Long-term clinical effectiveness of continuous positive airway pressure therapy versus non-invasive ventilation therapy in patients with obesity hypoventilation syndrome: a multicentre, open-label, randomised controlled trial

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Summary

Background Obesity hypoventilation syndrome is commonly treated with continuous positive airway pressure or non-invasive ventilation during sleep. Non-invasive ventilation is more complex and costly than continuous positive airway pressure but might be advantageous because it provides ventilatory support. To date there have been no long-term trials comparing these treatment modalities. We therefore aimed to determine the long-term comparative effectiveness of both treatment modalities.

Methods We did a multicentre, open-label, randomised controlled trial at 16 clinical sites in Spain. We included patients aged 15–80 years with untreated obesity hypoventilation syndrome and an apnoea-hypopnoea index of 30 or more events per h. We randomly assigned patients, using simple randomisation through an electronic database, to receive treatment with either non-invasive ventilation or continuous positive airway pressure. Both investigators and patients were aware of the treatment allocation. The research team was not involved in deciding hospital treatment, duration of treatment in the hospital, and adjustment of medications, as well as adjudicating cardiovascular events or cause of mortality. Treating clinicians from the routine care team were not aware of the treatment allocation. The primary outcome was the number of hospitalisation days per year. The analysis was done according to the intention-to-treat principle. This study is registered with ClinicalTrials.gov, number NCT01405976.

Findings From May 4, 2009, to March 25, 2013, 100 patients were randomly assigned to the non-invasive ventilation group and 115 to the continuous positive airway pressure group, of which 97 patients in the non-invasive ventilation group and 107 in the continuous positive airway pressure group were included in the analysis. The median follow-up was 5·44 years (IQR 4·45–6·37) for all patients, 5·37 years (4·36–6·32) in the continuous positive airway pressure group, and 5·55 years (4·53–6·50) in the non-invasive ventilation group. The mean hospitalisation days per patient-year were 1·63 (SD 3·74) in the continuous positive airway pressure group and 1·44 (3·07) in the non-invasive ventilation group (adjusted rate ratio 0·78, 95% CI 0·34–1·77; p=0·561). Adverse events were similar between both groups.

Interpretation In stable patients with obesity hypoventilation syndrome and severe obstructive sleep apnoea, non-invasive ventilation and continuous positive airway pressure have similar long-term effectiveness. Given that continuous positive airway pressure has lower complexity and cost, continuous positive airway pressure might be the preferred first-line positive airway pressure treatment modality until more studies become available.

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Introduction

Obesity hypoventilation syndrome is defined by the combination of obesity, daytime hypercapnia during wakefulness, and sleep-disordered breathing in the absence of other causes of hypoventilation.[1] Approximately 90% of patients with obesity hypoventilation syndrome have concomitant obstructive sleep apnoea,[2] with 73% having severe obstructive sleep apnoea.[3] Patients with obesity hypoventilation syndrome have a higher cardiovascular and respiratory morbidity than those with eucapnic obstructive sleep apnoea[4,5] and eucapnic obesity,[6,7] leading to increased risk of admission to hospital, health-care resource utilisation, and mortality.[7–16]

Ambulatory patients with obesity hypoventilation syndrome are typically treated with nocturnal positive airway pressure therapy during sleep. The most commonly prescribed treatment modalities are non-invasive ventilation or continuous positive airway pressure. Non-invasive ventilation consists of the application of positive-pressure ventilation, usually with

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Research in context

Evidence before this study

Obesity hypoventilation syndrome is commonly treated with either non-invasive ventilation or continuous positive airway pressure during sleep. Non-invasive ventilation therapy is more complex and costly but might be advantageous because it provides ventilatory support to improve hypoventilation. We searched PubMed for articles on obesity hypoventilation syndrome with the search terms "obesity hypoventilation syndrome" or "hypercapnic obstructive sleep apnea". We limited the search to English and Spanish. These articles were later subclassified and organised as editorial, review, or original research. The treatment intervention studies were classified as medium-term results (≤3 months of treatment) or long-term results (>3 months). All articles were read by the same researcher (JFM). Treatment intervention articles were summarised in a table with several outcomes to easily compare them. This process was updated every 3 months starting in June, 2007. The level of evidence for treatment intervention articles was classified in four levels (very low, low, moderate, and high) taking into account the study design, risk of bias, inconsistence, indirectness, imprecision, and number of patients. The effectiveness of non-invasive ventilation therapy has been assessed in several observational studies and few medium-term randomised controlled trials. Three randomised controlled trials compared the effect of medium-term (2 or 3 months) continuous positive airway pressure and non-invasive ventilation therapy, and they reported similar outcomes between the treatment groups. However, there are no long-term comparative studies to determine the potential advantages of either treatment modality.

Added value of this study

This multicentre, randomised controlled trial is the largest and with the longest period of follow-up in patients with obesity hypoventilation syndrome to date. Hospital resource utilisation (hospitalisation days per year), incidence of cardiovascular events, blood pressure, mortality, arterial blood gases, spirometric data, quality of life, clinical symptoms, and side-effects were similar between non-invasive ventilation and continuous positive airway pressure.

Implications of all the available evidence

Taking the data from the available literature as a whole, the comparative efficacy of medium-term and long-term treatments of non-invasive ventilation and continuous positive airway pressure are similar. Given that continuous positive airway pressure is cheaper and easier to implement than non-invasive ventilation, continuous positive airway pressure would be the preferable first line of treatment modality in patients with obesity hypoventilation syndrome and concomitant severe obstructive sleep apnoea. However, it is still plausible that non-invasive ventilation might have a superior effectiveness than continuous positive airway pressure in certain subgroups of patients. Therefore, a case-by-case evaluation is necessary until more studies become available.

bilevel pressure settings. The effectiveness of non-invasive ventilation has been assessed in several observational studies[4,6,7,17–24] and few medium-term randomised clinical trials.[3,25–28] Continuous positive airway pressure consists of a continuous preset pressure during the respiratory cycle to prevent obstructive apnoeas and hypopnoeas; however, in contrast to non-invasive ventilation, it does not provide additional ventilatory support.[22] In the first stage of the Pickwick Project, we did a randomised clinical trial comparing the medium-term efficacy (2 months) among non-invasive ventilation, continuous positive airway pressure, and lifestyle modification in 221 patients with obesity hypoventilation syndrome.[3] Both continuous positive airway pressure and non-invasive ventilation led to a significant reduction in $PaCO_2$ and bicarbonate when compared with lifestyle changes, but no significant difference was observed between the two positive airway pressure modalities. In addition, two smaller (36 and 60 patients) medium-term (3 months) randomised trials reported similar outcomes between continuous positive airway pressure and non-invasive ventilation.[27,28] Because of their short-term follow-up, these clinical trials focused mostly on surrogate endpoints (ie, daytime hypercapnia and symptoms). Although continuous positive airway pressure has lower cost and complexity than non-invasive ventilation, no long-term comparative studies to determine the potential advantages exist.

Since non-invasive ventilation has a wider physiological spectrum of treatment during sleep than continuous positive airway pressure,[22,29] we hypothesised that compared with continuous positive airway pressure, long-term non-invasive ventilation treatment should lead to better outcomes in patients with obesity hypoventilation syndrome. We therefore aimed to determine the long-term comparative effectiveness between non-invasive ventilation and continuous positive airway pressure.

Methods

Study design and participants

We did a multicentre, open-label, randomised controlled trial at 16 clinical sites in Spain. There were no changes in the protocol after trial commencement.

We sequentially screened patients between ages 15 and 80 years who were referred for pulmonary consultations because of suspected obesity hypoventilation syndrome or obstructive sleep apnoea at the 16 tertiary hospitals in Spain (appendix). Obesity hypoventilation syndrome was defined as obesity with a body-mass index of 30 kg/m² or more, stable hypercapnic respiratory failure ($PaCO_2$ ≥45 mm Hg, pH ≥7·35, and no clinical exacerbation during the previous 2 months), no significant spirometric

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evidence of chronic obstructive pulmonary disease (forced expiratory volume in 1 s [FEV_1] had to be >70% of predicted in cases for which FEV_1/forced vital capacity [FVC] ratio was <70), and no clinical evidence of neuromuscular, chest wall, or metabolic disease that could explain hypoventilation. Other inclusion criteria were severe obstructive sleep apnoea (apnoea-hypopnoea index ≥30 events per h), an absence of narcolepsy or restless legs syndrome, and a correctly executed 30-min treatment test of continuous positive airway pressure or non-invasive ventilation (appendix). The exclusion criteria were a psycho-physical inability to complete questionnaires, severe chronic debilitating illness, severe chronic nasal obstruction, and a lack of informed consent.

This study is the long-term follow-up of the Pickwick Project. The Pickwick Project consisted of two parallel randomised controlled trials done in two phases.[30] Patients without severe obstructive sleep apnoea (apnoea-hypopnoea index <30 events per h) were referred to the parallel study protocol (appendix).[26] The Pickwick Project was approved by the ethics committees of the 16 centres, and we obtained written informed consent from all patients.

Randomisation and masking

In the first phase of this study, an investigator in each centre randomly allocated ambulatory patients with obesity hypoventilation syndrome and severe obstructive sleep apnoea to one of three groups: non-invasive ventilation group, continuous positive airway pressure group, or control group), using a web-based electronic database (simple randomisation without predetermined allocation rate). Because of prespecified ethical reasons, after 2 months of follow-up, patients who were initially allocated to the control group were randomly reallocated to either the non-invasive ventilation group or the continuous positive airway pressure group by the same investigator using simple randomisation via the same web-based electronic database, which comprised the second phase of this study.

This study was not masked and both investigators and patients were aware of the treatment allocation. An investigator at each centre was in charge of patient selection, randomisation, and follow-up (data collection). The investigators were not responsible or involved in other aspects of clinical care or clinical decisions related to treatment in the hospital, duration of treatment in the hospital, emergency department visits, admission or transfer to the intensive care unit (ICU), classifying cardiovascular events, or any medication adjustments. The treating clinicians (routine care team) from different specialties were responsible for these tasks and they were unaware of the study protocol, and there was no mention of patient enrolment in the Pickwick Project in the electronic medical records (appendix).

Procedures

In the first phase of the Pickwick Project, the control group consisted of lifestyle changes. The follow-up period was 2 months for each patient from either of the three groups. This first phase was designed to assess the medium-term effect of non-invasive ventilation, continuous positive airway pressure, and lifestyle changes (ie, the control group) on daytime $PaCO_2$, quality of life, spirometry, 6-min walk distance (6-MWD), and polysomnography. In the second phase of the Pickwick Project, all patients who were randomly assigned to either the non-invasive ventilation or continuous positive airway pressure groups were followed-up for a minimum of 3 years and were instructed on lifestyle modification (appendix). Supplemental oxygen therapy was added if baseline daytime or nocturnal hypoxaemia was detected during positive airway pressure adjustment.[31]

Continuous positive airway pressure titration was done during conventional polysomnography based on standard recommendations (appendix).[32] The mean continuous positive airway pressure setting was 10·7 cm H_2O (SD 2·64).

The non-invasive ventilation modality was volume-targeted pressure support. The initial non-invasive ventilation adjustment was done during wakefulness. The expiratory positive airway pressure was set between 4 and 8 cm H_2O, and the inspiratory positive airway pressure was set between 18 and 22 cm H_2O (expiratory positive airway pressure included). The pressures were adjusted to obtain normal oxygen saturation, if possible, as measured by pulse oximetry and patient tolerance. The backup respiratory rate was adjusted to 12–15 breaths per min (close to the spontaneous respiratory rate if possible), and the target volume was set at between 5 and 6 mL/kg of actual bodyweight, allowing for an increase in the maximum pressure over the previously fixed inspiratory positive airway pressure if necessary. A check for mechanical ventilation phases (trigger, pressurisation, and cycle ending) was also done to avoid asynchronies and to refine the setting. After 30 min of continuous use, with patient adaptation and confirmation of an adequate patient-ventilator interaction, arterial blood gases were measured. The $PaCO_2$ level was used to further adjust the ventilator parameters. The final adjustment and titration was done by means of conventional polysomnography (appendix). The mean inspiratory positive airway pressure was 19·7 cm H_2O (SD 4·33) and expiratory positive airway pressure was 8·18 cm H_2O (SD 2·28), and the mean backup rate was 14 breaths per min (SD 3).

We evaluated patients on at least 12 occasions during 3 years: at baseline, first and second months, and every 3 months until completing 2 years, then every 6 months until completing 3 years (appendix p 34). Evaluations at the first and second months were done before the re-randomisation of the control group to either continuous positive airway pressure or non-invasive ventilation. These results were previously published.[3]

In the first, second, and third annual visits, we measured the incidence of new cardiovascular events

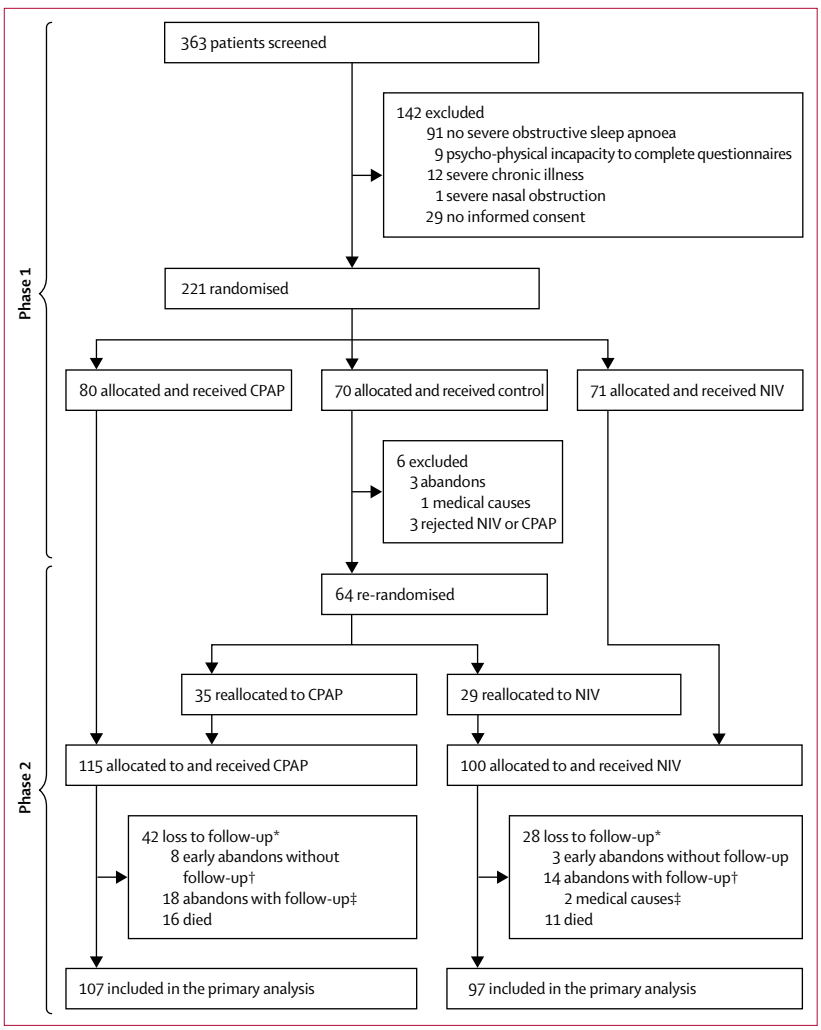

Figure 1: **Trial profile**
CPAP=continuous positive airway pressure. NIV=non-invasive ventilation. *In the CPAP group, 13 patients abandoned CPAP and four changed to NIV; in the NIV group, 13 patients abandoned NIV and four changed to CPAP. Patients who changed treatment after randomisation (ie, from CPAP to NIV or vice versa) were analysed in the original group according to the intention-to-treat principle. †Patients who abandoned the study early without follow-up were not included in the primary analysis. ‡These participants who were lost to follow-up but did not withdraw informed consent were included in the primary analysis and analyses of hospital resource utilisation, treatment type, and mortality.

including new hypertension diagnosis (counting initiation of antihypertensive treatment), atrial fibrillation, and hospitalisations for non-fatal myocardial infarction, unstable angina, stroke, transient ischaemic attack, heart failure, and cardiovascular death. At baseline and all subsequent visits, arterial blood gases on room air were obtained to assess $PaCO_2$, PaO_2, pH, and to calculate bicarbonate; sphygmomanometric blood pressure;[33] spirometric data (FEV_1 and FVC);[34] 6-MWD test;[35] and health-related quality-of-life tests using the Functional Outcomes of Sleep Questionnaire, the Medical Outcome Survey Short Form 36, and the visual analogical wellbeing scale (appendix).[36,37] We also assessed anthropometric data and clinical symptoms at baseline, first, second, and third annual visits. In the three subsequent annual visits, we also measured adherence to continuous positive airway pressure or non-invasive ventilation (using internal device hourly counters), continuous positive airway pressure or non-invasive ventilation settings, and adverse events.

After 3 years of follow-up, patients were followed-up every 3 months until the last patient attained at least 3 years of follow-up data to collect information about hospitalisation days and other hospital resource use, discontinuation of continuous positive airway pressure or non-invasive ventilation, and mortality. During all visits, we encouraged treatment adherence and made adjustments to supplemental oxygen therapy or positive airway pressure settings and masks if the patients required them.

Outcomes

The primary outcome was the number of hospitalisation days per year for any cause, which was assessed at every visit after the baseline visit. This outcome was obtained from the electronic medical records and during face-to-face interview with patients or relatives in case of death (appendix). The secondary outcome measures, which were assessed and obtained in the same fashion as the primary outcome, were other hospital resource utilisation (ie, emergency department visits, hospital admissions, and ICU admissions), incident cardiovascular events, all-cause mortality, blood pressure, arterial blood gas parameters (ie, $PaCO_2$, PaO_2, bicarbonate, and pH), respiratory functional outcomes (ie, FEV_1 and FVC), 6-MWD, and health-related quality of life. Additional prespecified outcome measures were anthropometric data (ie, bodyweight) and clinical symptoms such as lower extremity oedema, unrefreshing sleep, tiredness, nocturia, headache, and morning confusion. These symptoms were classified into four levels of intensity (from 1 to 4). Dyspnoea was classified using the Medical Research Council (MRC) scale[38] and sleepiness on the Epworth Sleepiness Scale (ESS).

Statistical analysis

We calculated the sample size to detect differences in the primary outcome variable, assuming an α error of 0·05 and a β error of 0·2. At the time of the study design, the mean hospital stay in patients receiving chronic non-invasive ventilation was 2·5 days per patient-year (SD 1·1).[7] We estimated that an intergroup mean difference of 0·5 or more days per patient-year (SD 1·1; 20% difference) could be clinically relevant. We estimated a sample size of at least 77 patients in each group, and estimated a 25% dropout rate or loss of follow-up leading to 96 patients per group needed to power the study to detect a significant difference.

We did a baseline bivariate analysis using a *t*-test (or equivalent non-parametric) or χ^2 test depending on quantitative or categorical variables, respectively. For

	Continuous positive airway pressure (n=107)	Non-invasive ventilation (n=97)	p values
Age (years)	60·0 (49·0–71·0)	65·0 (56·5–71·5)	0·056
Sex			0·090
Female	54 (50%)	61 (63%)	
Male	53 (50%)	36 (37%)	
Smokers	33 (31%)	18 (19%)	0·052
Number of packs smoked per year*	20·0 (10·0–30·0)	20·0 (20·0–22·5)	0·920
Drinkers†	8 (7%)	13 (13%)	0·249
Alcohol (g)*	37·0 (30·5–77·5)	45·0 (35·0–77·0)	0·645
BMI (kg/m^2)	42·7 (38·2–48·8)	42·9 (38·1–47·6)	0·604
Neck circumference (cm)	45·0 (41·0–48·0)	44·0 (42·0–47·0)	0·578
Epworth Sleepiness Scale	10·6 (5·19)	11·4 (4·96)	0·348
Functional Outcomes of Sleep Questionnaire	73·3 (21·7)	74·8 (21·1)	0·607
Medical Outcome Survey SF 36			
SF 36-Physical	34·7 (28·5–44·8)	36·7 (27·7–45·3)	0·786
SF 36-Mental	45·8 (31·6–50·1)	45·0 (32·7–53·2)	0·933
Visual analogical wellbeing scale	48·0 (30·8–66·6)	50·0 (37·5–58·3)	0·784
Dyspnoea MRC scale ≥2	58 (54%)	61 (63%)	0·209
Hypertension	71 (66%)	69 (71%)	0·546
Antihypertensive drugs*	2 (1–2)	2 (1–2)	0·532
Systolic blood pressure (mm Hg)	138 (130–145)	140 (130–150)	0·765
Diastolic blood pressure (mm Hg)	80 (70–90)	80 (70–90)	0·336
Diabetes	36 (34%)	40 (41%)	0·311
Antidiabetic medications	34 (32%)	39 (40%)	0·243
Dyslipidaemia	43 (40%)	47 (48%)	0·260
Treatment of dyslipidaemia	37 (35%)	39 (40%)	0·469
Stroke	10 (9%)	6 (6%)	0·445
Ischaemic heart disease	10 (9%)	8 (8%)	0·999
Arrhythmia	6 (6%)	11 (11%)	0·204
Chronic heart failure	13 (12%)	17 (18%)	0·325
Leg arteriopathy	5 (5%)	5 (5%)	0·999
Pulmonary hypertension	9 (8%)	8 (8%)	0·999
At least one cardiovascular morbidity	35 (33%)	33 (34%)	0·882
Cardiovascular morbidity‡	0 (0–1)	0 (0–1)	0·575
pH	7·40 (7·38–7·43)	7·40 (7·38–7·42)	0·440
PaO_2 (mm Hg)	60·0 (55·0–67·1)	61·0 (56·7–67·0)	0·787
$PaCO_2$ (mm Hg)	49·0 (47·0–52·0)	51·0 (48·0–54·0)	0·300
Bicarbonate (mmol/L)	29·5 (28·0–32·0)	29·8 (27·8–31·4)	0·693

(Table 1 continues in next column)

	Continuous positive airway pressure (n=107)	Non-invasive ventilation (n=97)	p values
(Continued from previous column)			
FEV_1 in percentage of predicted	77·0 (64·0–90·0)	77·0 (67·3–88·5)	0·728
FVC in percentage of predicted	82·4 (20·8)	77·1 (20·4)	0·069
6-MWD test (m)	372·5 (283·0–448·5)	378·0 (133·4–450·0)	0·770
Polysomnographic parameters§			
Total sleep time (h)	5·35 (1·37)	5·2 (1·23)	0·519
Sleep efficiency	72·9 (59·7–85·3)	72·2 (61·0–84·9)	0·920
Non-REM 1 and 2 (%)	85·0 (74·6–91·5)	85·4 (73·0–92·2)	0·676
Non-REM 3 (%)	6·0 (6·0–13·4)	3·8 (0·0–16·2)	0·342
REM sleep (%)	7·0 (3·3–14·0)	9·2 (3·1–14·3)	0·776
Arousal index	58·5 (31·7–85·0)	56·5 (32·0–75·5)	0·565
Apnoea-hypopnoea index	68·2 (41·6–92·4)	68·7 (48·5–97·1)	0·311
3% oxygen desaturation index	72·9 (39·0–98·2)	68·8 (44·0–94·0)	0·700
Mean SpO_2 during sleep	86 (81–90)	85 (82–88)	0·284
Total sleep time with SpO_2 <90% (%)	75·0 (48·7–94·2)	79·0 (51·8–95·8)	0·611
Oxygen therapy¶	29 (27%)	21 (22%)	0·417
Oxygen therapy flow (L/min)*	1·5 (1·3–2·)	2·0 (1·1–2·0)	0·519
Erythrocytes (cells per mL)	4·95 (0·58)	4·9 (0·62)	0·438
Fasting blood glucose (mg/dL)	106·0 (92·0–131·0)	107·5 (93·3–139·5)	0·340
Triglycerides (mg/dL)	131·0 (110·0–165·5)	138·5 (103·8–183·5)	0·735
Cholesterol (mg/dL)	187·4 (37·5)	186·1 (34·0)	0·787
High-density lipoproteins (mg/dL)	44·0 (38·0–51·8)	45·0 (40·0–55·0)	0·310
Low-density lipoproteins (mg/dL)	110·0 (95·0–132·0)	114·0 (94·0–137·5)	0·781
Creatinine (mg/dL)	0·85 (0·64–1·00)	0·85 (0·70–1·00)	0·669
C-reactive protein (mg/L)	1·8 (0·6–7·8)	1·6 (0·8–6·2)	0·720

Data are median (IQR), n (%), or mean (SD). BMI=body-mass index. SF 36=Short Form 36. PaO_2=partial pressure arterial oxygen. $PaCO_2$=partial pressure of carbon dioxide in arterial blood. FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. 6-MWD=6-min walk distance. MRC=Medical Research Council. REM=rapid eye movement. SpO_2=oxygen saturation. *Includes only patients who reported to be active smokers or drinkers, or patients with hypertension or with oxygen therapy. †People who drink more than 30 g of alcohol per day in men and 20 g in women. ‡Sum of cardiovascular morbidities (25% of the cohort had at least one cardiovascular comorbidity). §Polysomnography was done in baseline conditions without continuous positive airway pressure, non-invasive ventilation, or oxygen therapy in place. ¶Oxygen therapy was prescribed during the baseline visit.

Table 1: **Baseline characteristics**

the primary outcome, we used a mixed-effects model with negative binomial to assess group differences in hospitalisation days per year per patient. The model included an offset-term with logarithmic transformation

	Continuous positive airway pressure (n=107)	Non-invasive ventilation (n=97)	Mean difference (95% CI)	Negative binomial regression		Cox regression model*	
				Adjusted rate ratio (95% CI)	p value	Adjusted hazard ratio (95% CI)	p value
Primary outcome							
Hospitalisation days (per year per patient)	1·63 (3·74)	1·44 (3·07)	−0·19 (−1·13 to 0·75)	0·78 (0·34–1·77)	0·561	..	..
Secondary outcomes							
Health resource utilisation							
Hospital admissions							
At least one	48 (45%)	51 (53%)	..	..	..	1·12 (0·73–1·72)†	0·589
Events per year per patient	0·25 (0·47)	0·24 (0·41)	−0·01 (−0·13 to 0·11)	0·94 (0·58–1·51)	0·783	..	..
Emergency visits							
At least one	66 (62%)	58 (60%)	..	..	..	0·92 (0·62–1·35)†	0·653
Events per year per patient	0·48 (1·04)	0·40 (0·66)	−0·08 (−0·32 to 0·16)	0·87 (0·56–1·35)	0·532	..	..
ICU admissions							
At least one	6 (6%)	4 (4%)	..	..	..	0·81 (0·22–3·06)†	0·754
Events per year per patient	0·03 (0·17)	0·01 (0·04)	−0·02 (−0·06 to 0·01)	0·51 (0·09–2·87)	0·449	..	..
Cardiovascular event	16 (15%)	17 (18%)	..	..	..	1·17 (0·56–2·42)†	0·664
Mortality	16 (15%)	11 (11%)	..	..	..	0·82 (0·36–1·87)	0·631

Data are mean (SD) or n (%), unless otherwise stated. The models were adjusted by sex, age, smoking habits, and forced vital capacity, and included the random effect centre. Difference between treatments was computed as the difference of non-invasive ventilation with respect to continuous positive airway pressure. ICU=intensive care unit. *In the Cox models, no violations of the proportional hazards assumption occurred. †The hazard ratio associated to the time until the first event.

Table 2: **Primary and secondary outcomes for continuous positive airway pressure and non-invasive ventilation**

to account for the duration of follow-up of each patient. Other hospital resource utilisation such as emergency department visits, hospital admissions, and ICU admissions were assessed as number of events per patient-year and analysed as described for the primary outcome. A mixed-effects Cox model was used for new events of other resource hospital utilisation. Also, a mixed-effects Cox model was used for new cardiovascular events and overall mortality. A proportional-hazards assumption for models was tested by correlation test between the Schoenfeld residuals and the time.[39] Other secondary outcomes such as repeated measures derived from the arterial blood gases (ie, $PaCO_2$, PaO_2, pH, and calculated bicarbonate), spirometric data, 6-MWD test, health-related quality-of-life tests, and blood pressure during 3 years of follow-up were compared between treatments using a linear mixed-effects model.

We also did prespecified ancillary analysis. Bodyweight, ESS, and mean of adverse events presumably related to positive airway pressure treatment during 3 years of follow-up were compared between treatments using a linear mixed-effects model. On a yearly basis, we also assessed the presence of symptoms. Scores of 3 or more for any of these symptoms was categorised as habitual and a score of less than 3 as not habitual. The presence of habitual symptoms was compared between baseline and the rest of evaluations using the χ^2 test. Dyspnoea on the MRC scale was analysed similarly but a categorisation of 2 or more for habitual and less than 2 for not habitual was performed.

Exploratory post-hoc analysis of subgroup assessment based on adherence of continuous positive airway pressure or non-invasive ventilation and a simple cost analysis were also completed (appendix).

Because our randomisation was done in two phases with more probability of group imbalances, all models, except for the sensitivity analysis model, were adjusted for potentially unbalanced covariates with a p value of less than 0·1 in the baseline bivariate analysis, age, sex, smoking habits, and FVC. The centre was included as a random effect in all models and the patient was included as a random effect in the linear mixed-effects models. The differential effects between the two groups of the study (ie, continuous positive airway pressure and non-invasive ventilation) were analysed adding a treatment group and repeated measures interaction in the model.

We did an intention-to-treat analysis according to the population of the second randomisation (patients who changed treatment group after randomisation were analysed in the original group) and no imputation of missing data was done. Data management and statistical analyses were done using R (version 3.4.2) and SPSS (version 22.0). This study is registered with ClinicalTrials.gov, number NCT01405976.

Role of the funding source

The sponsors and funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had the final responsibility for the decision to submit for publication.

Results

From May 4, 2009, to March 25, 2013, we screened 363 patients who met the inclusion criteria, of which 142 were excluded (91 had an apnoea-hypopnoea index <30 events per h; figure 1). Of the remaining patients, 100 were allocated to the non-invasive ventilation group and 115 to the continuous positive airway pressure group. For the primary analysis, 97 patients were available in the non-invasive ventilation group and 107 in the continuous positive airway pressure group. Table 1 summarises the baseline characteristics of the two groups.

The median follow-up time for the primary outcome, hospital resource utilisation, and mortality was 5·37 years (IQR 4·36–6·32) years in the continuous positive airway pressure group and 5·55 years (4·53–6·50) in the non-invasive ventilation group, and 5·44 years (4·45–6·37) for all patients. The median follow-up time for the rest of the outcomes was 3·00 years (IQR 2·92–3·17) for the continuous positive airway pressure group and 3·01 years (2·91–3·14) for the non-invasive ventilation group. The median treatment adherence for continuous positive airway pressure was 6·0 h per day (IQR 3·0–7·0) and 72 (67%) of 107 used continuous positive airway pressure for more than 4 h per night. The median treatment adherence for non-invasive ventilation was 6·0 h per day (IQR 1·3–7·2) and 61 (63%) of 97 used non-invasive ventilation more than 4 h per night (appendix p 35).

The mean hospitalisation days per patient-year were 1·63 (SD 3·74) for the continuous positive airway pressure group and 1·44 (3·07) for the non-invasive ventilation group. No significant differences between both groups were observed (adjusted rate ratio 0·78, 95% CI 0·34–1·77; p=0·561; table 2; appendix pp 36, 38). Similar results were obtained without covariate adjustments (appendix p 37).

Events per patient-year for hospital and ICU admissions and emergency department visits were not significantly different between groups (table 2; appendix pp 37, 39, 41). Likewise, the adjusted hazard ratios (HRs) for the first event of these outcomes was not significantly different between groups (table 2; appendix pp 37, 42–47). Cardiovascular events occurred in 16 (15%) of 107 participants in the continuous positive airway pressure group and 17 (18%) of 97 in the non-invasive ventilation group. The adjusted HR was 1·17 (95% CI 0·56–2·42; p=0·664; table 2; figure 2; appendix pp 37, 48). Death occurred in 16 (15%) of 107 participants in the continuous positive airway pressure group and 11 (11%) of 97 in the non-invasive ventilation group. The adjusted HR was 0·82 (95% CI 0·36–1·87; p=0·631; table 2; figure 2; appendix pp 37, 49). The predominant cause of mortality was related to cardiovascular events (nine [56%] of 16 in the continuous positive airway pressure group and six [54%] of 11 in the non-invasive ventilation group; appendix pp 50, 51).

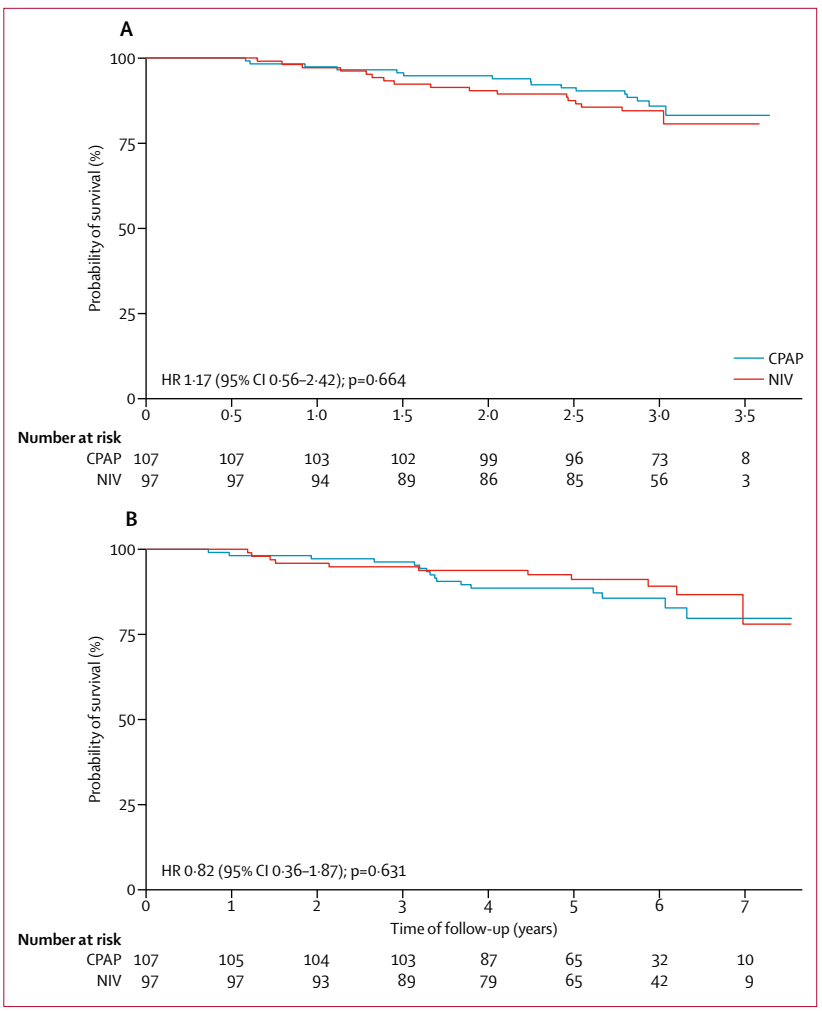

Figure 2: **Cardiovascular event (A) and overall mortality (B) survival curves for treatment intervention**
CPAP=continuous positive airway pressure. HR=hazard ratio. NIV=non-invasive ventilation.

Both systolic and diastolic blood pressures improved significantly with positive airway pressure but without group differences (figure 3; appendix pp 52, 53). Figure 4 and the appendix (pp 54, 55) illustrate longitudinal changes of the arterial blood gas parameters with continuous positive airway pressure and non-invasive ventilation. $PaCO_2$ improved significantly with both treatments without group differences. Similar findings were observed for bicarbonate, pH, and PaO_2. Both FEV_1 and FVC improved with positive airway pressure but without significant group differences (appendix pp 52, 56). The 6-MWD test did not improve with either positive airway pressure modality and there were no significant group differences (appendix pp 52, 57). Health-related quality-of-life tests improved

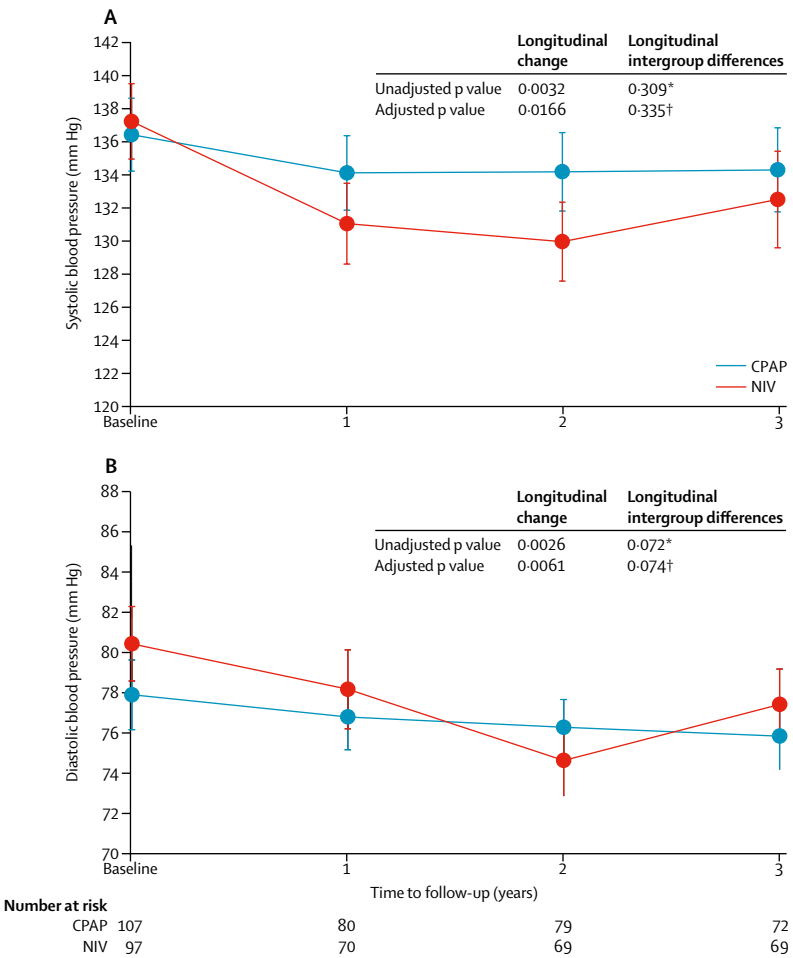

Figure 3: **Adjusted longitudinal changes of systolic and diastolic blood pressures during follow-up**
Data are mean and error bars are 95% CIs. Numbers at risk are the same in both panels. p values correspond to unadjusted and adjusted longitudinal changes for positive airway pressure and for the intergroup CPAP and NIV comparison from the linear mixed-effects regression model. CPAP=continuous positive airway pressure. NIV=non-invasive ventilation. *Unadjusted p values were adjusted only for centre of enrolment. †Adjusted p values were adjusted for centre of enrolment, age, sex, smoking status, and forced vital capacity.

with positive airway pressure without significant group differences (appendix pp 52, 58–60).

Bodyweight was reduced similarly in both groups (appendix p 61). ESS scores improved with positive airway pressure without differences between groups (appendix p 62). Other clinical symptoms (dyspnoea, lower extremity oedema, nocturia, unrefreshing sleep, fatigue, and headaches) also improved similarly with continuous positive airway pressure and non-invasive ventilation therapy (appendix pp 63–66). The prevalence of clinically significant dyspnoea (MRC dyspnoea scale ≥2) in the continuous positive airway pressure group decreased from 54% at baseline to 33% at 1-year follow-up (p<0·0032), and to 29% at 3 years of follow-up. Similarly, in the non-invasive ventilation group, the prevalence of dyspnoea decreased from 63% at baseline to 23% at 1-year follow-up (p<0·0001) and increased to 27% at 3 years of follow-up (appendix p 67). The improvement in dyspnoea was not significantly different between continuous positive airway pressure and non-invasive ventilation. The appendix (p 68) summarises continuous positive airway pressure and non-invasive ventilation settings. Both groups had a progressive and significant reduction in the need for daytime supplemental oxygen therapy: 29 (27%) of 107 patients at baseline to 12 (13%) of 93 at 36 months with continuous positive airway pressure (p=0·0104), and 21 (22%) of 97 at baseline to nine (11%) of 81 at 36 months with non-invasive ventilation (p=0·0402). Adverse events were similar between continuous positive airway pressure and non-invasive ventilation treatments (appendix pp 69–73).

In the exploratory post-hoc analysis, the subgroup with higher adherence had lower hospitalisation days per patient-year, hospital and ICU admissions, emergency department visits, and risk for ICU admission and mortality than the subgroup with lower adherence (appendix pp 19, 20, 74–95). The continuous positive airway pressure group had lower cost of treatment than the non-invasive ventilation group (€911·10 per patient-year) mainly due to the lower cost of continuous positive airway pressure ambulatory treatment compared with non-invasive ventilation ambulatory treatment (appendix pp 20, 96–100).

Discussion

This multicentre clinical trial is the largest study with the longest period of follow-up in patients with obesity hypoventilation syndrome to date. The study included ambulatory patients with obesity hypoventilation syndrome and severe obstructive sleep apnoea who were in stable chronic hypercapnic respiratory failure. The trial showed that there were no significant long-term differences in hospitalisation days, other hospital resource utilisation, blood pressure, cardiovascular events, mortality, respiratory function, and health-related quality of life between non-invasive ventilation and continuous positive airway pressure. Moreover, no significant group differences were observed in outcomes such as daytime sleepiness and related symptoms of obesity hypoventilation syndrome. In the post-hoc analysis, higher level of adherence to either non-invasive ventilation or continuous positive airway pressure was associated with lower hospitalisation days and reduced hospital resource utilisation and mortality. Lastly, continuous positive airway pressure therapy was less expensive than non-invasive ventilation therapy.

Previous randomised controlled trials of patients with obesity hypoventilation syndrome have compared non-invasive ventilation with continuous positive airway pressure.[3,27,28] However, these trials were limited by small sample sizes,[27,28] short-term follow-up of 1–3 months, and focused on non-patient-centred primary outcome of change in daytime $PaCO_2$. By contrast, our long-term clinical trial was designed to follow-up patients for a minimum of 3 years with patient-centred long-term

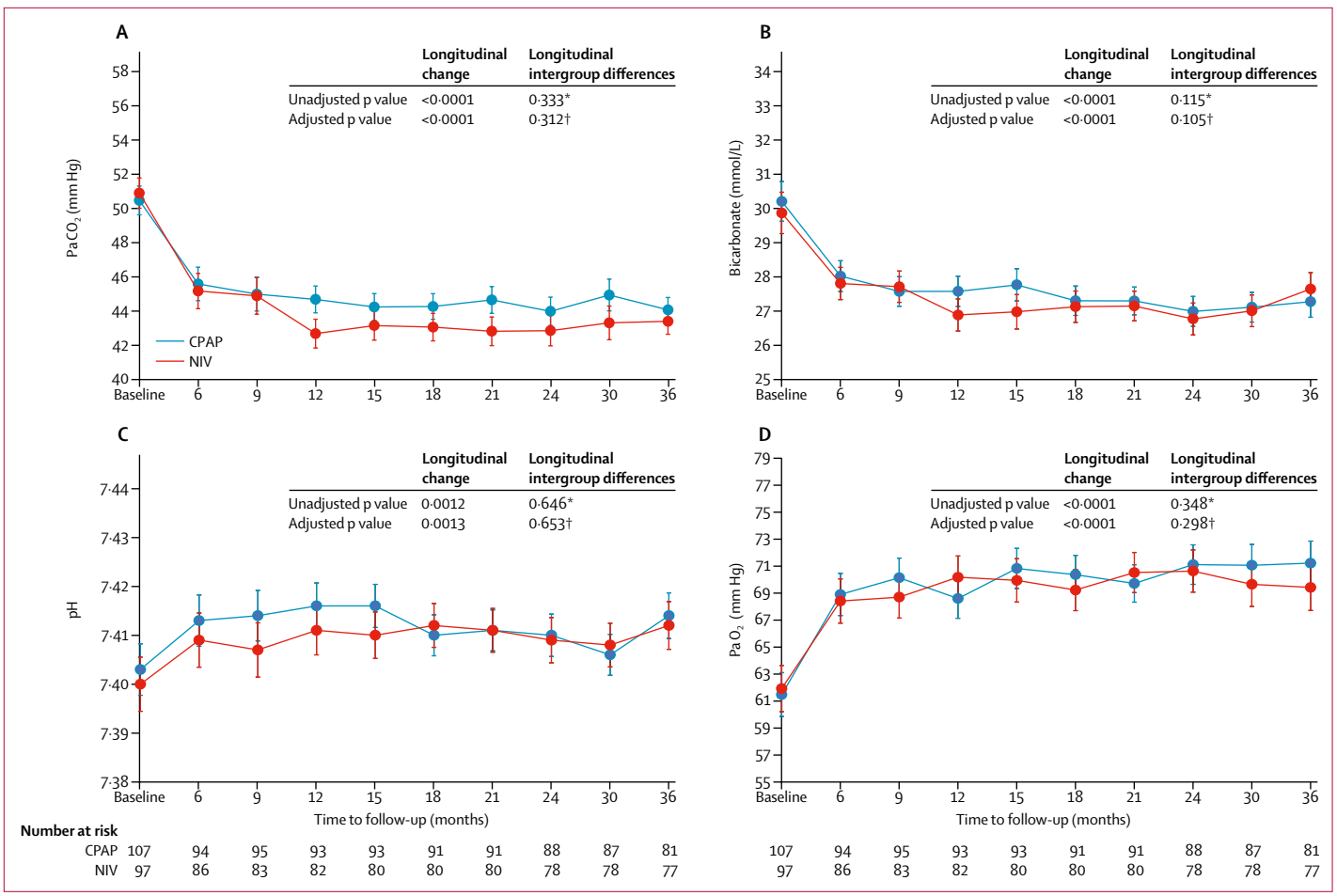

Figure 4: **Adjusted longitudinal changes of arterial blood gases, bicarbonate, and pH during follow-up**
Data are mean and error bars are 95% CIs. Numbers at risk are the same in all four panels. p values correspond to unadjusted and adjusted longitudinal changes for positive airway pressure and for the intergroup CPAP and NIV comparison from the linear mixed-effects regression model. CPAP=continuous positive airway pressure. NIV=non-invasive ventilation. *Unadjusted p values were adjusted only for centre of enrolment. †Adjusted p values were adjusted for centre of enrolment, age, sex, smoking status, and forced vital capacity.

primary and secondary outcomes. A few observational and registry studies have shown increased health-care resource utilisation in patients with obesity hypoventilation syndrome compared with the general population and patients who are obese without hypoventilation;[7] age-matched, sex-matched, and socioeconomic status-matched citizens;[16] and patients who are obese without hypoventilation.[40] In addition, there was a reduction in health-care resource utilisation after initiating nocturnal positive airway pressure therapy.[7] In our study, hospitalisation days in patients treated with positive airway pressure were even lower than a previous retrospective study[7] (2·5 days per year *vs* 1·6 days per year in our continuous positive airway pressure group and 1·4 days per year in our non-invasive ventilation group). A few studies reported that most hospitalisations and deaths in untreated patients with obesity hypoventilation syndrome were due to respiratory complications such as acute-on-chronic respiratory failure and pulmonary embolism.[14,40,41] However, in cohorts of patients with obesity hypoventilation syndrome treated with non-invasive ventilation for an average of 7 years or 2·5 years, 48% and 90% of the deaths, respectively, were due to cardiovascular events.[4,42] In our study, the most common cause of death in patients treated with positive airway pressure was of cardiovascular origin (56% for continuous positive airway pressure and 54% for non-invasive ventilation). This finding suggests that either treatment might reduce morbidity and mortality due to respiratory causes but has less effect on cardiovascular outcomes. However, it is important to acknowledge that without a control group in our trial, it is difficult to assess the long-term effect of continuous positive airway pressure or non-invasive ventilation therapy on cardiovascular outcomes in patients with obesity hypoventilation syndrome. Importantly, despite adequate adherence to positive airway pressure therapy, cardiovascular event rate remains clinically significant and highlights the importance of a holistic approach that includes

emphasis not only on positive airway pressure therapy but also on bodyweight reduction, increased level of activity, and appropriate management of comorbidities.

Observational studies of untreated patients with obesity hypoventilation syndrome have reported mortality for any cause of 24% at 1·5–2 years.[16,40] Two observational studies of patients with obesity hypoventilation syndrome admitted to the ICU due to acute-on-chronic hypercapnic respiratory failure reported 1-year mortality of 18% (55% of the patients were prescribed home positive airway pressure)[43] and 3-year mortality of 31% (percentage of home positive airway pressure prescription unknown).[41] Other observational studies have reported 5-year mortality with non-invasive ventilation treatment varying from 5% to 32%.[4,6,19–21] Mortality in our clinical trial was lower than the observational studies of untreated patients and similar to some of the observational studies of patients who were for the most part adherent to non-invasive ventilation therapy. Therefore, these data together with our adherence subgroup analysis suggests that positive airway pressure therapy might reduce mortality in patients with obesity hypoventilation syndrome.

Although the prevalence of hypertension in patients with obesity hypoventilation syndrome is very high, ranging between 55% and 88%,[3,5–7,20,25,26,40,44–49] there is a paucity of long-term longitudinal data on the progression of blood pressure in patients treated with continuous positive airway pressure or non-invasive ventilation. In a small cohort study of 6 weeks, positive airway pressure therapy led to a significant improvement in nocturnal beat-to-beat blood pressure measured non-invasively without any significant improvement in daytime blood pressure.[50] Our study shows significant improvement in daytime blood pressure with both treatment modalities without differences between groups. Given that our patients had concomitant severe obstructive sleep apnoea, it is not surprising that the degree of improvement in blood pressure was similar to what has been observed in patients with severe eucapnic obstructive sleep apnoea.

The degree of improvement in $PaCO_2$ in our study was within the lower limits of the range of improvement in $PaCO_2$ from observational studies (average of –6 mm Hg to –14 mm Hg).[6,17–19,21,23,24,42,44,51] Given that the level of adherence to therapy in our study was similar to the observational cohorts, the most likely explanation for the larger improvement of hypercapnia in the observational studies is that the patients had higher levels of hypercapnia at baseline and therefore there was more room for improvement (appendix). A similar argument might explain the lower improvement in the 6-MWD test observed in our study in comparison with an observational cohort study.[52]

Medium-term randomised controlled trials[3,25,53] and long-term observational studies[17–19] have previously reported an improvement in FVC and FEV_1 with non-invasive ventilation therapy. However, improvement in lung function has not been a universal finding.[23,44] In the present study, we observed significant improvements in FVC and FEV_1 independent of treatment allocation to either continuous positive airway pressure or non-invasive ventilation. It remains unclear whether this improvement is due to weight loss or intrinsic positive airway pressure action reducing lung microatelectasis. Collectively, the improvements in gas exchange, weight loss, and lung function led to a significant reduction in dyspnoea and the need for daytime supplemental oxygen. A few observational studies have reported improvement in dyspnoea with nocturnal non-invasive ventilation therapy.[44,51,54] Although we were not able to show improvement in dyspnoea after 2 months of therapy,[3] there was a significant reduction in dyspnoea at 12 months with both continuous positive airway pressure and non-invasive ventilation, and this improvement was sustained at 3 years of follow-up. It is plausible that longer duration of therapy is necessary to improve the sensation of dyspnoea with activities of daily living. It remains unclear why improvement in lung function and dyspnoea did not lead to improvement in 6-MWD. Although weight loss might have contributed to improvements in gas exchange and dyspnoea, it is unlikely that an average of 4 kg of weight loss can explain the extent of the observed improvement (appendix).

Our study has several limitations. Hospitalisation days for any cause was chosen as the primary outcome, as a marker of health-care resource utilisation, because when the study was designed in 2007 the only long-term outcome available in the literature was hospitalisation days per year. Patients with obesity hypoventilation syndrome have multiple comorbidities and positive airway pressure therapy could potentially improve comorbidities and ultimately lead to reduced hospitalisation days. The study was designed to show inequality between interventions under the assumption of a change in the mean differences for the primary outcome of –0·5 days per year. The mean difference for hospitalisation days was –0·19 days per year. However, –0·5 days per year is included in the confidence interval of hospitalisation days (–1·13 to 0·75). This imprecision leads to a certain degree of uncertainty in the inequality affirmation. Nevertheless, considering all of the outcomes, our interpretation of the data is that both interventions seem to have similar long-term effectiveness. In addition, the favourable cost analysis of continuous positive airway pressure means that although non-invasive ventilation might have a slightly higher effectiveness, continuous positive airway pressure is preferable given its lower cost. Sample size calculation had not been done a priori for the secondary outcomes, except for $PaCO_2$.[3] Consequently, the results of the secondary outcomes should be interpreted with caution. Much larger sample sizes will be required to show significant mortality differences between the two positive airway pressure treatment modalities. We did

not have a control group, but given the high mortality associated with untreated obesity hypoventilation syndrome, we felt it would be inappropriate to leave patients untreated in a long-term study. Our cohort was limited to patients with obesity hypoventilation syndrome who also have concomitant severe obstructive sleep apnoea. However, the great majority of patients with obesity hypoventilation syndrome have severe obstructive sleep apnoea,[3] therefore increasing the generalisability of our findings. Additionally, our external validity might be limited because the study was exclusively done in Spain, and patients from other ethnic or racial backgrounds could have different characteristics that might influence the results. Patients and investigators were not masked to treatment allocation. However, the treating clinicians in charge of making management decisions were independent of the research team and unaware of the clinical trial. During the initial trial phase, some patients were randomly assigned to the control group (ie, lifestyle changes) during the first 2 months and were then randomly reallocated to either the continuous positive airway pressure or non-invasive ventilation groups,[3] potentially leading to increased hospital resource utilisation and cardiovascular events. We therefore excluded the first 2 months (events and time) from our analysis of long-term outcomes. Finally, we did not use transcutaneous CO_2 as a direct measure of hypoventilation during polysomnographic positive airway pressure titration, although we increased the inspiratory positive airway pressure during non-invasive ventilation titration to achieve the best oxygenation level as a surrogate marker of hypoventilation.[3]

In conclusion, non-invasive ventilation and continuous positive airway pressure seem to have similar long-term effectiveness. Given that continuous positive airway pressure is cheaper than non-invasive ventilation, continuous positive airway pressure might be the preferable first-line treatment in stable patients with obesity hypoventilation syndrome and severe obstructive sleep apnoea, although a case-by-case follow-up assessment is recommended.

Contributors

All authors contributed to the study conception and design, acquisition of data, or analysis and interpretation of data. JFM, BM, IB, FJGdT, MÁS-Q, AR, CC-E, JT-S, MLA-Á, MFT, MG, SL-M, JMM, SM, TD-C, EC, CE, F-JV-P, MAN, MM-E, FB, and JC drafted the manuscript or revised the manuscript critically for important intellectual content. JFM, BM, IB, F-JV-P, MAN, and JC proofread the version to be published.

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Declaration of interests

We declare no competing interests.

Data sharing

Additional related documents such as study protocol, statistical analysis plan, and informed consent form will be available upon request from the Pickwick Project principal investigator (Juan Fernando Masa). Deidentified patients' data can be requested by researchers for use in independent scientific research and will be provided following review and approval of the research proposal (including statistical analysis plan) and completion of a data sharing agreement with the Pickwick Project Publications Committee. Investigator Data requests can be made anytime from 1 to 2 years after the publication of this trial. Requests should be sent to the corresponding author (fmasa@separ.es).

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