[Sleep Original Research]

CHEST

Long-term Noninvasive Ventilation in Obesity Hypoventilation Syndrome Without Severe OSA

The Pickwick Randomized Controlled Trial

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BACKGROUND: Noninvasive ventilation (NIV) is an effective form of treatment in obesity hypoventilation syndrome (OHS) with severe OSA. However, there is paucity of evidence in patients with OHS without severe OSA phenotype.

RESEARCH QUESTION: Is NIV effective in OHS without severe OSA phenotype?

STUDY DESIGN AND METHODS: In this multicenter, open-label parallel group clinical trial performed at 16 sites in Spain, we randomly assigned 98 stable ambulatory patients with untreated OHS and apnea-hypopnea index $<$ 30 events/h (ie, no severe OSA) to NIV or lifestyle modification (control group) using simple randomization through an electronic database. The primary end point was hospitalization days per year. Secondary end points included other hospital resource utilization, incident cardiovascular events, mortality, respiratory functional tests, BP, quality of life, sleepiness, and other clinical symptoms. Both investigators and patients were aware of the treatment allocation; however, treating physicians from the routine care team were not aware of patients' enrollment in the clinical trial. The study was stopped early in its eighth year because of difficulty identifying patients with OHS without severe OSA. The analysis was performed according to intention-to-treat and per-protocol principles and by adherence subgroups.

RESULTS: Forty-nine patients in the NIV group and 49 in the control group were randomized, and 48 patients in each group were analyzed. During a median follow-up of 4.98 years (interquartile range, 2.98-6.62), the mean hospitalization days per year $\pm$ SD was 2.60 $\pm$ 5.31 in the control group and 2.71 $\pm$ 4.52 in the NIV group (adjusted rate ratio, 1.07; 95% CI, 0.44-2.59; $P = .882$). NIV therapy, in contrast with the control group, produced significant longitudinal improvement in $Paco_2$, pH, bicarbonate, quality of life (Medical Outcome Survey Short Form 36 physical component), and daytime sleepiness. Moreover, per-protocol

ABBREVIATIONS: 6MWD = 6-min walk distance; ESS = Epworth Sleepiness Scale; HCO_3^- = bicarbonate; IQR = interquartile range; NIV = noninvasive ventilation; OHS = obesity hypoventilation syndrome; PAP = positive airway pressure; SF-36 = Medical Outcome Survey Short Form 36

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analysis showed a statistically significant difference for the time until the first ED visit favoring NIV. In the subgroup with high NIV adherence, the time until the first event of hospital admission, ED visit, and mortality was longer than in the low adherence subgroup. Adverse events were similar between arms.

INTERPRETATION: In stable ambulatory patients with OHS without severe OSA, NIV and lifestyle modification had similar long-term hospitalization days per year. A more intensive program aimed at improving NIV adherence may lead to better outcomes. Larger studies are necessary to better determine the long-term benefit of NIV in this subgroup of OHS.

TRIAL REGISTRY: ClinicalTrials.gov; No.: NCT01405976; URL: www.clinicaltrials.gov

CHEST 2020; ■(■):■-■

KEY WORDS: CPAP; noninvasive ventilation; obesity hypoventilation syndrome; sleep apnea

Obesity hypoventilation syndrome (OHS) is defined by the presence of obesity, sleep-disordered breathing, and chronic hypercapnic respiratory failure in the absence of other diseases causing daytime hypoventilation.[1] Most patients with OHS have severe OSA, but nocturnal hypoventilation may be the only respiratory sleep disorder present.[2] Approximately 27% of patients with OHS do not have severe OSA.[3] Patients with untreated OHS are at increased risk of cardiovascular and respiratory morbidity, mortality, and health-care resource utilization compared with patients with eucapnic OSA[4,5] and patients with eucapnic obesity.[4-12]

Patients with OHS with predominant and nonpredominant OSA have different phenotypes. Those with OHS and coexistent severe OSA tend to be younger, are mostly men, are more obese, have higher levels of sleepiness, have worse gas exchange, have a lower prevalence of cardiovascular comorbidities, have better exercise tolerance, and have fewer days hospitalized than patients with OHS without severe OSA.[13]

OHS is typically treated with positive airway pressure (PAP) (CPAP or noninvasive ventilation [NIV]).[14,15] Conceptually, CPAP may not be an effective treatment for patients with OHS without significant OSA.[16] NIV, in the form of bilevel PAP, can treat both apneic and nonapneic nocturnal hypoventilation. CPAP and NIV have been shown to have similar medium-term[3,17,18] and long-term[19] outcomes in three randomized controlled trials of patients with OHS with severe OSA. In contrast, there has been only one medium-term randomized controlled trial comparing NIV with lifestyle changes in patients with OHS but without severe OSA.[20] In this medium-term study, NIV led to significant improvement in Paco2, sleepiness, and polysomnographic parameters compared with the control group at 2 months. There are no long-term randomized controlled trials in this less prevalent OHS phenotype.

We performed a multicenter trial to determine the long-term comparative effectiveness of NIV and lifestyle modification with at least 3 years of follow-up using hospitalization days per year as the primary outcome

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*Collaborators from the Spanish Sleep Network are listed in the Acknowledgments.

FUNDING/SUPPORT: This study was supported by the Instituto de Salud Carlos III (Fondo de Investigaciones Sanitarias, Ministerio de Sanidad y Consumo) [Grant PI050402], the Spanish Respiratory Foundation 2005 (FEPAR), and Air Liquide Spain.

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DOI: https://doi.org/10.1016/j.chest.2020.03.068

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measure. This study is the long-term outcomes from the second parallel randomized controlled trial of the Pickwick project that has generated several prior publications from the same cohort of patients.[3,13,19-22]

Methods

Trial Design

We carried out a multicenter, open-label randomized controlled trial with two parallel groups. The study was stopped after 8.4 years of follow-up (May 2009 to November 2017) with the agreement of the 16 clinical centers because of the prespecified criterion of absence of new patient enrollment in the last year.

Participants

From May 2009 to October 2016, we sequentially screened patients between 15 and 80 years of age who were referred for pulmonary consultations because of suspected OHS or OSA at 16 tertiary care hospitals in Spain (see online supplement). OHS was defined as obesity (BMI $\geq$ 30 kg/m^2), stable hypercapnic respiratory failure (Paco2 $\geq$ 45 mm Hg, pH $\geq$ 7.35, and no clinical exacerbation during the previous 2 months), no significant spirometric evidence of COPD (FEV_1 had to be > 70% predicted in cases where FEV_1/FVC was < 70% predicted), and no clinical evidence of neuromuscular, chest wall, or metabolic disease that could explain hypoventilation. Other inclusion criteria were the following: (1) nonsevere OSA (apnea-hypopnea index < 30 events/h), (2) an absence of narcolepsy or restless legs syndrome, and (3) a correctly executed 30-min NIV treatment test (see online supplement). The exclusion criteria were the following: (1) a psychological-physical inability to complete questionnaires, (2) severe chronic debilitating illness, (3) severe chronic nasal obstruction, and (4) a lack of informed consent.[19]

The Pickwick project was approved by the ethics committees of all 16 centers, and written informed consent was obtained from all patients (e-Table 13).

Interventions

Ambulatory patients with OHS without severe OSA were randomized by an investigator in each center, via a web-based electronic database (simple randomization without predetermined allocation rate) to NIV or the control group and followed for a minimum of 3 years.

Patients randomized to NIV were also instructed on lifestyle modification. Supplemental oxygen therapy was added if baseline daytime or nocturnal hypoxemia was detected during baseline polysomnography (control group) or titration polysomnography (NIV arm) (see online supplement).[23]

Control Group: The lifestyle modification consisted of a 1,000-calorie diet and the maintenance of correct sleep hygiene and habits (see online supplement).

NIV Adjustment and Titration: The NIV modality was volume targeted pressure support (see online supplement for adjustment).

Masking Strategy

The study was open-label, and both investigators and patients were aware of the treatment allocation. An investigator at each center was in charge of patient selection, randomization, and follow-up (data collection), to encourage treatment adherence and perform adjustments to supplemental oxygen therapy or NIV settings and masks, if necessary. The investigators were not involved in other aspects of clinical care or clinical decisions (see online supplement).

Outcomes

Patients were evaluated on at least 12 occasions over 3 years: at baseline, first and second months, every 3 months until completing 2 years, and then every 6 months until completing 3 years (e-Table 1). Polysomnography was only performed at baseline and 2 months. The polysomnographic results were previously published.[20]

Primary Outcome: Hospitalization days for any cause were assessed at every visit after the baseline visit. This outcome was obtained from the electronic medical records and during face-to-face interviews with patients (or relatives in case of death) (see online supplement).

Secondary Outcomes: At every visit after the baseline visit, we assessed mortality and its causes, dropouts and their causes, other hospital resource utilization such as hospitalization days including ED visits, and hospital admissions, obtained in the same fashion as hospitalization days. In the first, second, and third annual visits, we measured the incidence of new cardiovascular events (see online supplement) obtained in the same way as hospitalization days. At every encounter including the baseline visit, we obtained arterial blood gases on room air (see online supplement) to assess $Paco_2$, Pao_2, and pH, and calculated bicarbonate (HCO_3^-). At each annual visit including the baseline visit, we measured BP with a sphygmomanometer[24] (see online supplement), spirometry (FEV_1 and FVC),[25] 6-min walk distance (6MWD),[26] and health-related quality of life using the Functional Outcomes of Sleep Questionnaire and the Medical Outcome Survey Short Form 36 (SF-36).

Other Outcomes: At baseline and first, second, and third annual visits, we assessed anthropometric data, clinical symptoms such as lower extremity edema, unrefreshing sleep, tiredness, nocturia, headache, and morning confusion. These symptoms were classified into four levels of intensity (from 1 to 4). Dyspnea was classified using the Medical Research Council scale[27] and sleepiness was assessed on the Epworth Sleepiness Scale (ESS). During each annual visit, we measured adherence to NIV using internal device hourly counters, NIV settings, and adverse events.

After 3 years of follow-up, patients were followed every 3 months until the study was stopped to collect information on hospitalization days and other hospital resource utilization, discontinuation of NIV treatment, and mortality.

Statistical Analysis

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 stay in patients receiving chronic NIV was 2.5 $\pm$ 1.1 days per patient per year.[7] We estimated that an intergroup mean difference of $\geq$ 0.5 $\pm$ 1.1 days per patient per year (20% difference) could be clinically relevant. We estimated a sample size of at least 77 patients in each group.

To assess group differences for the primary outcome (hospitalization days per year per patient) and other hospital resource utilization (events per year per patient), a generalized linear mixed-effects model for the negative binomial family was used. A mixed-effects Cox model was used for new events of other hospital resource utilization, new cardiovascular events, and overall mortality. Other secondary outcomes such as repeated measures derived from the arterial blood gas parameters, spirometry, 6MWD, health-related quality of life tests, and BP during 3 years of follow-up were

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compared between treatments using a linear mixed-effects model (see online supplement).

For the primary outcome and other hospital resource utilization, incident cardiovascular events, and mortality, a prespecified per-protocol analysis was also carried out (see online supplement).

Prespecified ancillary analysis for weight and ESS evolution was assessed by a linear mixed-effects model. Adverse events during the 3 years of follow-up and abandons because of medical causes were compared between arms using the Fisher exact test. A logistic regression model was used for symptoms (score ≥ 3 for habitual and < 3 for not habitual) and dyspnea (score ≥ 2 for habitual and < 2 for not habitual) (see online supplement).

Exploratory post hoc analysis of subgroup assessment based on high and low NIV adherence (> 4 or ≤ 4 h/d, respectively)[19] was also completed to assess hospital resource utilization, incident cardiovascular events, mortality, and prevalence of supplemental oxygen therapy (see online supplement).

Results

Study Participants

Of the 375 patients who met the initial inclusion criteria, 277 were excluded (221 had severe OSA with an apnea-hypopnea index ≥ 30 events/h). Of the 98 remaining patients, 49 were allocated to the NIV group and 49 to the control group (Fig 1). For the primary analysis, 96 patients were available, 48 in the NIV group and 48 in the control (lifestyle modification) group. In the NIV group, 24 patients abandoned NIV therapy and changed to the lifestyle modification group, and in all 24 cases this was because of the patients' decision to abandon NIV therapy. In the control group, 12 patients were started on NIV (two because of medical causes, one because of the patient's decision, and nine based on the

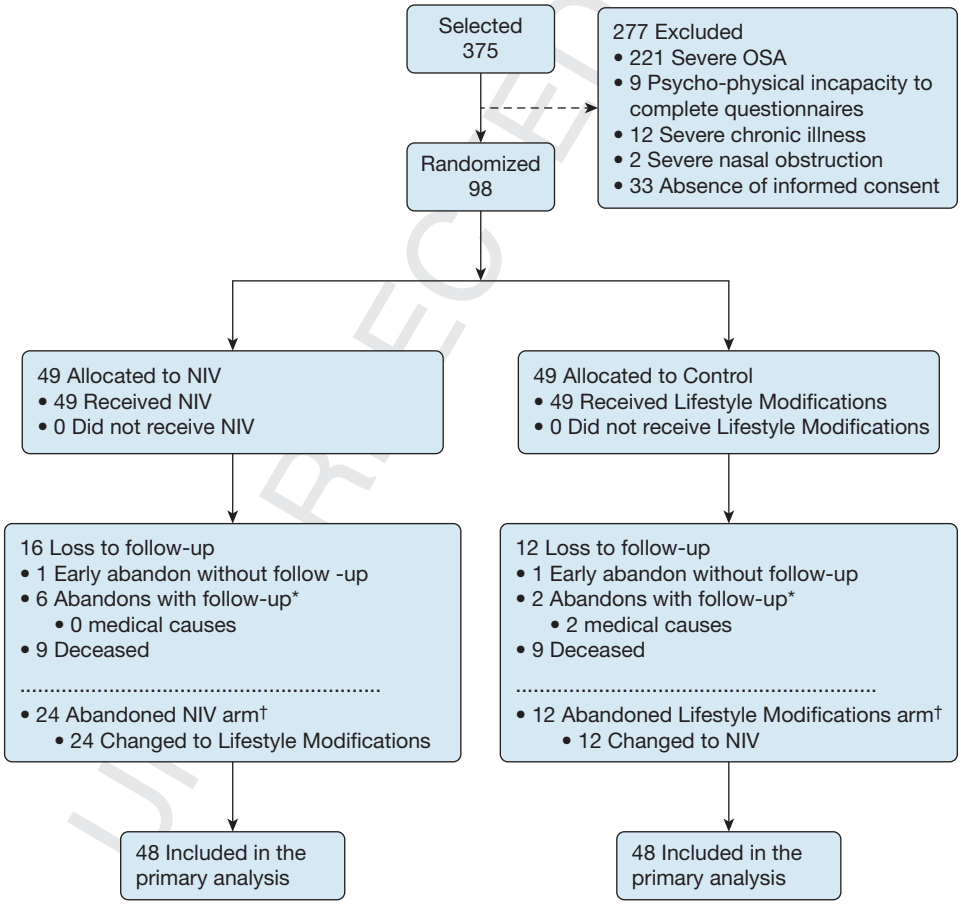

Figure 1 – *Flowchart of the study protocol. Of 375 selected patients, 277 were excluded and 98 were randomized to either NIV (n = 49) or lifestyle modification as the control group (n = 49). From the 49 patients included in the NIV arm, one abandoned the study early without follow-up and the rest (n = 48) were available for the primary analysis. From the 49 patients included in the control arm, one abandoned the study early without follow-up and the rest (n = 48) were available for the primary analysis. *Participants who at some point were lost to follow-up but did not withdraw informed consent, were followed to the end of the study to obtain data on hospital resource utilization (including the primary outcome of hospitalization days), treatment type, and mortality. †Patients who changed treatment after randomization (ie, from control group to NIV group, vice versa). NIV = noninvasive ventilation.*

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TABLE 1] Baseline Characteristics

Characteristics	Control Group (n = 48)	NIV Group (n = 48)
Age, y	68.5 (58.8-74.0)	67.0 (61.5-72.0)
Sex, female	40 (83.3)	37 (77.1)
Smokers	7 (14.6)	5 (10.4)
Smoking, pack-year[a]	40.0 (33.8-52.5)	35.0 (27.0-42.0)
Drinkers[b]	5 (10.6)	6 (12.5)
Alcohol, g[a]	27.0 ± 22.6	31.0 ± 8.83
BMI, kg/m^2	39.1 (35.6-43.1)	40.9 (35.0-44.5)
Neck circumference, cm	42.0 (40.0-45.0)	43.0 (39.0-46.0)
ESS	8.00 (5.00-12.0)	7.00 (4.00-12.5)
FOSQ	76.0 ± 18.4	71.8 ± 21.8
SF-36 physical	37.0 ± 7.79	35.0 ± 9.84
SF-36 mental	42.9 ± 10.8	40.7 ± 12.9
Dyspnea MRC scale score ≥ 2	29 (60.4)	25 (52.1)
Hypertension	37 (78.7)	36 (75.0)
Antihypertensive drugs[a]	2 (1-2)	2 (1-2)
Systolic BP, mm Hg	137 ± 15.0	138 ± 16.8
Diastolic BP, mm Hg	79.0 ± 12.2	77.7 ± 12.7
Diabetes	19 (39.6)	19 (39.6)
Antidiabetic medications	19 (39.6)	18 (38.3)
Dyslipidemia	26 (54.2)	18 (38.3)
Treatment of dyslipidemia	19 (40.4)	13 (28.3)
Stroke	5 (10.4)	6 (12.5)
Ischemic heart disease	4 (8.3)	4 (8.3)
Arrhythmia	3 (6.3)	6 (12.8)
Chronic heart failure[c]	6 (12.5)	15 (31.9)
Leg arteriopathy	7 (14.6)	5 (10.9)
Pulmonary hypertension	5 (10.6)	6 (12.8)
pH	7.40 ± 0.03	7.40 ± 0.03
Pa_{O_2}, mm Hg	66.2 ± 10.3	64.1 ± 10.3
Pa_{CO_2}, mm Hg	49.0 (47.0-50.0)	49.0 (48.0-52.2)
Bicarbonate, mmol/L	29.0 (27.4-31.1)	29.4 (28.3-31.3)
FEV_1, % predicted[c]	80.9 ± 19.9	72.0 ± 17.3
FVC, % predicted	82.3 ± 19.6	75.2 ± 20.7
6MWD, m	352 ± 101	313 ± 117
Polysomnographic parameters		
TST, h	5.30 (4.72-6.10)	5.55 (4.54-6.35)
Sleep efficiency	75.3 (63.8-86.7)	76.4 (58.8-80.8)
Stages 1 and 2 non-REM, %	66.0 (58.7-80.6)	71.4 (63.5-80.0)
Stage 3 non-REM, %	19.1 (6.90-28.3)	17.1 (8.32-23.1)
REM sleep, %	11.0 (6.25-17.2)	10.5 (6.32-15.5)
Arousal index	20.0 (12.0-24.4)	19.4 (14.4-28.4)
AHI	14.4 (9.99-21.9)	16.4 (6.37-22.2)
ODI	18.0 (12.0-25.0)	17.4 (11.5-30.0)
Mean Spo_2 during sleep	89.0 (85.5-92.0)	87.0 (84.0-90.0)
TST with Spo_2 < 90%, %	68.9 (14.7-93.9)	81.7 (46.9-97.3)
Oxygen therapy	16 (33.3)	12 (25.0)
Oxygen therapy flow, L/min[a]	1.50 (1.00-1.62)	1.50 (1.25-2.00)
Fasting blood glucose, mg/dL	106 (92.2-124)	110 (95.0-125)
Triglycerides, mg/dL	123 (100-162)	145 (98.5-163)
Cholesterol, mg/dL	195 ± 35.3	198 ± 49.4
HDL, mg/dL[c]	51.0 (46.0-56.0)	45.0 (39.5-55.2)
LDL, mg/dL	108 (96.2-133)	115 (93.9-140)
Creatinine, mg/dL	0.76 (0.68-0.87)	0.80 (0.64-0.98)
C-reactive protein, mg/L	1.10 (0.64-4.98)	1.40 (0.57-3.80)

Data presented as No. (%), median (interquartile range), or mean ± SD. 6MWD = 6-min walk distance; AHI = apnea-hypopnea index; ESS= Epworth Sleepiness Scale; FOSQ = Functional Outcomes of Sleep Questionnaire; MRC = Medical Research Council; NIV = noninvasive ventilation; ODI = 3% oxygen desaturation index; REM = rapid eye movement; SF-36 = Medical Outcome Survey Short Form 36; Spo_2 = oxygen saturation by pulse oximetry; TST = total sleep time.

[a]Includes only patients who reported to be active smokers or drinkers or patients with hypertension or with oxygen therapy.

[b]People who drink > 30 g of alcohol/d in men and 20 g in women.

[c]Intergroup comparison of chronic heart failure (P = .042), FEV_1 (P = .023), and HDL (P = .047).

clinical team's decision). No significant statistical differences were observed in abandons because of medical causes. Table 1 summarizes baseline characteristics of the two groups.

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The median follow-up for the primary outcome (and rest of hospital resource utilization) and mortality was 4.56 years (interquartile range [IQR], 2.72-6.50) in the NIV group and 5.39 years (IQR, 4.55-7.11) in the control group. The median follow-up for the rest of the outcomes was 2.23 years (IQR, 1.41-3.04) for NIV and 2.37 (IQR, 1.64-3.01) for the control group. The median treatment adherence in the NIV arm was 3.68 h/d (IQR, 0.00-6.24) (e-Fig 2).

Primary Outcome

The mean hospital days per year ± SD were 2.60 ± 5.31 for the control group and 2.71 ± 4.52 for the NIV group, without any significant differences between groups (rate ratio, 1.07; 95% CI, 0.44-2.59; $P = .882$) (Table 2). Similar results, although with different direction, were obtained in the per-protocol analysis (rate ratio, 0.92; 95% CI, 0.33-2.60; $P = .898$) (Table 2).

Secondary Outcomes

Hospital Resource Utilization: Events per year for hospital admissions and ED visits were not significantly different between groups (Table 2). Likewise, the hazard ratios for the first event of these outcomes were not significantly different between groups (e-Figs 3, 4; Table 2). In the per-protocol analysis, hospital admissions and ED visits decreased in the NIV arm with statistically significant differences for the time until the first ED visit (hazard ratio, 0.45; 95% CI, 0.24-0.85; $P = .0112$) (e-Fig 4, Table 2).

Incident Cardiovascular Events: Cardiovascular events occurred in 11 participants (23%) in the control group and 10 participants (21%) in the NIV group. The hazard ratio was 0.96 (95% CI, 0.40-2.30; $P = .927$) (e-Fig 5, Table 2). Similar results were observed in the per-protocol analysis (rate ratio, 1.21; 95% CI, 0.43-3.41; $P = .717$) (e-Fig 5, Table 2).

Mortality: Death occurred in nine participants (19%) in both arms (total of 18 deaths). The hazard ratio was 1.07 (95% CI, 0.41-2.82; $P = .893$) (e-Fig 6, Fig 2, Table 2). Similar results were found in the per-protocol analysis (rate ratio, 1.38; 95% CI, 0.50-3.79; $P = .529$) (e-Fig 6, Fig 2, Table 2). The predominant cause of mortality in the NIV group was related to cardiovascular events (six [67%] in the NIV group and three [33%] in the control group). The predominant cause of mortality in the control group was respiratory failure (four [44%] in the control group and two [22%] in the NIV group] (e-Fig 7, e-Table 2).

Arterial Blood Gases, BP, Spirometry, and 6MWD: $Paco_2$ and the physical component of the SF-36 improved significantly more with NIV treatment over time. Similar findings were observed for HCO_3^- and pH. Pao_2, diastolic BP, and FVC improved but without group differences (e-Figs 8-10; e-Tables 3, 4; Fig 2).

Ancillary Analysis

Prespecified Analyses: Weight was reduced similarly in both arms (e-Fig 11, e-Table 4). The reduction of the ESS score was statistically higher in the NIV group than the control group (e-Fig 12, e-Table 4). Other clinical symptoms changes remained similar in the control and NIV arms during the follow-up (e-Fig 13, e-Table 5). The prevalence of clinically significant dyspnea (Medical Research Council dyspnea scale score ≥ 2) decreased similarly in both groups but without statistically significant difference between groups (e-Fig 14).

Both NIV and control groups experienced a similar change in the need for daytime supplemental oxygen therapy and presence of adverse events (e-Tables 6-8).

Exploratory Post Hoc Analysis for the Adherence Subgroup: In the subgroup with high NIV adherence, the time until the first event of hospital admission, ED visits, and mortality were longer than in the low adherence subgroup (e-Figs 3-6, e-Tables 9-11). In the subgroup that was not adherent to NIV therapy, the need for supplemental oxygen therapy increased from 26% at baseline to 35.6% over 36 months. In contrast, in the subgroup that was adherent to NIV therapy, the need for supplemental oxygen decreased from 39.1% at baseline to 31.8% at 36 months. However, these differences did not reach statistical significance (e-Fig 15, e-Table 12).

Discussion

To our knowledge, this study is the only randomized controlled trial to date comparing long-term NIV with a control group in ambulatory patients with OHS who do not have concomitant severe OSA. The intention-to-treat analysis showed similar long-term results between the two arms in hospitalization days, other hospital resource utilization, BP, cardiovascular events, mortality, spirometry, and 6MWD. However, arterial blood gas parameters ($Paco_2$, HCO_3^-, and pH), one health-related quality of life measure (physical component of the SF-36), and daytime sleepiness outcomes were better with NIV. In the per-protocol analysis, NIV lead to lower ED

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TABLE 2] Primary and Secondary Outcomes for the Control and NIV Groups

Outcome	Control Group (n = 48)	NIV Group (n = 48)	Difference, Mean (95% CI)	Mixed-Effect Negative Binomial Regression Model		Mixed-Effect Cox Regression Model[a, b]	
				Rate Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI) With NIV	*P* Value
Primary outcome							
Days per year per patient							
ITT	2.60 ± 5.31	2.71 ± 4.52	0.11 (−1.89 to 2.11)	1.07 (0.44-2.59)	.882		
PP	2.32 ± 5.34	2.17 ± 4.30	−0.16 (−2.12 to 1.81)	0.92 (0.33-2.60)	.898		
Secondary outcomes							
Hospital admissions							
At least one							
ITT	29 (60)	26 (54)				0.99 (0.57-1.71)	.962
PP	23 (48)	19 (40)				0.83 (0.44-1.57)	.569
Events per year per patient							
ITT	0.37 ± 0.64	0.31 ± 0.47	−0.06 (−0.28 to 0.17)	0.93 (0.52-1.67)	.803		
PP	0.34 ± 0.66	0.28 ± 0.50	−0.05 (−0.29 to 0.18)	0.86 (0.43-1.73)	.667		
ED visits							
At least one							
ITT	36 (75)	32 (67)				0.73 (0.45-1.20)	.217
PP	30 (63)	22 (46)				0.45 (0.24-0.85)	.0112
Events per year per patient							
ITT	0.65 ± 0.74	0.54 ± 0.69	−0.11 (−0.4 to 0.18)	0.87 (0.55-1.37)	.547		
PP	0.66 ± 0.87	0.44 ± 0.71	−0.22 (−0.54 to 0.1)	0.69 (0.39-1.24)	.215		
Cardiovascular event							
ITT	11 (23)	10 (21)				0.96 (0.40-2.30)	.927
PP	7 (15)	8 (17)				1.21 (0.43-3.41)	.717
Mortality							
ITT	9 (19)	9 (19)				1.07 (0.41-2.82)	.893
PP	7 (15)	9 (19)				1.38 (0.50-3.79)	.529

Values are mean ± SD, No. (%), or as otherwise indicated. Difference between treatments was computed as the difference of the NIV group with respect to the control group. ITT = intention-to-treat; pp = per-protocol. See Table 1 legend for expansion of other abbreviation.

[a]The hazard ratio associated with the time until the first even.

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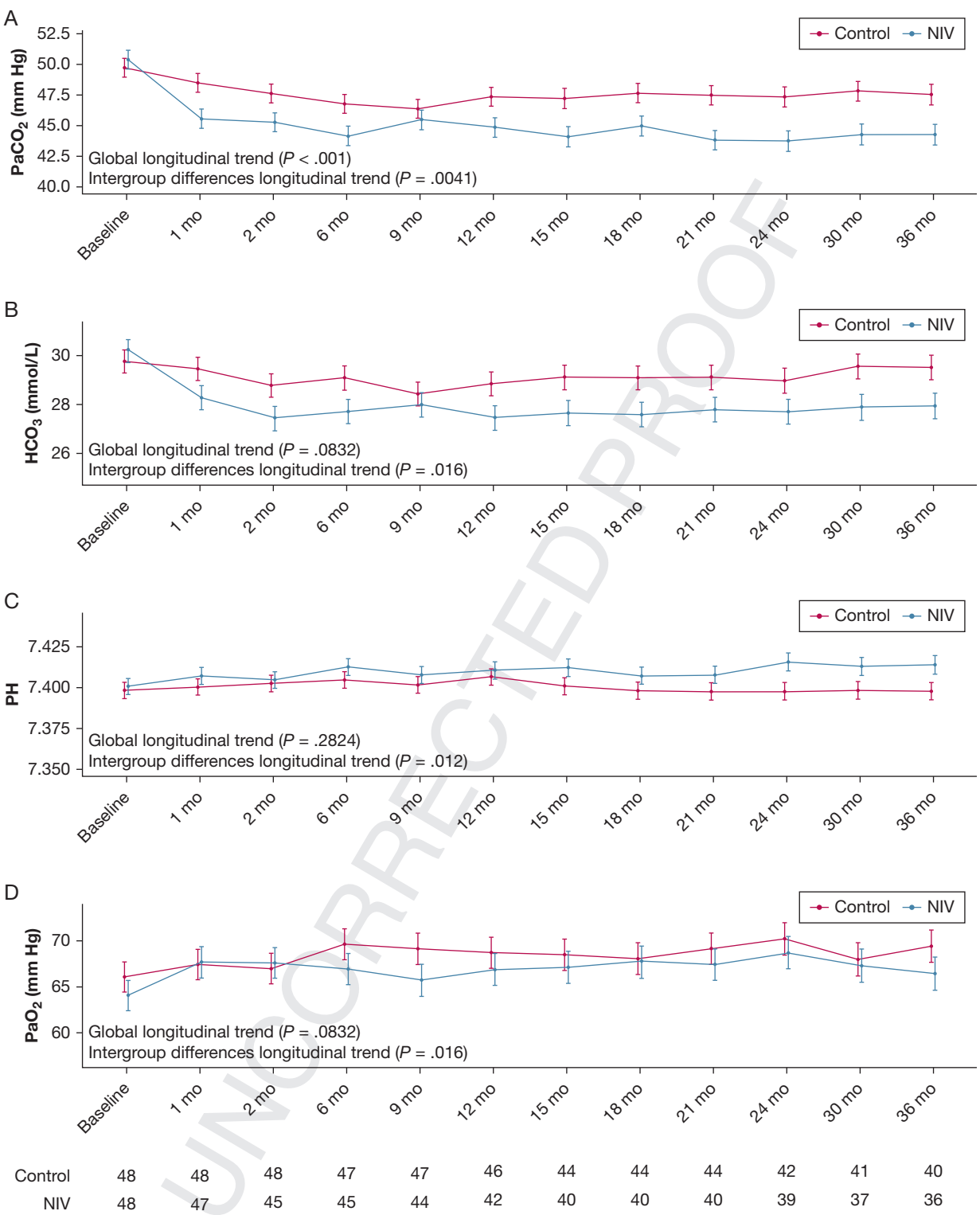

Figure 2 – *A-D, Adjusted longitudinal changes of arterial blood gases during follow-up (mean and 95% CI). P values correspond to longitudinal changes for treatments and for intergroup control and NIV comparison from linear mixed-effects regression model: (A) $Paco_2$ changes, (B) HCO_3^- changes, (C) pH changes, and (D) Pao_2 changes. HCO_3^- = bicarbonate. See Figure 1 legend for expansion of other abbreviation.*

visits. Post hoc analysis of adherence subgroups showed that high level of adherence to NIV was associated with reduced ED visits and mortality.

Most hospitalizations and deaths in untreated patients with OHS seem to be caused by respiratory complications such as acute-on-chronic respiratory

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failure and pulmonary embolism.[11,28,29] However, in cohorts of patients with OHS undergoing long-term NIV therapy,[4,30] and in our long-term results for patients with severe OSA, 55% of the deaths were of cardiovascular etiology.[19] This finding suggests that PAP may reduce morbidity and mortality because of respiratory causes but has less impact on cardiovascular outcomes. In the present study, although the overall mortality remained similar between groups, the predominant cause of mortality in the NIV arm was cardiovascular events and acute respiratory failure in the control group (e-Table 2). In the high NIV adherence subgroup, there were no deaths related to respiratory causes (e-Table 2). Therefore, in the OHS phenotype without severe OSA with higher preexisting cardiovascular morbidity, NIV may reduce acute-on-chronic respiratory failure, but this improvement may not be enough to reduce overall health-care resource utilization and mortality because NIV has limited impact on cardiovascular mortality. Another possibility for a lack of difference in the two groups (NIV and control groups) may be low NIV adherence. We observed an improvement in hospital resource utilization and overall mortality in the subgroup of patients with high NIV adherence when compared with the low adherence subgroup of NIV and the control group. The median adherence to NIV in the treatment arm in the present study (3.68 h/d; IQR, 0.00-6.24) was lower than in patients with OHS with severe OSA (6.0 h/d; IQR, 1.29-7.24).[19] This low adherence was mainly driven by the higher number of patients with NIV treatment abandonment during follow-up (49% in the present study vs 13% in the severe OSA phenotype), which may indicate lower patient-centered benefit.

$Paco_2$, HCO_3^-, and pH improved significantly with NIV, and the degree of improvement in $Paco_2$ (approximately 6 mm Hg) was similar to the improvement achieved with PAP therapy in the parallel randomized trial of the Pickwick study with severe OSA (approximately 7 mm Hg).[19] This degree of improvement in hypercapnia is similar to what we observed in the patients in this study after 2 months of therapy,[20] and is in line with prior clinical series of patients with OHS without severe OSA treated with NIV.[31-33] However, the degree of improvement in Pao_2 was lower than what was observed in patients with OHS with severe OSA treated with PAP therapy (approximately 3 vs 7 mm Hg).[19] In addition, the longitudinal improvement in spirometric parameters was also lower than in patients with OHS with severe OSA. Patients with OHS with severe OSA were more obese, and it is plausible that NIV was more effective in reducing microatelectasis, leading to greater improvement in lung volume and Pao2. Moreover, it is also plausible that a higher level of adherence is necessary to achieve resolution of microatelectasis, and the lower mean adherence to NIV may have also contributed to less robust improvement in awake hypoxemia in spite of the noticeable improvement in Paco2.

Taken together, the magnitude of improvement in patient-centered outcomes with NIV was lower in patients with OHS without severe OSA than in patients with OHS with severe OSA. This may be because of the phenotypic characteristic (ie, older, lower BMI, more women, less sleepy, more preexisting comorbidities) or lower NIV adherence. Poor adherence to NIV may be an important contributor to the lower-than-expected improvements given that patients who were adherent to long-term treatment NIV therapy experienced better outcomes.

There is a paucity of research on the effectiveness of various interventions to improve NIV adherence in patients with OHS. However, it is plausible that interventions used to improve CPAP adherence in OSA[34] may also be effective to improve adherence to NIV in patients with OHS. Therefore, educational interventions (ie, verbal or audiovisual information), enhanced support by regular meetings, telephone follow-up, or interactive applications for encouraging continued use of NIV or behavioral interventions designed to modify and promote adherence should be trialed in patients with OHS who exhibit low levels of adherence to long-term NIV therapy.

Limitations

Our target population was a small subgroup of a disorder that already has low prevalence of OHS (around 27% of the OHS population). Despite having 16 clinical centers and 8 years of follow-up, the study was stopped early because of difficulty identifying patients with OHS with no severe OSA in the last year of the study. Consequently, the study has lower power than estimated for the main outcome (60.17% based on the negative binomial regression model used in the analysis). Despite this weakness, our study provides important data in a subgroup of OHS that has rarely been studied in a longitudinal fashion in a randomized controlled trial. Although patients in both NIV and control groups

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crossed over to the other group, we tried to decrease this effect by performing both a per-protocol and subgroup analysis based on adherence to NIV. Another limitation is that NIV titration may have been suboptimal because we did not titrate NIV settings based on transcutaneous CO_2 levels during sleep (e-Appendix 1).

In summary, in the specific OHS phenotype without severe OSA, NIV was similar to lifestyle modification in outcomes such as hospital resource utilization, incident cardiovascular events, and mortality. However, NIV was more effective in improving daytime Paco2, some dimensions of quality of life, and sleepiness. A more intensive program aimed at improving NIV adherence may lead to better outcomes. Larger studies are necessary to better determine the long-term benefit of NIV in this subgroup of OHS; however, given the lower prevalence of this phenotype of OHS, it will be challenging to carry out long-term clinical trials with adequate enough sample size.

Acknowledgments

Author contributions: J. F. M. confirms that he had full access to all the data in the study and had the final responsibility for the decision to submit for publication. J. F. M., M. Á. S.-Q., F. J. G., I. B., F. J. V.-P., M. A. N., M. M.-E., F. B., A. R., C. C.-E., M. L. A.-Á., T. G.-G., M. G., S. L.-M., J. M. M., O. R., T. D.-C., E. C., C. E., B. M., J. C., J. A. R., J. B., E. O.-C., M. F. T., M. Á. M.-M., E. O.-C., D. L.-P., S. J. C., B. G., M. P., S. M., M. A. R., E. A., J. M.-M., C. S., J. N. S.-C., N. B. N. S., E. B., J. M. B., J. S.-G., R. G., M. A. G.-M., S. G., and M. B. made substantial contributions to study conception and design, acquisition of data, or analysis and interpretation of data. J. F. M., B. M., I. B., F. J. G., M. Á. S.-Q., A. R., C. C.-E., M. L. A.-Á., E. O.-C., T. G.-G., M. G., S. L.-M., J. M. M., S. M., T. D.-C., E. C., C. E., J. B., F. J. V.-P., M. A. N., M. M.-E., F. B., and J. C. drafted the article or revised the article critically for important intellectual content. J. F. M., B. M., I. B., F. J. V.-P., M. A. N., and J. C. performed the version to be published.

Financial/nonfinancial disclosures: None declared.

Role of sponsors: The sponsors and funders of the study had no involvement or any influence in study design; in the collection, analysis, and interpretation of data; in writing the manuscript; and in the decision to submit the manuscript for publication.

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Other contributions: We thank Verónica Rodríguez for her assistance in the translation of the manuscript and Vanessa Iglesias for her technical assistance.

Additional information: The e-Appendix, e-Figures, and e-Tables can be found in the Supplemental Materials section of the online article. Additional related documents such as study protocol, statistical analysis plan, and informed consent forms will be available on request from the Pickwick Project principal investigator (J. F. M.). Deidentified patient data can be requested by researchers for use in independent scientific research and will be provided after 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 (J. F. M).

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