SUPPLEMENTARY APENDIX

Title: Effectiveness of CPAP vs. Noninvasive Ventilation Based on Disease Severity in Obesity Hypoventilation Syndrome and Concomitant Severe Obstructive Sleep Apnea

Subtitle: The Pickwick Randomized Clinical Trial

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ADDITIONAL METHODS

Project promotion, centers and internal organization

The project was initially promoted by the National Pulmonologist Society (SEPAR) through the Spanish Sleep Network and Spanish Noninvasive Ventilation Network. Both directing committees asked Dr. Juan F Masa to develop the project, to obtain grants, and to find centers with the following characteristics: 1) a complete sleep laboratory; 2) a home ventilation program; 3) at least three years of experience in the aforementioned areas; and 4) participation in at least one previous multicenter study promoted by the Spanish Sleep Network or Spanish Noninvasive Ventilation Network.

Successive versions of the protocol were discussed between the researchers in three consecutive official meetings of SEPAR and in continuous correspondence between researchers by email for 18 months. In 2008, the final version of the protocol and funding were available. The coordinator center in Cáceres, Spain developed the following necessary tools to conduct a multicenter study: 1) a book collection; 2) electronic databases hosted on a website with a specific domain; 3) a notebook containing the project procedures (explained step-by-step) and the necessary questionnaires to standardize the work among centers; and 4) an external audit every three months to compare the operating variables between groups (dropouts due to medical causes and mortality) on which the continuity of the study depends. In 2009, the patient inclusion process was initiated, and one meeting was conducted with the researchers after the inclusion of the first five patients to make minor changes in the protocol if necessary.

The following actions were established a priori: 1) the preparation of monthly newsletters from the principal investigator to other researchers to report on the

comparative inclusion results between centers, encourage participant inclusion, and promptly communicate eventualities; 2) the establishment of an investigator meeting within the two annual official SEPAR meetings; and 3) policy publications with a forecast of the number of publications and authorship based on the number of patients included.

“Pickwick” project and present analysis

The present paper reports the results of the “Pickwick” study, which was designed to understand the mid- and long-term efficacy of CPAP and NIV in obesity hypoventilation syndrome (OHS) and includes two parallel studies (see Figure E1). Patients with OHS and severe obstructive sleep apnea (OSA) were randomized to continuous positive airway pressure (CPAP), noninvasive ventilation (NIV), or control group for two months of follow-up (first phase). Subsequently, for ethical reasons, patients included in the control group were re-randomized into CPAP and NIV groups to complete a follow-up of 36 months (second phase). Patients with OHS but without severe OSA (i.e. not clear candidates for CPAP treatment given the lack of severe OSA) were directly randomized to the NIV or control groups and followed for 36 months. The primary outcome for the first phase of the trial (i.e. 2 months) was $PaCO_2$, during wakefulness and the primary outcome for the second phase was days of hospitalization, with two independent sample size calculations performed. The present analysis corresponds to the second phase of the randomized clinical trial of patients with OHS with severe OSA to value CPAP and NIV effectiveness through severity groups.

CPAP/NIV treatment tolerance tests and explanation of treatments

Before randomization, we performed CPAP[1] and NIV tolerance tests. With the patient seated, we adjusted the ventilator in CPAP mode with a pressure of 7 cm H_2O for 15 minutes. Subsequently, the ventilator was switched to bi-level PAP mode during spontaneous breathing, with the expiratory pressure kept at 7 cm H_2O and the inspiratory positive airway pressure (IPAP) set at 16 cm H_2O for another 15 minutes. Patients who were unable to adapt, according to the investigator, were excluded.

Once randomized, we spent the necessary time with the patient to prioritize adaptation to treatment and explain the following to the patients: 1) the characteristics of their disease; treating their disease with NIV, CPAP, or lifestyle modifications (depending on the randomization treatment); and the importance of appropriate follow-up; 2) how lifestyle modifications or NIV/CPAP devices work and the features of the mask and headgears; and 3) the potential short- and long-term benefits of the treatments and the associated consequences in daily life.

The lifestyle modification consisted of the following recommendations: a 1,000-calorie diet and maintenance of adequate sleep hygiene and lifestyle habits such as avoiding supine sleep position, maintaining regular sleep habits and exercise, not consuming sedatives, stimulants, or alcohol, avoiding tobacco smoking, and avoidance of heavy meals within four hours before bedtime. Oxygen therapy was added if baseline daytime or nocturnal hypoxemia was detected.[2]

During follow-up oxygen therapy could be discontinued if daytime or nocturnal hypoxemia improved sufficiently based on the investigators' assessment.

CPAP titration

The initial CPAP was set at 4 cm H_2O. When obstructive events appeared, the pressure was increased 1 cm H_2O every 5 minutes until obstructive apneas resolved. Subsequently, the CPAP was increased every 10 minutes to achieve the elimination of hypopneas, thoracoabdominal paradoxical movement, flow limitation, and snoring. Once the respiratory events had disappeared, CPAP was checked during the REM period and in the supine position, and the pressure was increased if respiratory events recurred. After a period without events and with normal sleep architecture, CPAP was slowly reduced by 1 cm H_2O until the same events reappeared. Subsequently, CPAP was augmented until obstructive events were resolved and normal sleep architecture reappeared. At this point, the pressure was maintained or slightly increased, if necessary, until the end of the polysomnographic study. Oxygen therapy was added if nocturnal hypoxemia during CPAP titration was detected.[2] A priori, nasal masks were proposed, but in cases of significant oral leakage, oronasal masks could be used. A humidifier was always added with an oronasal mask and only if necessary, with a nasal mask.

NIV adjustment

While the patient was awake, the expiratory positive airway pressure (EPAP) was set between 4 and 8 cm H_2O, and the inspiratory positive airway pressure (IPAP) was set between 18 and 22 cm H_2O (EPAP included). The pressures were adjusted to obtain normal oxygen saturation, if possible, as measured by pulse oximetry and patient tolerance. The respiratory rate was adjusted to 12-15 breaths/minute (close to the spontaneous respiratory rate, if possible), and the target volume was set at between 5 and 6 ml/kg of actual weight, allowing for an increase in the maximum pressure over the previously fixed IPAP, if necessary. A check of mechanical ventilation phases (trigger, pressurization, and ending) was also performed to avoid asynchronies and to

refine the setting. After 30 minutes of continuous use, with patient adaptation and an adequate patient-ventilator interaction, arterial blood gases (ABG) were measured. The level of $PaCO_2$ from this ABG was used to further adjust the ventilator parameters. The final adjustment was performed by means of conventional polysomnography (PSG), with the EPAP increased for obstructive apneas and IPAP increased for hypopneas, flow limitation, snoring, or non-apneic hypoventilation, until oxygen saturation normalized or the optimal pressure was reached. No changes were made in the assured volume during nocturnal titration. Oxygen therapy was added if nocturnal hypoxemia was detected during NIV titration.[2]

The ventilators used across the centers were as follows: Breas Vivo 40 (General Electric, England), BiPAP AVAPS (Philips-Respironics, Netherlands), Trilogy 100 (Philips-Respironics, Netherlands), VS Ultra (ResMed, Australia), Monal T50 (Air Liquide, France), and Puritan Bennett 560 (Puritan Bennett, USA). Oronasal masks were initially proposed, but for those who tolerated oronasal masks poorly, a nasal mask could be used. A humidifier was always added with an oronasal mask and only if necessary with a nasal mask.

Measurement of arterial blood gases

ABG was measured following standard procedures[3]. All tests were performed after at least 10 min of rest, at approximately 12 p.m., with the patient seated comfortably and breathing room air for at least during 20 minutes (except when the test was performed for NIV or oxygen titrations). The sample was analyzed immediately.

Masking strategy

The study was open label and both the investigators and the patients were aware of the treatment allocation. An investigator at each center was in charge of patient selection, randomization and follow up (visit data collection), to encourage treatment adherence, and to make adjustments to supplemental oxygen therapy or PAP settings and masks, if necessary. The investigators were not responsible or involved in other aspects of clinical care or clinical decisions related to hospitalization, duration of hospitalization, visits to the emergency department, admission or transfer to the intensive care unit (ICU), classifying cardiovascular events or any adjustment to medications. Clinicians and specialists involved in routine patient care (i.e., cardiologists) were not informed of the existence of this trial and there was no mention in the electronic health system database about it. Therefore, specialists who were responsible for establishing the presence of new cardiovascular events, hospital admission, duration of hospitalization, intensive care unit (ICU) admission, changes in pharmacological treatments were unaware of the study protocol. Patients received information to contact the research team if any clinician or specialist recommended a change in their NIV or CPAP. In these cases, the research team contacted the clinical team to ensure they agree with continuing PAP treatment from there on.

Additional follow-up information for the entire OHS with severe OSA trial

Patients were evaluated on at least 12 occasions: at baseline, at first month, at second month, and every 3 months after that until completing 2 years and then every 6 months until completing 3 years of follow-up. Evaluations at the first and second months were performed before the re-randomization of the control group to CPAP or NIV and therefore, they were not taken into account in this analysis. These results were previously published.[4] At every visit after baseline one, we assessed the primary

(hospitalization days), some of the secondary outcomes, dropouts and their causes (see below) and mortality. Information was obtained from records in the official database of the health system using the electronic medical record system. This information was collected by the research team independent of the clinicians and specialists treating the patient. The research team also collected information on events that occurred outside of the regional health system during patient face-to-face interview (or their families in case of death). We also assessed other outcomes such as other hospital resource utilization (i.e., emergency department visits, hospital and ICU admissions and duration of stay) obtained in the same way as hospitalization days. In every visit including the baseline one, we assessed $PaCO_2$, PaO_2 and bicarbonate by means of arterial blood gases (ABG) while breathing room air. In the first, second- and third-year visits, we collected the incidence of new systemic hypertension or anti-hypertensive treatment, atrial fibrillation, hospitalization for nonfatal myocardial infarction, unstable angina, nonfatal stroke, transient ischemic attack, for heart failure episode and cardiovascular death obtained in the same way as hospitalization days from electronic medical records; adherence to CPAP or NIV using an hourly counter; CPAP or NIV settings; and side effects. At baseline, first, second and third year visits blood pressure was measured by certified nurse using a sphygmomanometer according to international guidelines[5] (see below) and we also assessed anthropometric body measures, clinical symptoms (classified into four levels of intensity: morning confusion, headache, nocturia, tiredness, unrefreshing sleep and lower extremity edema), dyspnea on the Medical Research Council scale,[6] sleepiness on the Epworth Sleepiness Scale (ESS), health-related quality-of-life (HRQL) tests using the Functional Outcomes of Sleep Questionnaire (FOSQ), the Medical Outcome Survey Short Form 36 (SF 36), and the Visual Analogue Well-being Scale (VAWS);[1,7] spirometry;[8] the six-minute walk distance (6-MWD) test, following

standard recommendations[9]. In all visits, we emphasized and encouraged treatment adherence.

Blood pressure was measured while the patient was seated at least for 5 minutes in a quiet atmosphere, with the right arm resting on a standard support. A properly sized cuff was positioned on the arm with the lower edge of the cuff 2 cm above the antecubital fosse. First, the cuff was inflated to 30 mm Hg above the palpated systolic pressure. Then, blood pressure was registered three times, with a pause of at least 30 seconds between measurements. The first and last Korotkoff sounds determined the systolic and diastolic blood pressure, respectively. The average of the measurements was used for the analysis.

Dropouts were defined as patients who decided to leave the study voluntarily or for one of the following medical reasons: 1) pH <7.33 in any evaluation during the follow-up; 2) hospital admission requiring NIV treatment for more than five days, conventional invasive mechanical ventilation for more than three days, or pH <7.33 while breathing room air upon hospital discharge; or 3) death. Survivors who maintained the informed consent were followed every three months to complete the three years of follow-up to obtain healthcare resource utilization, incident cardiovascular events, treatment used as lifestyle modification, oxygen therapy, CPAP or NIV and their adherence. After completing the three years of follow-up, patients were followed every 3 months until the last patient included attained at least 3 years of follow-up (October 2016) in order to collect hospital resource utilization, abandons of treatments and mortality. In patients who abandoned the study but maintained the inform consent, the mentioned variables were collected in the same way as during the 3 years of the study follow-up, although the patient interview could be done face-to-face or by phone.

During the study an authorized external committee had access to the periodic analysis (each 3 months) of number of dropouts for medical reasons and mortality. The committee compared results in the different groups to interrupt the study if one of the treatments was significantly worse.

Sample size estimations in Pickwick study

Sample size estimation for PaCO2 comparison used in the first phase

The sample size was calculated based on a previous study in which the mean PaCO2 in patients with OHS treated with NIV was 45.65 mm Hg.[7] We estimated the sample size required to detect average differences of 2.5 mm Hg between groups by comparison of two independent samples. For an SD of 5 and power of 0.8, with a two-sided significance level of 0.05, the estimated sample size was 64 patients per group.

Sample size estimation for hospital days/patient-year comparison used in the second phase

Sample size was calculated to detect differences in the primary outcome variable, assuming an alpha error of 0.05 and a beta error of 0.2. At the time of study design, the mean hospital stays in patients receiving chronic NIV was 2.5±1.1 days/patient-year.[6] We estimated that an intergroup mean difference of ≥0.5 (SD 1.1) days/patient-year (20% difference) could be clinically relevant. We estimated a sample size of at least 77 patients in each group.

Polysomnography measurements and event definitions

We performed polysomnography (PSG) at baseline, for titration and after two months of treatment with NIV and CPAP. The two last PSGs were performed with the patient using their home NIV or CPAP settings. Oxygen treatment was not applied during any of the PSGs. We used the American Academy of Sleep Medicine's[9] rule regarding

configuration, filters and sample signal rates. The neurological variables were measured using electroencephalogram, electrooculogram, and electromyogram (on the chin and both legs). Flow tracing was provided using a nasal pressure transducer cannula and an oronasal thermistor during baseline PSG without PAP treatments. For PSGs performed on PAP therapy, we used the internal flow signals of the CPAP or NIV devices. Thoracoabdominal motion was measured by piezoelectric or inductance bands. Oxygen saturation was measured with a pulse oximeter (average signaling time among centers varied from 2-4 seconds). An electrocardiogram and body position sensor was also obtained. The PSG studies were analyzed manually at each participating center according to the 2007 recommendations of the AASM[9] and the respiratory scoring according to the Spanish Sleep Network rule.[10]

Apnea was defined as the absence of airflow (≥90% reduction) for ≥10 seconds, and hypopnea was defined as a discernible airflow or band reduction (≥30% and <90%) for at least 10 seconds with a ≥3% drop in oxygen saturation or final arousal.[10]

A valid PSG recording required at least three hours of sleep time. In cases of an invalid recording, the test was repeated one additional time.

Data management, statistical analyses were performed using EXCEL 2010 (Microsoft Redmond, WA, USA), SPSS software (IBM SPSS Statistics, Version 22.0. Armonk, NY, USA) and STATA 12 (StataCorp, College Station, TX, USA).

ADDITONAL RESULTS

See Tables and Figures pages 21-33

ADDITONAL DISCUSSION

The Pickwick study was designed as two randomized clinical trials in parallel according to the presence or not of concomitant severe OSA. In the OHS trial including severe OSA, the control group was re-randomized to NIV or CPAP after two months of follow-up due to ethical reasons. In the clinical trial of OHS without concomitant severe OSA, patients were randomized to NIV or control for 3 years. The objective of this design was to avoid long-term CPAP treatment in patients with no OSA or mild to moderate OSA given that CPAP, conceptually, is not a treatment for nocturnal hypoventilation that is not a result of obstructive events.[11-13] In OHS patients without severe OSA, 2 months of treatment with NIV resulted in medium-term improvement in clinical symptoms, functional respiratory and polysomnographic parameters in comparison with the control group.[14] Given that there are no clinical trials of CPAP that have focused on patients with OHS who do not have severe OSA, we considered inappropriate to include OHS patients with no OSA or mild to moderate OSA in the long-term clinical trial that would randomize patients to either CPAP or NIV.

In clinical practice supplemental oxygen is frequently added to NIV or CPAP treatment in order to improve residual hypoxemia during sleep or during wakefulness (i.e. daytime oxygen use). However, it remains unclear whether long-term oxygen supplementation is beneficial or deleterious in patients with OHS.[2] Some studies have reported an increase in daytime PCO_2[15-18]or nocturnal transcutaneous PCO_2[18] in stable OHS patients treated with high concentration of oxygen (100% or 50% fraction of inspired oxygen), although low concentrations did not change the pH.[17] In the present study, the requirement for supplemental oxygen therapy was similar between CPAP and NIV in the four severity subgroups (high $PaCO_2$ and low $PaCO_2$,) (Tables E2).

In our exclusion criteria we incorporated other sleep disorders such as narcolepsy and restless legs syndrome because some symptoms such as daytime sleepiness may overlap with symptoms experienced in patients with OHS. Moreover, these conditions may have potentially interfered with PAP adherence. In addition, we excluded patients with severe chronic nasal obstruction due to the potential decrease in adherence and efficacy of PAP. Lastly, although we recognize that our spirometric criteria may have allowed the inclusion of some patients with mild COPD, we believe that this degree of mild obstructive defect on spirometry is less likely to be a significant contributor to the development of chronic respiratory failure and hypercapnia, particularly with an FEV_1 >70% of predicted. Moreover, the low prevalence of COPD (n=10 or 5%) should have minimally impacted our results.

There was a delay in registering our trial in the clinicaltrials.gov website. The reasons were mainly three: 1) challenges in dealing with the clinicaltrials.gov website back in 2008 because the website was not as intuitive as it is nowadays and did not have any sort of bookmarks that would allow us to easily see how the trial registration was being processed by the website; 2) difficulties with including two parallel randomised controlled trials that had two phases (medium-term and long-term) with two main outcomes (one primary outcome for each phase of the trial), two sample size calculations and many outcomes in the 2008 version of the clinicaltrials.gov website; and 3) our own inexperience using the 2008 website. Although we started the process of registering our clinical trial on the clinicaltrials.gov website on July 3, 2008 and responded to all the questions on the website until there were no additional red queries (requiring mandatory response), the first official posting did not occur until July 29, 2011.

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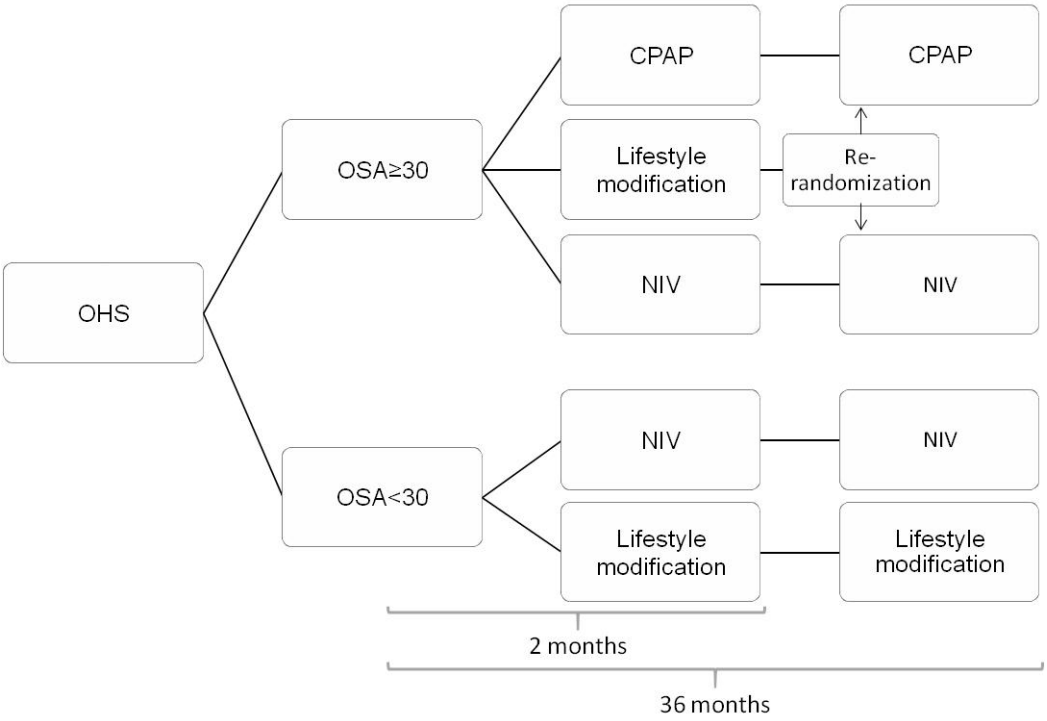
19. Figure E1: Flowchart of the Pickwick study



Abbreviations: OHS = obesity hypoventilation syndrome; OSA= obstructive sleep apnoea; NIV = noninvasive ventilation; and CPAP = continuous positive airway pressure.

1 ***Table E1:*** *Global characteristics of the population**

	Entire Cohort N=204
Age, years	62.0 [51.8;71.0]
Sex, male	89 (43.6%)
Smokers	51 (25.0%)
Smoking, pack/year†	30.0 [15.0;41.4]
Drinkers‡	39 (19.1%)
Alcohol, gr†	30.0 [16.0;45.0]
BMI, kg/m2	42.8 [38.2;48.2]
Neck circumference, cm	44.6 (4.63)
ESS¶	11.0 (5.08)
FOSQ	73.5 [58.0;91.0]
SF 36-Physical	36.1 [28.4;44.9]
SF 36-Mental	45.5 [32.1;53.1]
Dyspnea MRC scale ≥ 2	119 (58.3%)
Hypertension	140 (68.6%)
Diabetes	76 (37.3%)
Dyslipidemia	90 (44.1%)
Ischemic heart disease	18 (8.87%)
Heart failure	30 (14.7%)
Stroke	16 (7.84%)
Arrythmia	17 (8.33%)
Leg arteriopathy	10 (4.90%)
Pulmonary hypertension	17 (8.37%)
pH	7.40 [7.38;7.42]
PaO2, mmHg	60.8 [56.0;67.0]
PaCO2, mmHg	49.8 [47.2;52.9]
Bicarbonate, mmol/l	29.6 [27.9;31.8]
FEV1 in % of predicted	77.0 [66.0;89.0]
FVC, in % of predicted	80.0 [68.0;91.0]
6-MWD in meters	376 [267;450]
Polysomnographic parameters	
TST, hours	5.29 (1.30)
non-REM stage 1 and 2, %	85.2 [73.8;92.0]
non-REM stage 3, %	5.00 [0.00;14.0]
REM sleep %	7.70 [3.28;14.0]
Arousal index	56.5 [31.9;81.2]
AHI	68.4 [44.2;96.3]
ODI	70.8 [42.4;94.8]
Mean SpO2	85.0 [81.0;88.8]
TST with SpO2<90%, %	77.2 [51.0;94.8]

PAP adherence (>4h/day)	133 (65.2%)
Oxygen therapy	
Oxygen therapy flow, L/min†	50 (24.5%)

*= Data presented %, median (25;75 IQR) or mean (SD); † = Includes only patients who reported to be active smokers or drinkers or with oxygen therapy. ‡ = people who drink more than 30 g of alcohol/day in men and 20 g in women.

Abbreviations: SD = standard deviation; IQR = interquartile range; BMI = body mass index; EES = Epworth sleepiness scale; MRC = Medical Research Council; FEV1 = forced expiratory volume in the first second; FVC = forced vital capacity; 6-MWD = six-minute walk distance; TST = total sleep time; AHI = apnea-hypopnea index; ODI = 3% oxygen desaturation index; and SpO2 = oxygen saturation by pulse oximetry.

Table E2. *Characteristics of patients treated with NIV and CPAP based on baseline PaCO2 severity groups**

	Low $PaCO_2$			High $PaCO_2$		
	NIV	***CPAP***	***P overall***	***NIV***	***CPAP***	***P overall***
	N=44	***N=59***		***N=53***	***N=48***	
Age, years	63.5 [54.0;70.0]	60.0 [48.5;68.0]	0.116	66.0 [59.0;72.0]	61.0 [51.0;72.2]	0.401
Sex, male	20 (45.5%)	31 (52.5%)	0.608	16 (30.2%)	22 (45.8%)	0.157
Smokers	9 (20.5%)	21 (35.6%)	0.118	9 (17.0%)	12 (25.0%)	0.493
Smoking, pack/year†	30.0 [12.5;43.5]	23.8 [15.0;36.2]	0.868	30.0 [11.8;45.4]	40.0 [15.3;49.5]	0.764
Drinkers‡	14 (31.8%)	9 (15.3%)	0.078	8 (15.1%)	7 (14.6%)	1.000
Alcohol, gr†	30.0 [20.0;58.0]	26.0 [20.0;39.0]	0.611	15.5 [9.50;40.2]	30.0 [30.0;32.0]	0.464
BMI, kg/m2	41.9 [38.6;45.3]	41.5 [37.8;47.2]	0.831	43.9 (6.81)	44.8 (7.33)	0.494
Neck circumference, cm	45.0 [42.2;47.0]	45.0 [41.2;47.0]	0.942	44.2 (3.99)	45.3 (5.53)	0.302
ESS¶	11.0 [8.50;14.0]	11.0 [6.50;14.0]	0.302	11.1 (4.94)	10.9 (5.61)	0.792
FOSQ	84.5 [69.0;96.0]	77.0 [60.2;90.8]	0.172	69.3 (20.1)	69.7 (22.3)	0.925
SF 36-Physical	39.4 [30.7;46.1]	38.1 [28.9;45.8]	0.845	33.0 [27.4;44.3]	32.7 [28.5;40.2]	0.885
SF 36-Mental	44.5 [31.3;53.3]	45.7 [30.1;52.4]	0.829	43.2 (12.5)	44.9 (12.2)	0.494
Dyspnea MRC scale ≥ 2	26 (59.1%)	29 (49.2%)	0.423	35 (66.0%)	29 (60.4%)	0.705
Hypertension	25 (56.8%)	38 (64.4%)	0.564	44 (83.0%)	33 (68.8%)	0.147
Diabetes	16 (36.4%)	23 (39.0%)	0.948	24 (45.3%)	13 (27.1%)	0.091
Dyslipidemia	18 (40.9%)	22 (37.3%)	0.866	29 (54.7%)	21 (43.8%)	0.367
Ischemic heart disease	4 (9.30%)	5 (8.47%)	1.000	4 (7.55%)	5 (10.4%)	0.733
Heart failure	8 (18.2%)	8 (13.6%)	0.715	9 (17.0%)	5 (10.4%)	0.506
Stroke	4 (9.09%)	5 (8.47%)	1.000	2 (3.77%)	5 (10.4%)	0.252
Arrythmia	7 (15.9%)	3 (5.08%)	0.094	4 (7.55%)	3 (6.25%)	1.000
Leg arteriopathy	4 (9.09%)	4 (6.78%)		1 (1.89%)	1 (2.08%)	1.000
Pulmonary hypertension	4 (9.30%)	5 (8.47%)	1.000	4 (7.55%)	4 (8.33%)	1.000
pH	7.40 [7.39;7.42]	7.42 [7.38;7.43]	0.639	7.40 (0.03)	7.40 (0.04)	0.998
PaO_2, mmHg	62.2 [58.0;69.0]	64.0 [56.9;71.0]	0.636	60.0 (8.50)	58.1 (8.11)	0.241

$PaCO_2$, mmHg	47.0 [46.0;48.0]	47.3 [46.8;48.7]	0.322	53.0 [51.0;55.0]	52.0 [51.0;56.2]	0.609
Bicarbonate, mmol/l	27.9 [26.8;30.0]	28.9 [27.0;30.8]	0.205	30.6 [29.0;32.0]	30.4 [28.2;34.1]	0.920
FEV_1 in % of predicted	81.0 [71.5;91.0]	82.0 [71.0;92.5]	0.623	74.0 [63.0;87.0]	70.5 [61.0;84.0]	0.686
FVC, in % of predicted	80.0 [70.5;90.0]	87.0 [75.0;96.0]	0.142	74.2 (20.4)	76.8 (19.1)	0.502
6-MWD in meters	398 [334;480]	366 [296;464]	0.455	340 [240;426]	380 [256;436]	0.414
Polysomnographic parameters						
TST, hours	5.30 [4.38;6.04]	5.40 [4.25;6.50]	0.774	5.19 (1.35)	5.42 (1.24)	0.392
non-REM stage 1 and 2, %	85.3 [77.9;90.9]	85.9 [74.6;91.5]	0.918	86.2 [72.0;92.2]	81.8 [75.8;90.8]	0.628
non-REM stage 3, %	5.00 [0.00;10.1]	6.40 [0.60;11.6]	0.473	2.80 [0.00;16.3]	5.75 [1.15;15.2]	0.418
REM sleep %	8.80 [2.37;14.4]	6.95 [2.55;13.8]	0.749	9.70 [4.10;13.5]	7.25 [4.65;14.0]	0.922
Arousal index	52.0 [34.6;74.3]	53.5 [29.8;71.7]	0.636	56.4 (31.0)	64.7 (33.2)	0.202
AHI	68.0 [48.8;89.9]	68.3 [43.1;97.0]	0.631	76.6 [46.5;97.5]	64.4 [41.6;90.2]	0.300
ODI	69.0 [53.4;85.0]	72.0 [36.0;95.9]	0.682	66.5 [41.4;94.3]	78.4 [50.4;98.2]	0.397
Mean SpO_2	85.0 [83.0;89.0]	87.7 [83.2;90.0]	0.240	84.0 [81.0;87.0]	84.0 [77.0;87.8]	0.793
TST with SpO_2<90%, %	76.0 [45.5;95.0]	62.5 [45.1;91.4]	0.355	79.2 [54.0;96.4]	89.0 [62.0;96.8]	0.468
PAP adherence (>4h/day)	28 (63.6%)	37 (62.7%)	1.000	33 (62.3%)	35 (72.9%)	0.354
Oxygen therapy	7 (15.9%)	13 (22.0%)	0.599	14 (26.4%)	16 (33.3%)	0.588
Oxygen therapy flow, L/min†	2.00 [2.00;3.50]	1.50 [1.00;2.00]	0.128	1.75 [1.12;2.00]	1.75 [1.38;2.00]	0.761

**= Data presented %, median (25;75 IQR) or mean (SD); † = Includes only patients who reported to be active smokers or drinkers or with oxygen therapy. ‡ = people who drink more than 30 g of alcohol/day in men and 20 g in women.*

Abbreviations: SD = standard deviation; IQR = interquartile range; BMI = body mass index; EES = Epworth sleepiness scale; MRC = Medical Research Council; FEV1 = forced expiratory volume in the first second; FVC = forced vital capacity; 6-MWD = six-minute walk distance; TST = total sleep time; AHI = apnea-hypopnea index; ODI = 3% oxygen desaturation index; and SpO2 = oxygen saturation by pulse oximetry.

Table E3: Adjusted values of ABG parameters from linear mixed-effects model during the follow-up related to intervention treatment group in high PaCO2 subgroup*.

		NIV			*CPAP*			*NIV– CPAP differences*			
	Participants (NIV-CPAP)	***Mean***	***Lower 95% CI***	***Upper 95% CI***	***Mean***	***Lower 95% CI***	***Upper 95% CI***	***Mean***	***Lower 95% CI***	***Upper 95% CI***	***p value***
$PaCO_2$, mmHg											
Baseline	101 (53-48)	53.93	52.15	55.71	54.07	52.34	55.81	-0.14	-2.45	2.17	0.9050
6 months	91 (49-42)	45.35	43.52	47.17	47.71	45.88	49.55	-2.37	-4.79	0.05	0.0549
9 months	88 (47-41)	45.14	43.30	46.98	45.61	43.76	47.46	0.48	-2.00	2.95	0.7052
12 months	89 (48-41)	43.85	42.02	45.68	44.73	42.88	46.58	-0.88	-3.32	1.56	0.4779
15 months	88 (47-41)	44.21	42.37	46.05	44.84	42.99	46.69	-0.63	-3.07	1.81	0.6122
18 months	88 (47-41)	43.87	42.03	45.71	45.43	43.58	47.28	-1.55	-4.00	0.89	0.2119
21 months	88 (47-41)	43.54	41.70	45.38	44.74	42.89	46.59	-1.20	-3.64	1.25	0.3356
24 months	86 (47-39)	43.36	41.52	45.20	44.66	42.79	46.54	-1.30	-3.77	1.17	0.3006
30 months	85 (47-38)	44.39	42.55	46.23	46.61	44.71	48.50	-2.22	-4.70	0.27	0.0798
36 months	82 (46-36)	44.31	42.45	46.16	45.26	43.33	47.19	-0.95	-3.47	1.57	0.4574
PO_2, mmHg											
Baseline	101 (53-48)	60.09	57.14	63.05	57.51	54.62	60.40	2.58	-1.28	6.44	0.1890
6 months	91 (49-42)	67.15	64.12	70.17	65.70	62.64	68.76	1.45	-2.60	5.50	0.4818
9 months	88 (47-41)	67.17	64.15	70.20	66.57	63.50	69.63	-2.08	-6.20	2.03	0.3207
12 months	89 (48-41)	68.25	65.21	71.29	67.38	64.29	70.47	0.87	-3.21	4.95	0.6754
15 months	88 (47-41)	67.01	63.95	70.06	66.47	63.36	69.58	0.54	-3.58	4.65	0.7983
18 months	88 (47-41)	67.20	64.14	70.26	68.14	65.05	71.23	-0.94	-5.03	3.16	0.6530
21 months	88 (47-41)	68.43	65.37	71.49	67.21	64.12	70.30	1.22	-2.87	5.32	0.5579
24 months	86 (47-39)	69.08	66.02	72.14	69.26	66.11	72.40	-0.18	-4.32	3.96	0.9329
30 months	85 (47-38)	68.09	65.03	71.15	66.23	63.06	69.40	1.86	-2.31	6.03	0.3805
36 months	82 (46-36)	67.47	64.39	70.55	67.45	64.22	70.68	0.02	-4.21	4.25	0.9937

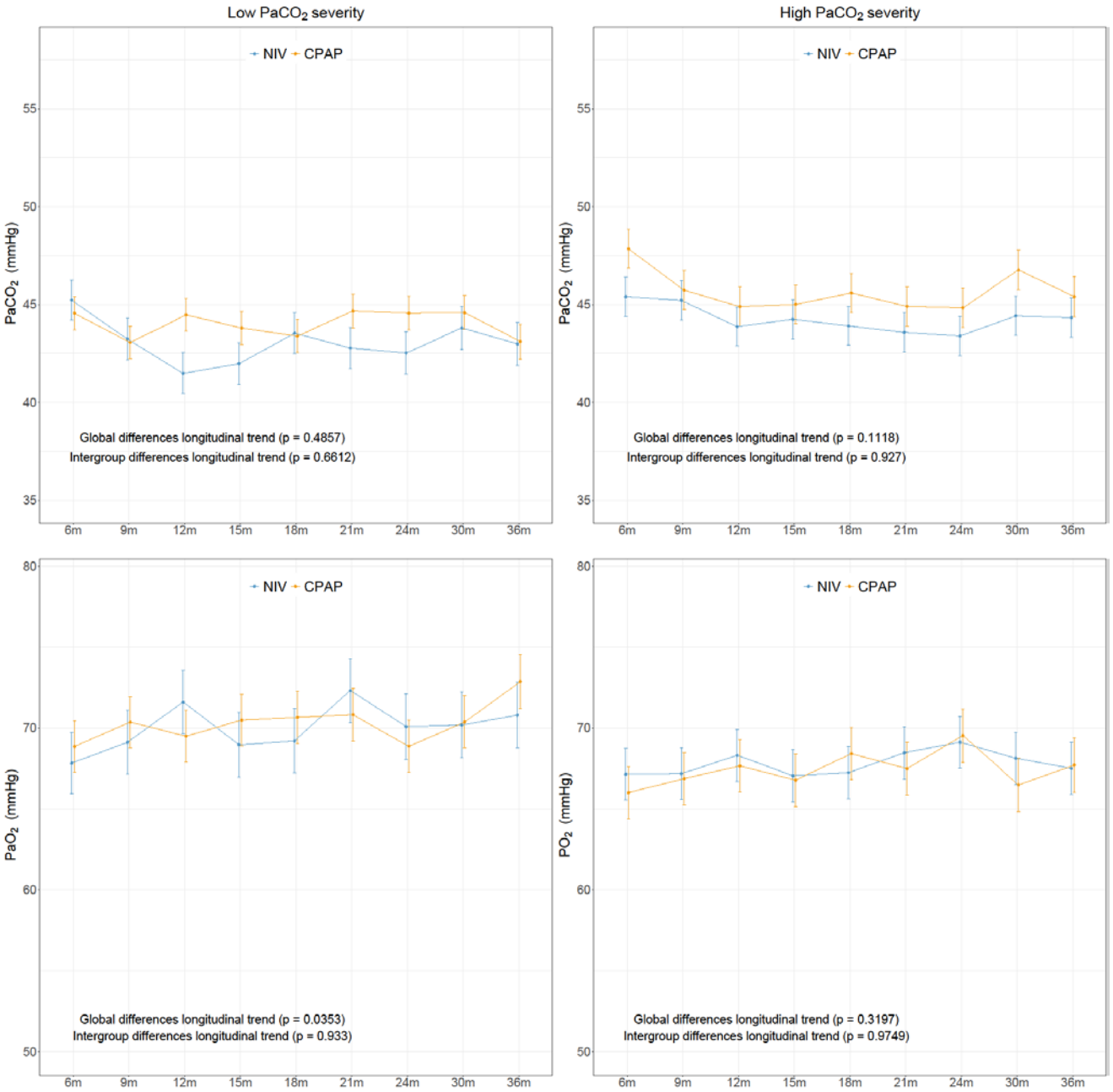
**= adjusted by age, sex smoking status, body mass index (BMI), and adherence. Abbreviations: NIV = noninvasive ventilation; CPAP = continuous positive airway pressure; ABG = arterial blood gases; and CI = confidence interval.*

Table E4: Adjusted values of ABG parameters from linear mixed-effects model during the follow-up related to intervention treatment group in low PaCO2 subgroups*.

		NIV			*CPAP*			*NIV– CPAP differences*			
	Participants (VNI-CPAP)	***Mean***	***Lower 95% CI***	***Upper 95% CI***	***Mean***	***Lower 95% CI***	***Upper 95% CI***	***Mean***	***Lower 95% CI***	***Upper 95% CI***	***p value***
$PaCO_2$, mmHg											
Baseline	103 (44-59)	47.28	45.57	48.99	47.62	46.16	49.08	-0.34	-2.54	1.86	0.7615
6 months	89 (37-52)	45.15	43.31	46.99	44.66	43.12	46.20	0.49	-1.86	2.85	0.6820
9 months	84 (32-52)	43.16	41.21	45.11	43.16	41.62	44.69	-1.46	-3.93	1.00	0.2446
12 months	86 (34-52)	41.40	39.49	43.30	44.55	43.01	46.09	-3.15	-5.56	-0.75	0.0104
15 months	85 (33-52)	41.89	39.97	43.82	43.88	42.34	45.41	-1.98	-4.41	0.44	0.1091
18 months	83 (33-50)	43.45	41.53	45.38	43.44	41.88	45.00	0.01	-2.43	2.46	0.9917
21 months	83 (33-50)	42.69	40.77	44.62	44.72	43.16	46.29	-2.03	-4.47	0.41	0.1032
24 months	80 (31-49)	42.44	40.46	44.41	44.62	43.05	46.20	-2.19	-4.68	0.30	0.0848
30 months	80 (31-49)	43.71	41.74	45.69	44.65	43.07	46.22	-0.93	-3.42	1.56	0.4615
36 months	76 (31-45)	42.90	40.92	44.87	43.16	41.53	44.79	-0.26	-2.79	2.26	0.8368
PO_2, mmHg											
Baseline	103 (44-59)	63.15	59.67	66.62	63.55	60.59	66.52	-0.41	-4.84	4.03	0.8564
6 months	89 (37-52)	67.39	63.68	71.10	68.59	65.47	71.71	-1.19	-5.93	3.54	0.6202
9 months	84 (32-52)	68.74	64.92	72.56	70.13	67.04	73.21	0.06	-4.80	4.91	0.9817
12 months	86 (34-52)	71.23	67.41	75.05	69.28	66.18	72.38	1.95	-2.86	6.76	0.4261
15 months	85 (33-52)	68.53	64.63	72.43	70.27	67.16	73.37	-1.74	-6.61	3.14	0.4839
18 months	83 (33-50)	68.80	64.94	72.66	70.46	67.32	73.60	-1.66	-6.53	3.21	0.5027
21 months	83 (33-50)	71.90	68.04	75.76	70.62	67.41	73.83	1.28	-3.63	6.19	0.6080
24 months	80 (31-49)	69.70	65.77	73.64	68.68	65.52	71.85	1.02	-3.93	5.97	0.6856
30 months	80 (31-49)	69.81	65.87	73.74	70.19	67.03	73.35	-0.38	-5.33	4.56	0.8795
36 months	76 (31-45)	70.42	66.48	74.35	72.68	69.44	75.93	-2.27	-7.27	2.73	0.3733

*= *adjusted by age, sex smoking status, body mass index (BMI), and adherence. Abbreviations: NIV = noninvasive ventilation; CPAP = continuous positive airway pressure; ABG = arterial blood gases; and CI = confidence interval.*

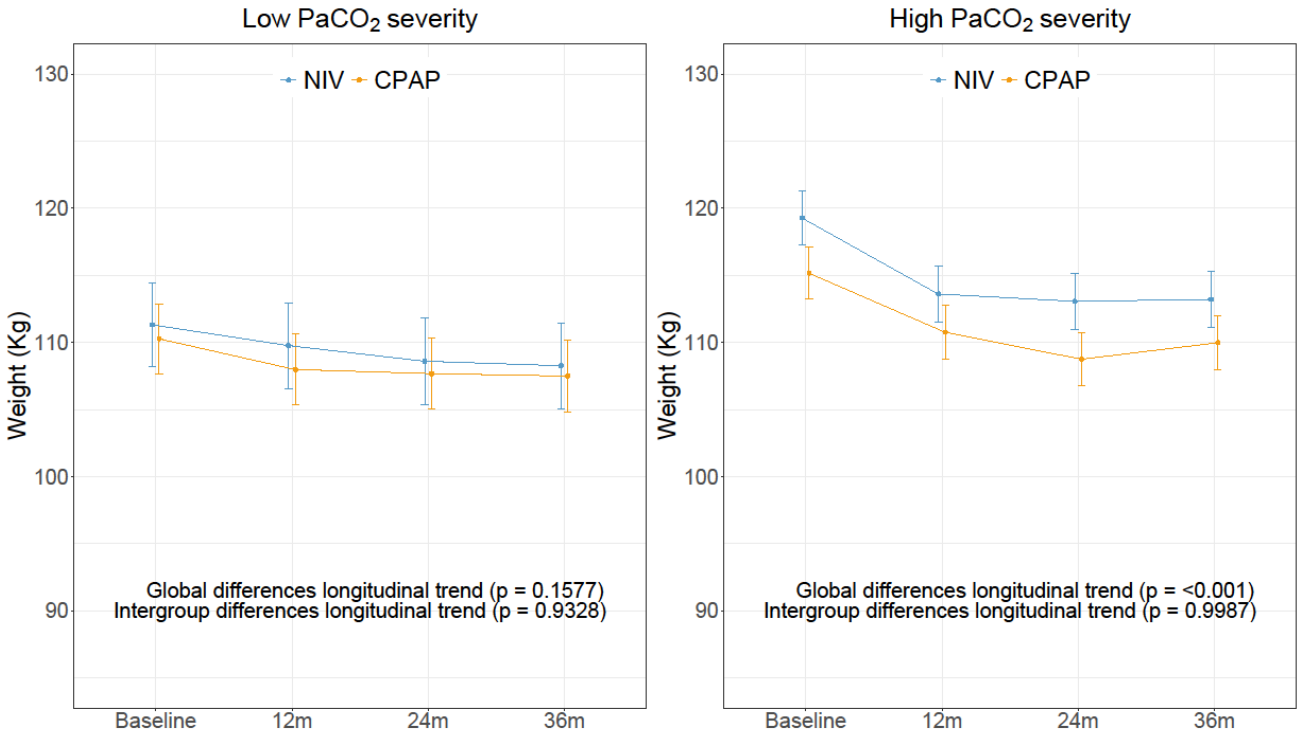
Figure E2. Adjusted longitudinal ABG changes by baseline values during the follow/up in the low and high PaCO2 severity subgroups



Adjusted for longitudinal ABG parameters (mean and SE) by baseline values from linear mixed-effects models during the follow-up related to intervention treatment groups in low and high $PaCO_2$ severity subgroups. P values correspond to adjusted (PaO_2, $PaCO_2$ at baseline) longitudinal changes for ABG and for the inter-group CPAP and NIV comparison.

Abbreviations: ABG = arterial blood gases; CPAP = continuous positive airway pressure; NIV = noninvasive ventilation; and SE = standard error.

Figure E3: Adjusted longitudinal weight changes during the follow/up in the low and high PaCO2 severity subgroups



Adjusted longitudinal weight changes during the follow/up (mean and SE) from linear mixed/effects models related to intervention treatment groups in low and high $PaCO_2$ severity subgroups. P values correspond to adjusted (adjusted by age, sex smoking status, body mass index (BMI) at baseline, and adherence) longitudinal changes for weight and for the inter/group for CPAP and NIV comparison. Abbreviations: CPAP = continuous positive airway pressure; NIV = noninvasive ventilation; and SE = standard error.

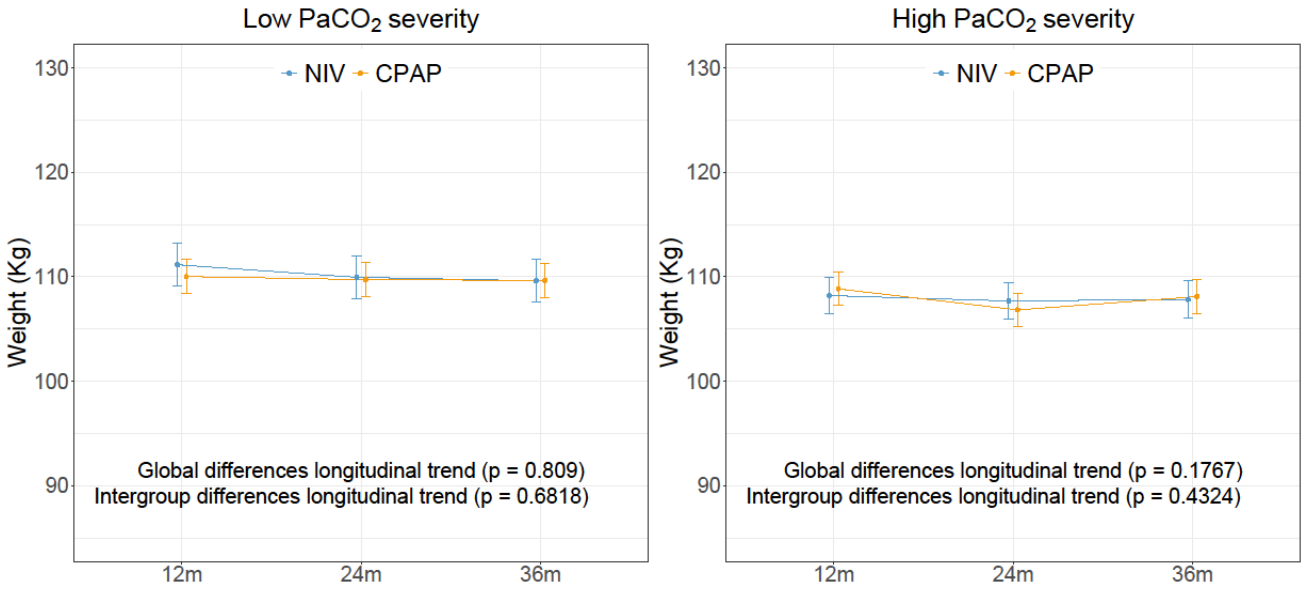
Table E5: Adjusted values of weight from linear mixed/effects models during the follow/up related to intervention treatment groups in $PaCO_2$ and AHI severity subgroups*.

		NIV			*CPAP*			*NIV– CPAP differences*			
	Participants (NIV-CPAP)	***Mean***	***Lower 95% CI***	***Upper 95% CI***	***Mean***	***Lower 95% CI***	***Upper 95% CI***	***Mean***	***Lower 95% CI***	***Upper 95% CI***	***p value***
Low $PaCO_2$											
Baseline	103 (44-59)	111.32	105.20	117.43	110.27	105.09	115.46	1.04	-6.58	8.66	0.7870
12 months	84 (32-51)	109.77	103.44	116.10	107.98	102.72	113.24	1.79	-6.08	9.66	0.6538
24 months	81 (31-49)	108.60	102.25	114.95	107.67	102.40	112.95	0.92	-6.98	8.83	0.8173
36 months	79 (31-47)	108.26	101.91	114.61	107.49	102.19	112.79	0.77	-7.14	8.69	0.8474
High $PaCO_2$											
Baseline	101 (53-48)	119.28	115.23	123.34	115.17	111.35	119.00	4.11	-0.85	9.07	0.1035
12 months	89 (47-42)	113.61	109.49	117.74	110.76	106.84	114.69	2.85	-2.26	7.96	0.2727
24 months	88 (46-42)	113.06	108.93	117.20	108.75	104.83	112.68	4.31	-0.81	9.43	0.0983
36 months	87 (46-41)	113.21	109.08	117.35	109.98	106.04	113.93	3.23	-1.90	8.36	0.2159

**= adjusted by age, sex smoking status, body mass index (BMI) at baseline, and adherence.*

Abbreviations: NIV = noninvasive ventilation; CPAP = continuous positive airway pressure; AHI = apnea and hypopnea index; and CI = confidence interval

Figure E4: Adjusted longitudinal weight changes by baseline values during the follow/up in the low and high $PaCO_2$ severity subgroups



Adjusted for longitudinal ABG parameters (mean and SE) by baseline values from linear mixed/effects models related to intervention treatment groups in low and high $PaCO_2$ severity subgroups. P values correspond to adjusted longitudinal changes for weight and for the inter/group for CPAP and NIV comparison. Abbreviations: CPAP = continuous positive airway pressure; NIV = noninvasive ventilation; and SE = standard error.

70 **Table E6**: Ethical committees from centers evolved in the study

CEICs	***City***	***Code***	***Date***	***Responsible researcher***
San Pedro de Alcantara hospital	Caceres	Pickwick/08	2008/03/25	JF Masa
Txagorritxu hospital	Vitoria	2008/005	2008/01/22	C Egea
Arnau de Vilanova hospital	Lleida	CEIC/646	2009/02/26	F Barbe
Lucus Agusti hospital	Lugo	Pickwick/08	2008/03/25	R Golpe
Doce de Octubre hospital	Madrid	07/277	2008/02/04	J Diaz de Atauri
General Yague hospital	Burgos	Pickwick/07	2007/12/20	ML Alonso
Marques de Valdecilla hospital	Santander	2009.44	2009/04/24	MR Carpizo
Gregorio Marañon hospital	Madrid	09/08	2008/02/27	S Lopez/Martin
La Paz hospital	Madrid	HULP/2642	2008/02/29	A Santiago
Jimenez Diaz Foundation	Madrid	04/08	2008/04/22	C Melchor
Virgen Macarena hospital	Sevilla	2008/52	2008/01/22	JM Benitez
Miguel Servet hospital	Zaragoza	2008/14	2008/10/10	JM Marin
Val de Hebron hospital	Barcelona	RTF/066	2009/05/06	S Marti
Virgen del Rocio hospital	Sevilla	Pickwick/CI	2008/04/29	A Romero
San Juan hospital	Alicante	HUSJ/08/3/10	2008/03/10	E Chiner
Las Palmas hospital	Las Palmas	CHMI/484	2010/11/26	M Bengoa

71 Abbreviations: CEIC= Clinical investigation ethical committee