.2 ± 8.5	12.9 ± 10.1	<0.001	<0.001

ESS: Epworth Sleepiness Scale; BDI: Beck Depression Inventory; SF-36: 36-item Short Form Health Survey. [#]: intensive *versus* standard group at 24 months.
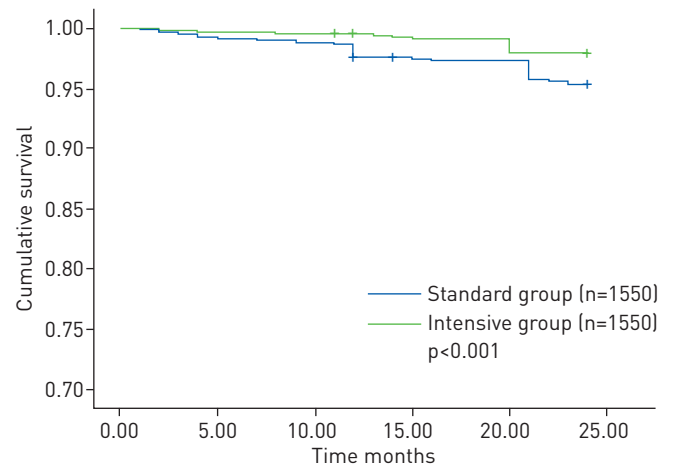
FIGURE 2 Kaplan–Meier survival analysis for cardiovascular death in the standard and intensive

(95% CI) 1.07 (1.03–1.11); p<0.001). Sex, current smoking, previous history of diabetes, hypertension, coronary heart disease, arrhythmia, stroke, TIA, OSAHS severity and questionnaires score improvement were not associated with CVD mortality in this group of OSA patients.

2) ⩾6 h of CPAP use per night. Older age and BMI were associated with CVD mortality (HR HR (95% CI) 1.07 (1.03–1.10); p<0.001 and 1.07 (1.03–1.1), respectively; p<0.001). There were no other significant predictors of CVD mortality in this group.

Cost evaluation

According to the Greek National Health Insurance system, the mean annual cost of intensive intervention was estimated as €100 per patient above the annual cost of the standard intervention, based on the additional visits, education and phone calls, described in detail in the methods section. Collectively, we estimate an increased cost of 30% for the intensive intervention *versus* the standard intervention. After analysing the costs of each of the two interventions, the differences in costs were statistically significant (p<0.001), with the most expensive strategy being the intensive group (annual cost per patient €430±42 *versus* 330±23). However, according to our data, intensive follow-up *versus* standard follow-up is superior for life expectancy, and has significantly lower cardiovascular morbidity with its associated cost (€815.5 per patient). Thus, intensive follow-up of a patient suffering from moderate-to-severe OSAHS is more effective and economic than standard follow-up, due to the sum of money saved as a result of lower treatment costs for CVD (table 5).

Discussion

Good CPAP adherence is medically essential to patients' health and economically important to society, as it can potentially alleviate the substantial cost burden of the health-related consequences of OSAHS. As it is important to establish whether CPAP usage can be increased and whether this would improve health outcomes, we tested the hypothesis that provision of additional education and support to OSAHS patients beginning CPAP therapy would improve CPAP use and treatment outcomes. The study groups, intensive and standard follow-up, were comparable at baseline; therefore, factors that may have affected the patients' adherence to CPAP treatment were equally distributed among the study groups. After the 24-month follow-up, we found that patients who received intensive CPAP support had used their CPAP device for more days and for more hours per night, and more of them achieved regular use of CPAP, compared with the standard group. Furthermore, although both groups showed significant improvements in ESS, BDI and SF-36 scores compared with baseline, these scores improved more in the intensive group.

Adherence to CPAP treatment has been extensively investigated in the literature. Although several studies have shown a significant improvement in symptoms, quality of life and daytime function in patients treated with nasal CPAP, adherence to CPAP treatment is frequently poor. As there are no evidenced-based guidelines for the follow-up of patients with OSAHS who are treated with CPAP, there is considerable variation in practice. Additionally, since race, ethnicity and culture could influence the degree of CPAP adherence, a range of different strategies may need to be developed. Many psychological and educational interventions have been proposed as a means of increasing the hours of use of CPAP therapy. These interventions include education about the risks of OSAHS, outcome expectancies for CPAP treatment and CPAP self-efficacy; supportive measures, such as strategically timed follow-up appointments and telephone

TABLE 4 Cox multivariable regression analyses of variables associated with cardiovascular death

Variable	B	HR (95%CI)	p-value
Intensive intervention[#]	-0.94	0.39 (0.21–0.73)	0.003
Sex[¶]	0.16	1.16 (0.52–2.61)	0.71
Age	0.08	1.08 (1.05–1.11)	<0.001
Current smoking	1.75	5.74 (2.15–15.3)	<0.001
BMI	0.062	1.06 (1.03–1.1)	0.001
Diabetes	0.20	1.23 (0.62–2.41)	0.56
Hypertension	-0.77	0.46 (0.27–0.80)	0.006
CHD	-0.51	0.59 (0.14–2.56)	0.49
Arrhythmia	0.19	1.22 (0.47–3.15)	0.68
CVA	0.40	1.5 (0.76–2.98)	0.25
TIA	0.62	1.86 (0.63–5.57)	0.26
AHI	0.002	1.002 (0.99–1.01)	0.69
ESS improvement	0.008	1.008 (0.97–1.04)	0.66
BDI improvement	0.003	1.003 (0.97–1.03)	0.808
SF-36 physical component improvement	-0.019	0.98 (0.96–0.99)	0.026
SF-36 mental component improvement	-0.021	1.12 (0.98–1.32)	0.012
Hours of CPAP use	-0.51	0.59 (0.54–0.67)	<0.001
Group >6 h of CPAP use[+]	-4.4	0.12 (0.003–0.05)	<0.005

BMI: body mass index; CHD: coronary heart disease; CVA: cerebrovascular accident; TIA: transient ischaemic attack; AHI: apnoea–hypnoea index; ESS: Epworth Sleepiness Scale; BDI: Beck Depression Inventory; SF-36: 36-item Short Form Health Survey; CPAP: continuous positive airway pressure. [#]: *versus* standard intervention; [¶]: male *versus* female; [+]: *versus* group <6 h CPAP use.

calls; and reinforcement of the patients' perception of the improvement in symptoms following CPAP therapy [7, 8, 12, 14, 16, 30–38].

Several small, randomised controlled trials with 1-, 3- or 6-month follow-up periods have evaluated such interventions [39–45]. Large effect sizes in terms of an increase in the hours of nightly use of CPAP have been suggested by these studies; however, the interpretation of the data is limited by the small sample size, short-term follow-up and uncertain treatment components. Among them, the study by WIESE *et al.* [40] is of particular interest, as the increased CPAP adherence was attributed to a video for patient education, which showed patients who represented different ethnicities discussing misconceptions about OSAHS and barriers to CPAP use. Moreover, in a recent study with a large number of patients, a group educational programme resulted in better adherence to CPAP therapy compared with individual education; however, the study only assessed CPAP adherence up to 28 days [46]. Collectively, these findings suggest that combination strategies, including multiple simultaneous interventions, are the most likely to be effective.

There are only limited data from long-term randomised clinical trials evaluating an intensive follow-up programme aimed at improving CPAP compliance [47–52]. Three studies found no significant difference between intensive and standard care alone regarding compliance with CPAP treatment or quality of life [47, 49, 52]. In a study by FALCONE *et al.* [48] in which 206 patients were randomised into two groups, patients in the educational support group, who had the opportunity to review their own PSG charts before and after CPAP, showed better adherence after 12 months of therapy. Another randomised clinical trial showed enhanced CPAP use in a small sample of participants who received a 12-month telemedicine intervention [50]. The current study overcame specific limitations of previous CPAP adherence intervention studies by: recruiting an adequate sample size of Greek patients, a typical Mediterranean population; allocating patients randomly to the intervention arms; and assessing adherence outcomes up to 24 months follow-up, a significantly longer time period than in many of the previous studies in this region. Compared with previous long-term randomised studies, there was a higher percentage of days with CPAP use in the intensive group (mean 89.6% *versus* 66–80% of days in other studies) and a higher mean use per effective day (mean 7 h *versus* 2.9–6.3 h in other studies). Furthermore, according to the most widely used definition of CPAP adherence (a minimum of 4 h·day^{-1} for at least 70% of days), we found that 93.4% of patients were regularly using CPAP 2 years after CPAP initiation in the intensive group *versus* 75.4% in the standard group. These adherence rates higher than those previously reported [50] and similar to those observed with other approaches over a 12-month period [48].

TABLE 5 Comparison of cardiovascular disease (CVD) medical care cost in the standard and intensive follow-up groups

	Annual cost of medical care for CVD per patient €	Hospitalisation due to CVD %	Total cost of CVD hospitalisations €
Standard group	815.5	6.2%	78 369.6
Intensive group	815.5	2.9%	36 656.7
Difference		3.3%	
Cost-saving			41 712.9

Several factors were important in producing good CPAP compliance in the intensive group. First, our follow-up programme was designed to maximise the compliance rate over the long-term in our participants, by incorporating elements that have been suggested by previous investigators. Apart from the intensive patient education and the role of the CPAP nurse, troubleshooting when necessary with rapid involvement of sleep physicians to solve compliance issues, the role of the patients' partner/family should be emphasised. As collaborative spousal involvement has been associated with higher adherence [53], and because we have encountered negative attitudes towards CPAP in some OSAHS patients who were not accompanied by a partner, the presence of the partner/family was always requested in the intensive group. Furthermore, as patients and their families bring specific cultural ideas and have developed beliefs and expectations regarding CPAP before they have even tried the treatment, early intervention to modify these beliefs and improve early CPAP acceptance is considered a critical determinant of continued use. Secondly, a good doctor–patient relationship should be considered a major factor for adherence in the Greek population, as has already been shown in a previous study that investigated the factors affecting antihypertensive medication adherence in Greece [54]. Although it remains unclear which aspect of the consultation with the sleep specialist led to higher CPAP adherence, the increased time spent with the patient, discussing OSAHS and the importance of adhering to CPAP therapy, is likely to have played a major role. Thirdly, we implemented frequent phone calls and intensive support during the first week of therapy, based on studies showing that long-term patient adherence is typically established within the first week of CPAP therapy [34, 55–57].

The results of this study also indicate that compliant CPAP treatment has an impact on patients' quality of life, mood and daytime sleepiness, in accordance with other studies indicating that long-term adherence to CPAP therapy improves symptoms, functional status, depressive symptoms and vigilance in patients with OSAHS [57–60]. It should be noted that the questionnaire scores improved significantly even with the relatively low levels of CPAP usage found in our standard group of patients. However, the greater improvements in sleepiness, quality of life and mood among patients receiving intensive support are important, since these are the features that drive patients to seek therapy. Additionally, the hospitalisation rate and death rate due to CVD were significantly greater in the standard group compared with the intensive group, indicating a beneficial effect of good CPAP compliance on cardiovascular mortality and morbidity. Furthermore, apart from the intensive intervention, SF-36 physical and mental component score improvements and ⩾6 hours of CPAP use per night were associated with prolonged life expectancy. In the standard group, the magnitude of the effect of CPAP treatment on hospitalisation [61, 62] and on death rate due to CVD [61, 63] was similar to that in previous studies, whereas in the intensive group we found a lower risk of death, in accordance with the study of DOHERTY et al. [64]. There are studies suggesting that there is an association between the number of hours of CPAP use and the magnitude of positive effects on daytime symptoms such as daytime sleepiness, or on OSAHS-related conditions such as hypertension. It may be the case that the recommended minimum CPAP usage of 4 h per night and 70% of nights per week is enough to improve daytime sleepiness, but not to normalise issues related to hypertension or other cardiovascular comorbidities [65].

This study had limitations that deserve comment. First, the cohort of patients presented here was carefully selected, without major health problems. All patients were Greek, and were diagnosed and treated in the same centre, with optimal patient education and care. It remains unclear to what extent these findings may be generalised to populations with different cultural and racial backgrounds. Secondly, although good CPAP compliance was achieved in the majority of OSAHS patients in our programme, we cannot be certain which of the components of the intensive programme were the critical factors leading to the excellent long-term CPAP compliance. Thirdly, the study did not include a cost–benefit analysis. Although this study was not designed to make a cost–benefit analysis, after analysing the costs of each of the two interventions, the intensive intervention entailed an additional cost of 30% above the cost of the standard intervention, due to

the limited home visits, phone calls and extra consultations with the sleep physician. However, this cost must be compared with the benefit of the decreased hospitalisation and death rate due to CVD with its associated cost, which was lower in the intensive group. Therefore, comparison of the standard intervention with the intensive intervention could result in cost savings, making the intensive intervention the most favourable intervention, which may be easily reproduced in any sleep medicine centre and the clinical improvements it generates may outweigh the allocation of resources it requires. Lastly, although many studies show no difference in short-term compliance and response to CPAP therapy when portable monitoring and CPAP autotitration at home are compared with in laboratory PSG, our sleep laboratory undertook attended CPAP titration by PSG. The total costs for auto-CPAP titration would be much lower, but more studies are needed to evaluate cost-effectiveness. However, aside from central sleep apnoea, relevant gas exchange abnormality and significant comorbidities, if uvulopalatopharyngoplasty or severe nasal obstruction is present, standard CPAP titration should be considered [66]. Furthermore, according to the Greek National Health Insurance system, CPAP for adults is covered only after a formal in lab CPAP titration study that shows the effectiveness of CPAP therapy in ameliorating OSAHS.

In conclusion, our study findings suggest that long-term CPAP use can be improved more by intensive than by standard patient follow-up support. The patients who received intensive CPAP support showed significantly greater improvements in ESS, BDI and SF-36 scores, as well as lower hospitalisation and death rates, compared with the patients receiving standard support, suggesting that an intensive programme could be worthwhile. Several factors seem to be important for producing good CPAP compliance in the intensive group, including patient education, the role of the CPAP nurse, a good doctor–patient relationship, and the role of the partner/family. Future studies are needed to determine which of the components of the intensive programme are the critical factors for achieving excellent long-term CPAP compliance rates, as well as which patients are most likely to benefit and should be referred for intensive intervention.

References

1   Epstein LJ, Kristo D, Strollo PJ Jr, et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. J Clin Sleep Med 2009; 5: 263–276.
2   Punjabi NM. The epidemiology of adult obstructive sleep apnea. Proc Am Thorac Soc 2008; 5: 136–143.
3   Loke YK, Brown JW, Kwok CS, et al. Association of obstructive sleep apnea with risk of serious cardiovascular events: a systematic review and meta-analysis. Circ Cardiovasc Qual Outcomes 2012; 5: 720–728.
4   Punjabi NM, Caffo BS, Goodwin JL, et al. Sleep-disordered breathing and mortality: a prospective cohort study. PLoS Med 2009; 6: e1000132.
5   Young T, Palta M, Dempsey J, et al. Burden of sleep apnea: rationale, design, and major findings of the Wisconsin Sleep Cohort study. WMJ 2009; 108: 246–249.
6   Ballester E, Badia JR, Hernández L, et al. 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.
7   Weaver TE. Adherence to positive airway pressure therapy. Curr Opin Pulm Med 2006; 12: 409–413.
8   Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. Proc Am Thorac Soc 2008; 5: 173–178.
9   Mermigkis C, Bouloukaki I, Antoniou KM, et al. CPAP therapy in patients with idiopathic pulmonary fibrosis and obstructive sleep apnea: does it offer a better quality of life and sleep? Sleep Breath 2013; 17: 1137–1143.
10 Papandreou C, Schiza SE, Bouloukaki I, et al. Effect of Mediterranean diet versus prudent diet combined with physical activity on OSAS: a randomised trial. Eur Respir J 2012; 39: 1398–1404.
11 Schiza SE, Mermigkis C, Panagiotis P, et al. C-reactive protein evolution in obstructive sleep apnoea patients under CPAP therapy. Eur J Clin Invest 2010; 40: 968–975.
12 Rose MW. Positive airway pressure adherence: problems and interventions. Sleep Med Clin 2006; 1: 533–539.
13 Stepnowsky CJ Jr, Moore PJ. Nasal CPAP treatment for obstructive sleep apnea: developing a new perspective on dosing strategies and compliance. J Psychosom Res 2003; 54: 599–605.
14 Bollig SM. Encouraging CPAP adherence: it is everyone's job. Respir Care 2010; 55: 1230–1239.
15 Kohler M, Smith D, Tippett V, et al. Predictors of long-term compliance with continuous positive airway pressure. Thorax 2010; 65: 829–832.
16 Sawyer AM, Gooneratne NS, Marcus CL, et al. A systematic review of CPAP adherence across age groups: clinical and empiric insights for developing CPAP adherence interventions. Sleep Med Rev 2011; 15: 343–356.
17 Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991; 14: 540–545.
18 Ware JE. SF-36 Physical and Mental Health Summary Scales: A User's Manual. Boston, New England Medical Center Hospital, The Health Institute, 1994.
19 Ware JE Jr, Kosinski M, Bayliss MS, et al. Comparison of methods for the scoring and statistical analysis of SF-36 health profile and summary measures: summary of results from the Medical Outcomes Study. Med Care 1995; 33: Suppl., AS264–AS279.
20 Martinez TY, Pereira CA, dos Santos ML, et al. Evaluation of the short-form 36-item questionnaire to measure health-related quality of life in patients with idiopathic pulmonary fibrosis. Chest 2000; 117: 1627–1632.
21 Beck AT, Beamesderfer A. Assessment of depression: the depression inventory. Mod Probl Pharmacopsychiatry 1974; 7: 151–169.
22 Beck AT. Psychometric properties of the Beck Depression Inventory: twenty-five years of evaluation. Clin Psychol Rev 1988; 8: 77–100.
23 Richter P, Werner J, Heerlein A, et al. On the validity of the Beck Depression Inventory. A review. Psychopathology 1998; 31: 160–168.

24   Iber C, Ancoli-Israel S, Chesson AL, *et al.* The AASM Manual for the Scoring of Sleep and Associated Events. Westchester, American Academy of Sleep Medicine 2007.

25   Kribbs NB, Pack AI, Kline LR, *et al.* Objective measurement of patterns of nasal CPAP use by patients with obstructive sleep apnea. *Am Rev Respir Dis* 1993; 147: 887–895.

26   Allender S, Scarborough P, Peto V, *et al.* European cardiovascular disease statistics 2008. http://www.herzstiftung.ch/uploads/media/European_cardiovascular_disease_statistics_2008.pdf Date last accessed: April 21, 2014. Date last updated: February 29, 2008.

27   Tountas G. Hellas Health I Study Total Results. (Article in Greek). www.neahygeia.gr/pdf/HellasHealth_I_sunolika_apotelesmata.pdf Date last accessed: April 21, 2014. Date last updated: November 1, 2006.

28   Stradling JR, Davies RJ. Is more NCPAP better? *Sleep* 2000; 23: Suppl. 4, S150–S153.

29   Weaver TE, Maislin G, Dinges DF, *et al.* Relationship between hours of CPAP use and achieving normal levels of sleepiness and daily functioning. *Sleep* 2007; 30: 711–719.

30   Weaver TE, Sawyer AM. Adherence to continuous positive airway pressure treatment for obstructive sleep apnoea: implications for future interventions. *Indian J Med Res* 2010; 131: 245–258.

31   Aloia MS, Di Dio L, Ilniczky N, *et al.* Improving compliance with nasal CPAP and vigilance in older adults with OAHS. *Sleep Breath* 2001; 5: 13–21.

32   Smith I, Nadig V, Lasserson TJ. Educational, supportive and behavioural interventions to improve usage of continuous positive airway pressure machines for adults with obstructive sleep apnoea. *Cochrane Database Syst Rev* 2009; 2: CD007736.

33   Sin DD, Mayers I, Man GC, *et al.* Long-term compliance rates to continuous positive airway pressure in obstructive sleep apnea: a population-based study. *Chest* 2002; 121: 430–435.

34   Haniffa M, Lasserson TJ, Smith I. Interventions to improve compliance with continuous positive airway pressure for obstructive sleep apnoea. *Cochrane Database Syst Rev* 2004; 4: CD003531.

35   Shapiro GK, Shapiro CM. Factors that influence CPAP adherence: an overview. *Sleep Breath* 2010; 14: 323–335.

36   Engleman HM, Wild MR. Improving CPAP use by patients with the sleep apnoea/hypopnoea syndrome (SAHS). *Sleep Med Rev* 2003; 7: 81–99.

37   Wild MR, Engleman HM, Douglas NJ, *et al.* Can psychological factors help us to determine adherence to CPAP? A prospective study. *Eur Respir J* 2004; 24: 461–465.

38   Andreu AL, Chiner E, Sancho-Chust JN, *et al.* Effect of an ambulatory diagnostic and treatment programme in patients with sleep apnoa. *Eur Respir J* 2012; 39: 305–312.

39   Wang W, He G, Wang M, *et al.* Effect of patient education and progressive muscle relaxation alone or combined on adherence to continuous positive airway pressure treatment in obstructive sleep apnea patients. *Sleep Breath* 2012; 16: 1049–1057.

40   Jean Wiese H, Boethel C, Phillips B, *et al.* CPAP compliance: video education may help!. *Sleep Med* 2005; 6: 171–174.

41   Richards D, Bartlett DJ, Wong K, *et al.* Increased adherence to CPAP with a group cognitive behavioral treatment intervention: a randomized trial. *Sleep* 2007; 30: 635–640.

42   Deng T, Wang Y, Sun M, *et al.* Stage-matched intervention for adherence to CPAP in patients with obstructive sleep apnea: a randomized controlled trial. *Sleep Breath* 2013; 17: 791–801.

43   Hoy CJ, Vennelle M, Kingshott RN, *et al.* Can intensive support improve continuous positive airway pressure use in patients with the sleep apnea/hypopnea syndrome? *Am J Respir Crit Care Med* 1999; 159: 1096–1100.

44   Antic NA, Catcheside P, Buchan C, *et al.* The effect of CPAP in normalizing daytime sleepiness, quality of life, and neurocognitive function in patients with moderate to severe OSA. *Sleep* 2011; 34: 111–119.

45   Palmer S, Selvaraj S, Dunn C, *et al.* Annual review of patients with sleep apnea/hypopnea syndrome – a pragmatic randomised trial of nurse home visit *versus* consultant clinic review. *Sleep Med* 2004; 5: 61–65.

46   Lettieri CJ, Walter RJ. Impact of group education on continuous positive airway pressure adherence. *J Clin Sleep Med* 2013; 9: 537–541.

47   Holmdahl C, Schöllin IL, Alton M, *et al.* CPAP treatment in obstructive sleep apnea: a randomised, controlled trial of follow-up with a focus on patient satisfaction. *Sleep Med* 2009; 10: 869–874.

48   Falcone VA, Damiani MF, Quaranta VN, *et al.* Polysomnograph chart view by patients: a new educational strategy to improve compliance in sleep apnea therapy. *Respir Care* 2014; 59: 193–198.

49   Meurice JC, Ingrand P, Portier F, *et al.* A multicentre trial of education strategies at CPAP induction in the treatment of severe sleep apnoea-hypopnoea syndrome. *Sleep Med* 2007; 8: 37–42.

50   Sparrow D, Aloia M, Demolles DA, *et al.* A telemedicine intervention to improve adherence to continuous positive airway pressure: a randomised controlled trial. *Thorax* 2010; 65: 1061–1066.

51   Damjanovic D, Fluck A, Bremer H, *et al.* Compliance in sleep apnoea therapy: influence of home care support and pressure mode. *Eur Respir J* 2009; 33: 804–811.

52   Olsen S, Smith SS, Oei TP, *et al.* Motivational interviewing (MINT) improves continuous positive airway pressure (CPAP) acceptance and adherence: a randomized controlled trial. *J Consult Clin Psychol* 2012; 80: 151–163.

53   Glazer Baron K, Gunn HE, Czajkowski LA, *et al.* Spousal involvement in CPAP: does pressure help? *J Clin Sleep Med* 2012; 8: 147–153.

54   Tsiantou V, Pantzou P, Pavi E, *et al.* Factors affecting adherence to antihypertensive medication in Greece: results from a qualitative study. *Patient Prefer Adherence* 2010; 4: 335–343.

55   Weaver TE, Kribbs NB, Pack AI, *et al.* Night-to-night variability in CPAP use over the first three months of treatment. *Sleep* 1997; 20: 278–283.

56   Budhiraja R, Parthasarathy S, Drake CL, *et al.* Early CPAP use identifies subsequent adherence to CPAP therapy. *Sleep* 2007; 30: 320–324.

57   Aloia MS, Arnedt JT, Stanchina M, *et al.* How early in treatment is PAP adherence established? Revisiting night-to-night variability. *Behav Sleep Med* 2007; 5: 229–240.

58   Avlonitou E, Kapsimalis F, Varouchakis G, *et al.* Adherence to CPAP therapy improves quality of life and reduces symptoms among obstructive sleep apnea syndrome patients. *Sleep Breath* 2012; 16: 563–569.

59   Pichel F, Zamarrón C, Magán F, *et al.* Health-related quality of life in patients with obstructive sleep apnea: effects of long-term positive airway pressure treatment. *Respir Med* 2004; 98: 968–976.

60 Sin DD, Mayers I, Man GCW, *et al.* Can continuous positive airway pressure therapy improve the general health status of patients with obstructive sleep apnea? A clinical effectiveness study. *Chest* 2002; 112: 1679–1685.

61 Marin JM, Carrizo SJ, Vicente E, *et al.* 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.

62 Barbé F, Durán-Cantolla J, Sánchez-de-la-Torre M, *et al.* 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.

63 Anandam A, Patil M, Akinnusi M, *et al.* Cardiovascular mortality in obstructive sleep apnoea treated with continuous positive airway pressure or oral appliance: an observational study. *Respirology* 2013; 18: 1184–1190.

64 Doherty LS, Kiely JL, Swan V, *et al.* Long-term effects of nasal continuous positive airway pressure therapy on cardiovascular outcomes in sleep apnea syndrome. *Chest* 2005; 127: 2076–2084.

65 Barbé F, Durán-Cantolla J, Capote F, *et al.* Long-term effect of continuous positive airway pressure in hypertensive patients with sleep apnea. *Am J Respir Crit Care Med* 2010; 181: 718–726.

66 Corral-Peñafiel J, Pepin JL, Barbe F. Ambulatory monitoring in the diagnosis and management of obstructive sleep apnoea syndrome. *Eur Respir Rev* 2013; 22: 312–324.