JAMA | Original Investigation

# Effect of Home Noninvasive Ventilation With Oxygen Therapy vs Oxygen Therapy Alone on Hospital Readmission or Death After an Acute COPD Exacerbation
## A Randomized Clinical Trial

Patrick B. Murphy, PhD; Sunita Rehal, MSc; Gill Arbane, BSc (Hons); Stephen Bourke, PhD; Peter M. A. Calverley, PhD; Angela M. Crook, PhD; Lee Dowson, MD; Nicholas Duffy, MD; G. John Gibson, MD; Philip D. Hughes, MD; John R. Hurst, PhD; Keir E. Lewis, MD; Rahul Mukherjee, MD; Annabel Nickol, PhD; Nicholas Oscroft, MD; Maxime Patout, MD; Justin Pepperell, MD; Ian Smith, MD; John R. Stradling, PhD; Jadwiga A. Wedzicha, PhD; Michael I. Polkey, PhD; Mark W. Elliott, MD; Nicholas Hart, PhD

**IMPORTANCE** Outcomes after exacerbations of chronic obstructive pulmonary disease (COPD) requiring acute noninvasive ventilation (NIV) are poor and there are few treatments to prevent hospital readmission and death.

**OBJECTIVE** To investigate the effect of home NIV plus oxygen on time to readmission or death in patients with persistent hypercapnia after an acute COPD exacerbation.

**DESIGN, SETTING, AND PARTICIPANTS** A randomized clinical trial of patients with persistent hypercapnia ($Paco_2$ >53 mm Hg) 2 weeks to 4 weeks after resolution of respiratory acidemia, who were recruited from 13 UK centers between 2010 and 2015. Exclusion criteria included obesity (body mass index [BMI] >35), obstructive sleep apnea syndrome, or other causes of respiratory failure. Of 2021 patients screened, 124 were eligible.

**INTERVENTIONS** There were 59 patients randomized to home oxygen alone (median oxygen flow rate, 1.0 L/min [interquartile range {IQR}, 0.5-2.0 L/min]) and 57 patients to home oxygen plus home NIV (median oxygen flow rate, 1.0 L/min [IQR, 0.5-1.5 L/min]). The median home ventilator settings were an inspiratory positive airway pressure of 24 (IQR, 22-26) cm $H_2O$, an expiratory positive airway pressure of 4 (IQR, 4-5) cm $H_2O$, and a backup rate of 14 (IQR, 14-16) breaths/minute.

**MAIN OUTCOMES AND MEASURES** Time to readmission or death within 12 months adjusted for the number of previous COPD admissions, previous use of long-term oxygen, age, and BMI.

**RESULTS** A total of 116 patients (mean [SD] age of 67 [10] years, 53% female, mean BMI of 21.6 [IQR, 18.2-26.1], mean [SD] forced expiratory volume in the first second of expiration of 0.6 L [0.2 L], and mean [SD] $Paco_2$ while breathing room air of 59 [7] mm Hg) were randomized. Sixty-four patients (28 in home oxygen alone and 36 in home oxygen plus home NIV) completed the 12-month study period. The median time to readmission or death was 4.3 months (IQR, 1.3-13.8 months) in the home oxygen plus home NIV group vs 1.4 months (IQR, 0.5-3.9 months) in the home oxygen alone group, adjusted hazard ratio of 0.49 (95% CI, 0.31-0.77; $P$ = .002). The 12-month risk of readmission or death was 63.4% in the home oxygen plus home NIV group vs 80.4% in the home oxygen alone group, absolute risk reduction of 17.0% (95% CI, 0.1%-34.0%). At 12 months, 16 patients had died in the home oxygen plus home NIV group vs 19 in the home oxygen alone group.

**CONCLUSIONS AND RELEVANCE** Among patients with persistent hypercapnia following an acute exacerbation of COPD, adding home noninvasive ventilation to home oxygen therapy prolonged the time to readmission or death within 12 months.

**TRIAL REGISTRATION** clinicaltrials.gov Identifier: NCT00990132

*JAMA*. 2017;317(21):2177-2186. doi:10.1001/jama.2017.4451
Published online May 21, 2017.

Editorial page 2167

Supplemental content

CME Quiz at jamanetwork.com/learning

**Author Affiliations:** Author affiliations are listed at the end of this article.

**Corresponding Author:** Patrick B. Murphy, PhD, Lane Fox Respiratory Unit, St Thomas' Hospital, Westminster Bridge Rd, London SE1 7EH, England (patrick.murphy@gstt.nhs.uk).

Chronic obstructive pulmonary disease (COPD) is characterized by recurrent exacerbations that can cause intermittent periods of severe clinical deterioration requiring hospitalization and ventilator support. Although treating patients with COPD and acute respiratory failure with noninvasive ventilation improves outcomes,[1,2] persistent hypercapnia after an exacerbation is associated with excess mortality[3,4] and early rehospitalization.[5] In 2013, the 28-day COPD readmission rate was around 20%,[6] and there were financial penalties in place in the United Kingdom and United States for such early readmissions. These data have contributed to readmission prevention being a priority area for clinicians.

One treatment option would be to use noninvasive ventilation in addition to oxygen therapy in the home setting. Small, uncontrolled studies demonstrating the physiological efficacy of home noninvasive ventilation in patients with COPD[7-9] have led to its prescription across Europe.[10] However, subsequent clinical studies failed to demonstrate either physiological (reduced hypercapnia) or clinical (mortality) efficacy,[11,12] and questions remain regarding whether the application of the intervention was optimized in these randomized clinical trials.

The lack of improvement in chronic respiratory failure may explain the failure of earlier trials,[13] which is a theory supported by data from Köhnlein et al[14] that demonstrated both improvement of chronic respiratory failure and a mortality reduction. However, the participants in this trial were atypical of most patients with severe COPD and had relatively preserved exercise capacity and a low exacerbation and hospital admission rate, which limits the clinical applicability of these findings. In contrast, the Respiratory Support in COPD after Acute Exacerbation (RESCUE) trial,[15] which targeted patients with frequent exacerbations, failed to demonstrate a clinical benefit of home noninvasive ventilation when added to standard care.

In this multicenter randomized clinical trial conducted in the United Kingdom, it was hypothesized that the addition of home noninvasive ventilation to home oxygen therapy would prolong the time to readmission or death among patients with persistent hypercapnia following an acute life-threatening exacerbation of COPD requiring acute noninvasive ventilation.

### Key Points

**Question** Does the addition of home noninvasive ventilation to home oxygen therapy prolong time to readmission or death for patients with chronic obstructive pulmonary disease and persistent hypercapnia following a life-threatening exacerbation?

**Findings** In this randomized clinical trial of 116 patients, the addition of home noninvasive ventilation significantly prolonged time to readmission or death from 1.4 months to 4.3 months.

**Meaning** The addition of home noninvasive ventilation to home oxygen therapy may improve outcomes in patients with severe chronic obstructive pulmonary disease and persistent hypercapnia following hospital admission.

## Methods

### Trial Design and Patients

The trial was a phase 3, multicenter, open-label, parallel-group randomized clinical trial with a 1:1 allocation to home oxygen therapy alone or home noninvasive ventilation plus home oxygen therapy. The trial was approved by St Thomas' Hospital research ethics committee (09/H0802/2) and by local research and development committees at participating centers. All recruited patients provided written informed consent and all trial procedures conformed to local policies. The trial protocol and statistical analysis plan appear in Supplement 1.

Patients were recruited from 13 UK centers and were followed up for 12 months. Patients admitted with acute decompensated hypercapnic exacerbations of COPD requiring acute noninvasive ventilation were screened for eligibility at least 2 weeks after resolution of decompensated acidosis (arterial pH >7.30) and within 4 weeks of attaining clinical stability (eMethods in Supplement 2). Patients were required to have persistent hypercapnia ($Paco_2$ >53 mm Hg) and hypoxemia ($Pao_2$ <55 mm Hg or <60 mm Hg; ≥1 of polycythemia, pulmonary hypertension, or cor pulmonale; >30% of sleep time with oxygen saturation <90% as measured by pulse oximetry); and arterial pH greater than 7.30 while breathing room air.

Arterial blood gas analysis was performed after at least 1 night without noninvasive ventilation support and after receiving oxygen therapy overnight. Chronic respiratory failure was attributed to severe COPD provided that the forced expiratory volume in the first second of expiration ($FEV_1$) was less than 50% of predicted, the ratio of $FEV_1$ to forced vital capacity was less than 60%, and the patient had a smoking history of greater than 20 pack-years and was in the absence of (1) obesity (body mass index [calculated as weight in kilograms divided by height in meters squared] >35), (2) clinically significant obstructive sleep apnea syndrome (if clinically suspected by attending physician from history, examination, or baseline oximetry, it was then investigated with attended limited respiratory polygraphy; eMethods in Supplement 2), and (3) neuromuscular or chest wall disease.

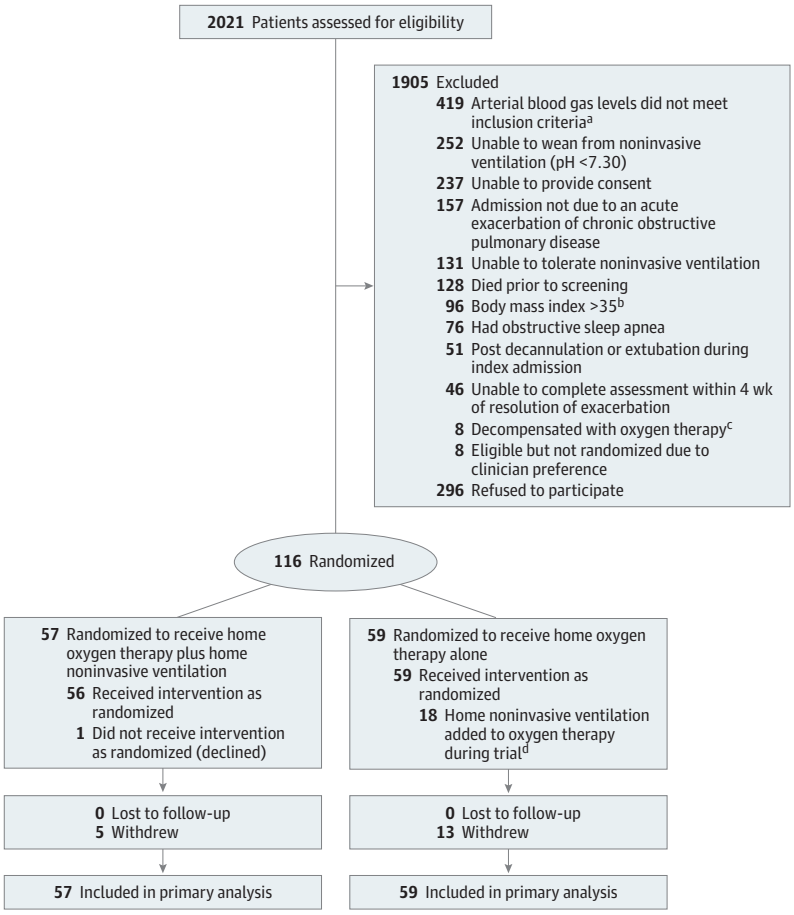
Patients were excluded if they (1) were not assessed within 4 weeks of resolution of the index COPD exacerbation, (2) required intubation and invasive mechanical ventilation during the index exacerbation, (3) were currently using noninvasive home mechanical ventilation, (4) exhibited cognitive impairment or unstable psychiatric morbidity, (5) were undergoing renal replacement therapy, (6) had active unstable coronary artery syndrome, (7) were younger than 18 years, and (8) were homeless. Additional exclusion criteria appear in **Figure 1**.

Eligible patients were transferred for assessment to a specialist noninvasive ventilation center if they met the above criteria during the index admission and within the time frame after discharge or transfer.

### Randomization and Masking

Patients were randomized by the Oxford Clinical Trials Unit using computer-based minimization software (Minim). Minimization summates the imbalance within each stratification variable if a patient is allocated to a particular treatment group,

Figure 1. Participant Flow Diagram




[a] Defined as absence of hypercapnia ($PaCO_2$ <53 mm Hg), hypoxemia ($PaO_2$ >60 mm Hg), or both.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Defined as an arterial pH of less than 7.30 when morning arterial blood gas measured after use of oxygen therapy alone.

[d] Seventeen patients received home noninvasive ventilation after hospital readmission (consistent with trial protocol) and, at the discretion of the treating clinician, 1 patient received home noninvasive ventilation prior to reaching the primary outcome.

and the next treatment to be randomized is chosen depending on which treatment would minimize the imbalance.[16]

The minimization criteria were age (<65 years vs ≥65 years), body mass index (≤20 vs >20), current long-term oxygen therapy use (yes vs no), frequency of COPD-related readmissions during previous 12 months (<3 vs ≥3), and recruitment center. Although there was no suitable sham option for noninvasive ventilation, and the supervising clinicians were unblinded to treatment allocation, the trial staff conducting the outcome assessments were blinded to treatment allocation.

## Intervention

Noninvasive ventilation was initiated using nasal, oronasal, or total face masks per patient preference. Noninvasive ventilation was delivered using the Harmony 2 ventilator (Philips Respironics) or the VPAP IIISTa ventilator (ResMed) with each center restricted to a single model. Patients underwent daytime noninvasive ventilation acclimatization, followed by nocturnal titration with oxygen entrained at the daytime prescription rate (eMethods and eAppendix 1 in Supplement 2). The aim was to achieve control of nocturnal hypoventilation with a high-pressure ventilation strategy.[17]

In both patient groups, oxygen therapy was initiated at the lowest flow rate required to increase the $PaO_2$ level to greater than 60 mm Hg without producing decompensated respiratory failure, which was defined as an arterial pH of less than 7.30 on the morning blood gas measurement after overnight use of oxygen without noninvasive ventilation. All patients were instructed to use oxygen therapy for at least 15 hours daily. The patients allocated to home oxygen therapy plus home noninvasive ventilation were instructed to use the ventilator for a minimum of 6 hours nightly.

All patients had medical management optimized for COPD according to guidelines from the British Thoracic Society[18] that included regular, triple-inhaled bronchodilator therapy (long-acting β-agonist, long-acting antimuscarinic, and steroid), as-needed inhaled short-acting β-agonist therapy, sputum clearance techniques where appropriate, smoking cessation support, and education on COPD self-management. Patients allocated to home oxygen therapy alone could receive acute noninvasive ventilation during hospital readmissions for decompensated respiratory failure with the intention of being weaned and discharged back to oxygen alone unless there was a breach in the safety criteria (eMethods in Supplement 2).

## Outcome and Assessments

The primary outcome was time to readmission or death within 12 months after randomization (ie, time from randomization

to either hospital readmission or death from any cause). Patients readmitted to the hospital prior to study withdrawal were censored at the time of hospital readmission. Patients who withdrew were censored at the time of study withdrawal and were considered as not meeting the primary end point. Any patients who were readmitted to the hospital prior to withdrawal were censored at the time of the hospital readmission. Baseline descriptive data were recorded in line with local and national guidelines and included collection of anthropometric data, sex (self-reported), and spirometry and arterial blood gas analysis.

Secondary exploratory outcomes included all-cause mortality, exacerbation frequency (exacerbation defined in eMethods, eAppendix 1, and eAppendix 2 in Supplement 2), change in arterial $Paco_2$ and $Pao_2$ while breathing room air, change in control of sleep-disordered breathing (as measured by 4% oxygen desaturation index, mean nocturnal oxygen saturation as measured by pulse oximetry, total sleep time with oxygen saturation as measured by pulse oximetry <90%, mean nocturnal transcutaneous carbon dioxide, and maximum nocturnal transcutaneous carbon dioxide), breathlessness as measured using the Medical Research Council dyspnea score[19] (categorical scale from 1-5; higher scores indicate more limitations on daily activities due to breathlessness), health-related quality of life measured using the Severe Respiratory Insufficiency Questionnaire (0 = worst quality of life, 100 = best quality of life),[20] and the St George's Respiratory Questionnaire (0 = best quality of life, 100 = worst quality of life; minimally important clinical difference of 4)[21,22] at each follow-up assessment.

Hospital readmission and exacerbation data were collected at each follow-up visit (6 weeks, 3 months, 6 months, and 12 months) and vital status at trial completion was established using the National Health Service information center for patients lost to follow-up. We performed sensitivity analyses on the primary outcome to assess for robustness post hoc.

### Sample Size Calculation and Statistical Analysis

The sample size was based on UK audit data (M. W. Elliott, MD, Department of Respiratory Medicine, Leeds University Hospital, oral communication, 2008), assuming a readmission rate of 55% at 12 months in patients after an admission requiring treatment with noninvasive ventilation for an acute exacerbation of COPD. If home noninvasive ventilation reduced readmissions to 25% at 12 months, and assuming a loss to follow-up of 22%, 116 patients would be needed to provide 80% power with a 2-sided significance level of .05.

Data are presented as mean (standard deviation) or median (interquartile range [IQR]) as appropriate. All primary and secondary analyses were assessed for superiority and were analyzed according to the intention-to-treat principle, including all randomized patients in whom an outcome was available. The primary outcome defined as time from randomization to hospital readmission or death was analyzed using a Cox proportional hazards regression model adjusted for minimization variables (age, body mass index, current long-term oxygen therapy use, frequency of COPD readmissions over 12 months). To avoid overstratification, recruiting center was not included in the adjusted model.[23]

Sensitivity analyses using best-case and worst-case scenarios were performed post hoc to assess the robustness of the primary outcome analysis. The best-case scenario assumed patients who withdrew were neither readmitted to the hospital nor died and were censored 12 months after randomization. The worst-case scenario assumed patients who withdrew were readmitted to the hospital or died and were censored at the point of withdrawal. These analyses explore the most extreme scenarios for patients who withdrew prior to reaching the primary end point.

Other post hoc analyses included time to hospital readmission 28 days after randomization and were analyzed using a Cox proportional hazards regression model for comparison with previous studies. The per-protocol analysis excluded patients (1) who switched treatment during the trial prior to achieving the primary end point and (2) whose average daily use of noninvasive ventilation was less than 4 hours. Additional analyses included center as a fixed effect and as a random effect, with the latter being a post hoc analysis. Unadjusted hazard ratios (HRs) for treatment effects are also presented. Full details appear in the statistical analysis plan in Supplement 1.

All-cause mortality was analyzed using a Cox proportional hazards regression model. A post hoc analysis of the number of exacerbations per year was performed using (1) negative binomial regression due to clustering of exacerbations within patients and (2) linear mixed-effects regression models with a random effect for center to assess continuous variables. Statistical significance was concluded at the 2-sided significance level of .05 for all analyses. All analyses were conducted using Stata software version 14.1 (StataCorp).

## Results

### Patients

Of the 2021 patients screened, 124 were eligible, and 116 patients were randomized between February 27, 2010, and April 6, 2015 (Figure 1). There were 57 patients randomized to home oxygen therapy plus home noninvasive ventilation and 59 patients to home oxygen therapy alone. The final patient visit occurred on April 23, 2016. Sixty-four patients (28 in the home oxygen therapy alone group and 36 in the home oxygen therapy plus home noninvasive ventilation group) completed the 12-month study period.

Eighteen patients withdrew from the study, 12 before reaching the primary outcome (10 patients in the home oxygen therapy alone group and 2 in the home oxygen therapy plus home noninvasive ventilation group). Seventeen patients initially randomized to receive home oxygen therapy alone had home noninvasive ventilation added after reaching the primary outcome of readmission, which was consistent with the trial protocol (eMethods in Supplement 2).

At the discretion of the treating clinician (on trial day 2) and prior to reaching the primary outcome, 1 patient randomized to the home oxygen therapy alone group was instructed to add home noninvasive ventilation but remained in the home oxygen therapy group for analysis purposes. Baseline

Table 1. Baseline Characteristics

| | Home Oxygen Therapy Plus NIV (n = 57) | Home Oxygen Therapy Alone (n = 59) | Total (N = 116) |
|---|---|---|---|
| Age, mean (SD), y[a] | 66.4 (10.2) | 67.1 (9.0) | 66.7 (9.6) |
| Body mass index, median (IQR)[a,b] | 21.5 (18.8-24.5) | 22.2 (17.9-26.9) | 21.6 (18.2-26.1) |
| Prior use of long-term oxygen therapy, No. (%)[a] | 40 (70) | 40 (68) | 80 (69) |
| ≥3 COPD-related readmissions within past year, No. (%)[a] | 30 (53) | 31 (53) | 61 (53) |
| Female sex, No. (%) | 29 (51) | 32 (54) | 61 (53) |
| Smoking history, median (IQR), pack-years | 42.0 (30.5-60.0) | 45.0 (31.0-55.0) | 44.0 (31.0-60.0) |
| Apnea Hypopnea Index, median (IQR), /h[c] | 2.4 (0.9-6.2) | 2.0 (0.8-3.9) | 2.2 (0.8-5.1) |
| Neck circumference, median (IQR), cm | 36.3 (33.0-40.0) | 38.6 (35.3-41.0) | 37.0 (34.5-40.0) |
| Waist circumference, median (IQR), cm | 90.0 (78.0-100.5) | 87.5 (78.0-106.0) | 88.0 (78.0-102.0) |
| $FEV_1$, mean (SD), L | 0.6 (0.2) | 0.6 (0.2) | 0.6 (0.2) |
| $FEV_1$ % predicted, mean (SD) | 24.0 (8.6) | 22.9 (8.6) | 23.4 (8.6) |
| Forced vital capacity, mean (SD), L | 1.8 (0.8) | 1.5 (0.6) | 1.7 (0.7) |
| Forced vital capacity % predicted, mean (SD) | 57.4 (19.7) | 49.3 (20.4) | 53.2 (20.4) |
| Ratio of $FEV_1$ to forced vital capacity, mean (SD) | 0.3 (0.1) | 0.4 (0.1) | 0.4 (0.1) |
| $Pao_2$ while breathing room air, mean (SD), mm Hg | 48 (9) | 48 (8) | 48 (8) |
| $Paco_2$ while breathing room air, mean (SD), mm Hg | 59 (7) | 59 (7) | 59 (7) |
| Arterial pH while breathing room air, mean (SD) | 7.40 (0.04) | 7.40 (0.03) | 7.40 (0.04) |
| St George's Respiratory Questionnaire summary score, median (IQR)[d] | 74.7 (63.7-81.7) | 71.0 (62.6-78.6) | 73.8 (63.3-80.3) |
| Severe Respiratory Insufficiency Questionnaire summary score, mean (SD)[e] | 45.8 (15.0) | 46.9 (15.6) | 46.4 (15.2) |
| Medical Research Council dyspnea score, median (IQR)[f] | 5.0 (4.0-5.0) | 5.0 (4.0-5.0) | 5.0 (4.0-5.0) |

Abbreviations: COPD, chronic obstructive pulmonary disease; $FEV_1$, forced expiratory volume in the first second of expiration; IQR, interquartile range; NIV, noninvasive ventilation.

[a] Minimization variable used during the randomization process to enhance the chance of creating balanced groups.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] There were 25 patients in the home oxygen therapy plus home noninvasive mechanical ventilation group and 19 in the home oxygen therapy alone group.

[d] On a scale of 0 to 100 in which 0 is the best quality-of-life score and 100 is the worst.

[e] On a scale of 0 to 100 in which 100 is the best quality-of-life score and 0 is the worst.

[f] On a categorical scale of 1 to 5; higher scores indicate more limitation on daily activities due to breathlessness.

characteristics appear in **Table 1**. The groups were well balanced for important baseline variables, including minimization factors. The randomized cohort had severe COPD as evidenced by severe airflow obstruction (mean [SD] $FEV_1$ of 0.6 L [0.2 L] and mean [SD] ratio of $FEV_1$ to forced vital capacity of 0.4 [0.1]) and hypercapnia respiratory failure (mean [SD] $Paco_2$ of 59 [7] mm Hg). There was no evidence of significant obstructive sleep apnea in randomized patients (eTable 1 in Supplement 2).

The dropout rate was within the prespecified power calculation and the retention and follow-up numbers appear in eTable 2 in Supplement 2. The median follow-up time was 12.2 months (IQR, 8.9-12.9 months) for the home oxygen therapy plus home noninvasive ventilation group and 8.1 months (IQR, 2.3-12.6 months) for the home oxygen therapy alone group.

## Intervention

There was no significant between-group difference in the oxygen therapy flow rates after baseline titration (median oxygen flow rate, 1.0 L/min [IQR, 0.5-2.0 L/min] for the home oxygen therapy alone group vs 1.0 L/min [IQR, 0.5-1.5 L/min] for the home oxygen therapy plus home noninvasive ventilation group; $P$ = .11).

The median ventilator settings at hospital discharge in the home oxygen therapy plus home noninvasive ventilation group were an inspiratory positive airway pressure of 24 cm $H_2O$ (IQR, 22-26 cm $H_2O$), an expiratory positive airway pressure of 4 cm $H_2O$ (IQR, 4-5 cm $H_2O$), and a backup rate of 14 breaths/minute (IQR, 14-16 breaths/minute). Ventilator use at 6 weeks was 4.7 hours per night (IQR, 2.5-5.6 hours per night), which increased during the trial to 7.6 hours per night (IQR, 3.6-8.4 hours per night) at 12 months (eTable 3 in Supplement 2).

## Delivery and Efficacy of Home Noninvasive Ventilation

There was a statistically significant reduction in nocturnal transcutaneous carbon dioxide levels on the night after initiation of noninvasive ventilation, which persisted to 12 months; however, at 6 months the between-group difference was not statistically significant (adjusted mean difference, −0.63 kPa [95% CI, −1.55 to 0.30 kPa], $P$ = .18; eTable 4 in Supplement 2).

There was a statistically significant between-group difference in daytime $Paco_2$ at 6 weeks and 3 months favoring the home oxygen therapy plus home noninvasive ventilation group, but not at 12 months. There was no corresponding improvement in oxygenation (**Table 2**).

Table 2. Daytime Gas Exchange

| Visit | No. of Patients | | Mean (95% CI), mm Hg | | Treatment Effect Within Each Group (95% CI), mm Hg[a] | | Mean Between-Group Difference Adjusted for Baseline Values (95% CI) | P Value | Mean Between-Group Difference Fully Adjusted Model (95% CI)[b] | P Value |
|---|---|---|---|---|---|---|---|---|---|---|
| | HO + NIV | HO Alone | HO + NIV | HO Alone | HO + NIV | HO Alone | | | | |
| $Paco_2$ | | | | | | | | | | |
| Baseline[c] | 57 | 59 | 59 (57 to 61) | 59 (57 to 61) | | | | | | |
| Wk 6 | 42 | 34 | 53 (50 to 56) | 57 (53 to 61) | −6.2 (−8.6 to −3.8) | −0.8 (−4.4 to 2.8) | −5.0 (−8.8 to −1.1) | .01 | −5.0 (−9.0 to −1.3) | .01 |
| 3 mo | 40 | 34 | 53 (51 to 55) | 56 (53 to 59) | −6.3 (−8.5 to −4.1) | −1.9 (−4.9 to 1.1) | −3.8 (−6.9 to −0.7) | .02 | −4.0 (−7.1 to −0.8) | .02 |
| 6 mo | 39 | 26 | 53 (51 to 56) | 52 (49 to 56) | −5.9 (−8.4 to −3.5) | −5.5 (−9.0 to −2.0) | 0.5 (−3.2 to 4.1) | .82 | 0.6 (−3.0 to 4.1) | .75 |
| 12 mo | 31 | 27 | 54 (50 to 58) | 56 (51 to 60) | −5.9 (−8.9 to −2.9) | −2.3 (−6.1 to 1.5) | −3.0 (−7.4 to 1.4) | .18 | −2.3 (−6.5 to 1.9) | .28 |
| $Pao_2$ | | | | | | | | | | |
| Baseline[c] | 57 | 59 | 48 (46 to 50) | 48 (46 to 50) | | | | | | |
| Wk 6 | 42 | 34 | 53 (50 to 56) | 52 (48 to 56) | 5.0 (1.6 to 8.3) | 2.8 (−0.9 to 6.5) | 1.3 (−3.1 to 5.6) | .57 | 1.6 (−2.6 to 5.9) | .46 |
| 3 mo | 40 | 34 | 53 (50 to 56) | 54 (50 to 58) | 4.7 (0.8 to 8.6) | 4.5 (0.6 to 8.4) | −0.6 (−5.4 to 4.2) | .81 | −2.1 (−6.8 to 2.6) | .37 |
| 6 mo | 39 | 25 | 55 (52 to 58) | 56 (52 to 59) | 6.4 (3.2 to 9.6) | 7.7 (4.1 to 11.3) | −0.9 (−5.3 to 3.4) | .67 | −0.6 (−5.1 to 3.9) | .79 |
| 12 mo | 32 | 26 | 55 (50 to 59) | 56 (51 to 62) | 7.0 (2.9 to 11.0) | 7.0 (1.8 to 12.2) | −0.8 (−0.6 to 4.5) | .78 | −0.1 (−5.3 to 5.3) | .99 |

Abbreviations: HO, home oxygen; NIV, noninvasive ventilation.

[a] Mean difference from baseline.

[b] Adjusted for baseline values, number of chronic obstructive pulmonary disease readmissions within past year, prior use of long-term oxygen therapy, age, and body mass index with a random effect for center.

[c] Missing results were replaced with mean imputations.

## Primary Outcome: Time to Readmission or Death

The median time to readmission or death was 4.3 months (IQR, 1.3-13.8 months) in the home oxygen therapy plus home noninvasive ventilation group compared with 1.4 months (IQR, 0.5-3.9 months) in the home oxygen therapy alone group (**Figure 2**). For readmission or death within 12 months, there was an adjusted HR of 0.49 (95% CI, 0.31-0.77; $P = .002$) and an unadjusted HR of 0.54 (95% CI, 0.34-0.84; $P = .007$). The 12-month risk of readmission or death was 63.4% in the home oxygen therapy plus home noninvasive ventilation group compared with 80.4% in the home oxygen therapy alone group, resulting in an absolute risk reduction of 17.0% (95% CI, 0.1%-34.0%).

The per-protocol and sensitivity analyses also were consistent with these results (eResults and eTable 5 in Supplement 2). A post hoc analysis of 28-day readmission identified a significant treatment effect with an unadjusted HR of 0.27 (95% CI, 0.12-0.63; $P = .003$) and an adjusted HR of 0.26 (95% CI, 0.11-0.61; $P = .002$) (eFigure in Supplement 2). The majority of readmissions during follow-up were related to respiratory concerns (201/209 readmissions).

## All-Cause Mortality

A similar number of patients in both treatment groups died during the event triggering primary outcome completion (5 in the home oxygen therapy plus home noninvasive ventilation group and 4 in the home oxygen therapy alone group). Twelve-month mortality was not significantly different between groups (16 patients [28%] in the home oxygen therapy plus home noninvasive ventilation group vs 19 patients [32%] in the home oxygen therapy alone group; unadjusted HR, 0.68 [95% CI, 0.35-1.32], $P = .26$; adjusted HR, 0.67 [95% CI, 0.34-1.30], $P = .23$) with most causes of death being respiratory (eTable 6 in Supplement 2).

## Acute COPD Exacerbation Frequency

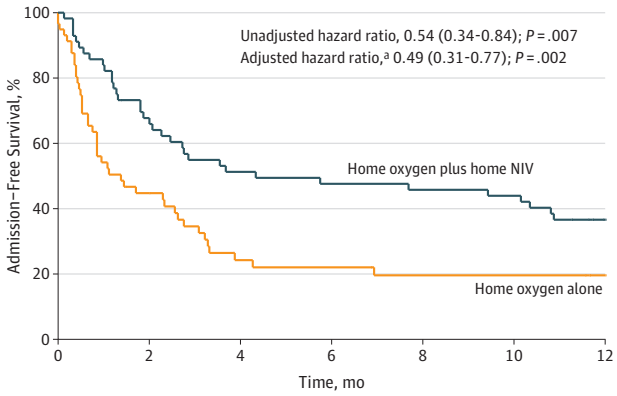
There was a reduction in the COPD exacerbation rate in the home oxygen therapy plus home noninvasive ventilation group (median, 3.8 exacerbations per year [IQR, 1.7-6.0 exacerbations per year]) compared with the home oxygen therapy alone group (median, 5.1 exacerbations per year [IQR, 1.0-9.2 exacerbations per year]; unadjusted rate ratio, 0.64 [95% CI, 0.44-0.94], $P = .02$; adjusted rate ratio, 0.66 [95% CI, 0.46-0.95], $P = .03$; eTable 7 in Supplement 2).

## Health-Related Quality of Life

At 6 weeks, the Severe Respiratory Insufficiency Questionnaire mean score was 50.6 in the home oxygen therapy plus home noninvasive ventilation group and 49.2 in the home oxygen therapy alone group with an unadjusted between-group difference of 4.85 (95% CI, 0.43-9.27; $P = .03$) and an adjusted between-group difference of 4.48 (95% CI, 0.02-8.94; $P = .05$), indicating improved health-related quality of life in the home oxygen therapy plus home noninvasive ventilation group at this time point.

At 3 months, the St George's Respiratory Questionnaire mean score was 62.9 in the home oxygen therapy plus home noninvasive ventilation group compared with 66.0 in the home

Figure 2. Kaplan-Meier Survival Plot of Time to Readmission or Death From Randomization to the End of Trial Follow-up at 1 Year




No. at risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Home oxygen plus home NIV | 57 | 37 | 28 | 26 | 25 | 24 | 16 |
| Home oxygen alone | 59 | 23 | 11 | 10 | 8 | 8 | 6 |

The median follow-up times were 8.1 months (interquartile range, 2.3-12.6 months) for the home oxygen therapy alone group and 12.2 months (interquartile range, 8.9-12.9 months) for the home oxygen therapy plus home noninvasive ventilation (NIV) group.

[a] Adjusted for number of chronic obstructive pulmonary disease readmissions within past year, prior use of long-term oxygen therapy, age, and body mass index.

oxygen therapy alone group with a significant unadjusted between-group difference of −4.30 (95% CI, −8.39 to −0.21; $P$ = .04) and a significant adjusted between-group difference of −4.85 (95% CI, −8.83 to −0.88; $P$ = .02), indicating a beneficial effect of home noninvasive ventilation on health-related quality of life at this time point. There were no significant differences demonstrated thereafter (**Table 3**).

## Discussion

In this randomized clinical trial, an improvement in time to readmission or death was observed when home noninvasive ventilation was added to home oxygen therapy in patients with persistent hypercapnia following a life-threatening acute exacerbation of COPD. These data support the screening of patients with COPD after receiving acute noninvasive ventilation to identify persistent hypercapnia and introduce home noninvasive ventilation.

The current data differ from the RESCUE trial,[15] even though the trial designs were similar. The RESCUE trial showed no difference in time to readmission or death within 12 months. Differences in the study population and protocol may explain the discordant results because the RESCUE trial[15] enrolled patients with a less stringent $Paco_2$ criterion (daytime $Paco_2$ >45 mm Hg) following cessation of acute noninvasive ventilation, whereas the current trial only recruited patients if the daytime $Paco_2$ was greater than 53 mm Hg at least 2 weeks after resolution of acute respiratory acidemia. Furthermore, and unlike the RESCUE trial,[15] the current study also required demonstration of chronic hypoxemia and thus targeted patients with more severe COPD. Such patients with chronic respiratory failure have previously been shown to benefit from noninvasive ventilation in physiological studies.[7,9]

The early, within-hospital assessment of hypercapnia in the RESCUE trial may have led to the inclusion of patients with spontaneously reversible hypercapnia and consequently a better prognosis.[24] Consistent with this conjecture, the control group as well as the treatment noninvasive ventilation group of the RESCUE study showed a reduction in daytime $Paco_2$ within 6 weeks of enrollment,[15] supporting the rationale that the trajectory of recovery for hypercapnia determines the likelihood of response to home noninvasive ventilation. However, the improvement in hypercapnia demonstrated could be accounted for by regression to the mean rather than a true physiological effect. Based on previous data from the investigators,[17] the current trial protocol adopted a high-pressure titration strategy with a demonstrated effect on nocturnal hypoventilation.

Despite the delay in time to readmission or death with enhanced control of nocturnal ventilation and reduced exacerbation frequency, there was only an initial modest effect on health-related quality of life with the addition of home noninvasive ventilation. This is perhaps unsurprising given the severity of disease in the COPD cohort enrolled and the high levels of physical impairment at baseline. The results of the current trial are reassuring, suggesting that home noninvasive ventilation added to home oxygen therapy in this population improved the overall clinical outcome without adding to the health burden of the patient, countering earlier concerns raised by the Australian trial of Non-invasive Ventilation in Chronic Airflow Limitation.[12]

The participant flow diagram (Figure 1) shows that 2021 patients were screened and considered eligible for the trial. Although only 6% of screened patients were recruited into the trial, one-third of the screened patients were ineligible because they could either not wean from acute noninvasive ventilation due to clinical instability, they died prior to screening, or they were unable to provide consent. These factors highlight that this was a cohort of patients with severe disease, contributing to the recruitment rate observed. The process of assessing the patients during the recovery phase, and only recruiting those patients with a $Paco_2$ of greater than 53 mm Hg, helped to ensure the cohort was enriched with patients with chronic respiratory failure, which is the cohort most

Table 3. Health-Related Quality of Life

| Visit | No. of Patients | | Mean (95% CI) | | Treatment Effect Within Each Group (95% CI)[a] | | Between-Group Difference Adjusted for Baseline Values (95% CI) | P Value | Between-Group Difference Fully Adjusted Model (95% CI)[b] | P Value |
|---|---|---|---|---|---|---|---|---|---|---|
| | HO + NIV | HO Alone | HO + NIV | HO Alone | HO + NIV | HO Alone | | | | |
| Severe Respiratory Insufficiency Questionnaire (0 = worst quality-of-life score; 100 = best) | | | | | | | | | | |
| Baseline[c] | 57 | 59 | 45.8 (41.9 to 49.7) | 46.9 (42.9 to 50.9) | | | | | | |
| Week 6 | 43 | 36 | 50.6 (46.0 to 55.1) | 49.2 (44.1 to 54.3) | 3.8 (0.5 to 7.2) | −2.0 (−5.8 to 1.7) | 4.9 (0.4 to 9.3) | .03 | 4.5 (0.0 to 8.9) | .05 |
| 3 mo | 40 | 32 | 52.1 (47.6 to 56.5) | 49.9 (45.4 to 54.3) | 3.9 (0.4 to 7.5) | −0.2 (−4.0 to 3.7) | 3.7 (−0.8 to 8.2) | .10 | 3.5 (−1.0 to 8.1) | .13 |
| 6 mo | 40 | 26 | 50.7 (46.4 to 54.9) | 53.2 (47.0 to 59.5) | 3.2 (−0.4 to 6.7) | −0.6 (−5.2 to 4.1) | 2.0 (−3.0 to 6.9) | .43 | 1.5 (−3.5 to 6.6) | .56 |
| 12 mo | 35 | 26 | 49.8 (44.3 to 55.3) | 53.9 (47.6 to 60.2) | 1.5 (−1.9 to 4.9) | 0.7 (−3.9 to 5.3) | 0.1 (−5.0 to 5.2) | .96 | −0.4 (−5.4 to 4.7) | .89 |
| St George's Respiratory Questionnaire (0 = best quality-of-life score; 100 = worst) | | | | | | | | | | |
| Baseline[c] | 57 | 59 | 71.9 (68.1 to 75.7) | 69.0 (65.6 to 72.5) | | | | | | |
| Week 6 | 44 | 37 | 68.3 (63.8 to 72.8) | 65.7 (62.2 to 69.3) | −2.7 (−5.3 to 0) | −2.0 (−5.8 to 1.7) | 0.4 (−3.4 to 4.2) | .84 | 0.7 (−3.2 to 4.5) | .74 |
| 3 mo | 39 | 35 | 62.9 (58.0 to 67.7) | 66.0 (62.4 to 69.5) | −6.2 (−9.4 to −3.0) | −1.4 (−4.8 to 2.1) | −4.3 (−8.4 to −0.2) | .04 | −4.9 (−8.8 to −0.9) | .02 |
| 6 mo | 40 | 27 | 67.3 (62.8 to 71.9) | 61.9 (56.0 to 67.7) | −2.4 (−5.1 to 0.4) | −3.2 (−8.7 to 2.3) | 2.2 (−2.8 to 7.1) | .40 | 3.0 (−2.0 to 8.0) | .24 |
| 12 mo | 36 | 28 | 69.0 (64.0 to 74.0) | 64.5 (59.4 to 69.5) | 0.3 (−3.3 to 4.0) | −0.8 (−5.2 to 3.6) | 2.27 (−2.59 to 7.14) | .36 | 2.3 (−2.6 to 7.1) | .36 |

Abbreviations: HO, home oxygen; NIV, noninvasive ventilation.

[a] Mean difference from baseline.

[b] Adjusted for baseline values, number of chronic obstructive pulmonary disease readmissions within past year, prior use of long-term oxygen therapy, age, and body mass index with a random effect for center.

[c] Missing baseline results were replaced with mean imputation.

likely to benefit from the addition of home noninvasive ventilation therapy.

Patients with established chronic respiratory failure secondary to COPD have poor outcomes with limited treatment options available.[3,4] The driver of the clinical improvement in the home oxygen therapy plus home noninvasive ventilation group was readmission avoidance with no significant difference in mortality observed between the treatment group and the standard care home oxygen therapy alone group for both the event triggering the primary outcome and at 12 months. However, the study was not powered to detect a difference for this outcome. This study has major clinical relevance because readmission avoidance is beneficial to the patient in terms of preservation of lung function and health-related quality of life[25] as well as providing a direct and indirect cost saving.

The results of this study support the use of in-home, high-pressure noninvasive ventilation in patients who have persistent hypercapnia for 2 to 4 weeks after resolution of respiratory acidemia requiring acute noninvasive ventilation. There are physiological mechanisms that underpin the effect of home noninvasive ventilation when added to home oxygen therapy that could explain the clinical benefit of reduced hospital readmission. Previous physiological studies have shown that home noninvasive ventilation in patients with severe COPD improves ventilatory response to hypercapnia,[7] which could be expected to act as a clinically relevant effect of treatment, allowing a more robust and adaptive response to the adverse physiological challenge of an acute $Paco_2$ increase during an exacerbation.

Furthermore, imaging data suggest that high-pressure noninvasive ventilation may contribute to airway remodeling and improved ventilation-perfusion matching.[26] In addition, the observation of an improvement in gas exchange with a reduction in $Paco_2$ and exacerbation frequency is supported by data that have shown that hypercapnia decreases secretion of IL-6 and tumor necrosis factor in the lungs and impairs lung neutrophil function in an animal model of lung infection.[27] Future experiments are required to investigate this observation.

## Limitations

This study has a number of limitations. First, the lack of a double-blind design for this trial is a potential criticism. The use of a sham device group was considered because this approach has been used previously in continuous positive airway pressure trials in patients with obstructive sleep apnea.[28] However, the use of a device modified to deliver zero pressure support through a nasal or face mask could result in an increase in dynamic dead space,[29] which would have the potential to worsen respiratory failure. In addition, sham continuous positive airway pressure can affect sleep architecture, the clinical significance of which is unknown.[30] There was further concern regarding the effectiveness of blinding in sham device trials because both patients and clinicians have been able to identify the sham intervention, limiting the scientific justification of this approach.[31,32] The unblinded trial design and lack of a sham device, with blinded assessment in terms of the outcome, is consistent with other clinical trials in this field.[11,12,14,15]

Second, the trial design was pragmatic in that it made provision for patients initially allocated to home oxygen therapy to have home noninvasive ventilation added if they breached safety criteria after reaching the primary outcome. Eighteen patients initially allocated to home oxygen therapy alone had home noninvasive ventilation added to their management strategy. In 17 of 18 cases (94%), the addition of home noninvasive ventilation occurred after the primary end point was reached, thus not affecting the primary analysis. This protocol design may have contributed to the apparent dilution of treatment effect of home noninvasive ventilation on daytime hypercapnia, nocturnal hypoventilation, and quality of life after 3 months because home noninvasive ventilation had been added by this time point to the treatment of more than half the remaining patients in the home oxygen therapy alone group.

Third, the statistical analysis plan for the study included a number of secondary outcomes that should be considered exploratory because no corrections were used for multiple comparisons. The secondary outcomes were included to provide mechanistic support for the primary outcome. The use of a single level of significance for secondary outcomes is consistent with other data in this area.[14,15]

## Conclusions

Among patients with persistent hypercapnia following an acute exacerbation of COPD, adding home noninvasive ventilation to home oxygen therapy prolonged the time to readmission or death within 12 months.

ARTICLE INFORMATION

**Accepted for Publication:** April 20, 2017.

**Published Online:** May 21, 2017. doi:10.1001/jama.2017.4451

**Author Affiliations:** Lane Fox Unit, Guy's and St Thomas' NHS Foundation Trust, London, England (Murphy, Arbane, Patout, Hart); Asthma, Allergy, and Lung Biology, King's College London, London, England (Murphy, Hart); MRC Clinical Trials Unit at University College London, Institute of Clinical Trials and Methodology, London, England (Rehal, Crook); Respiratory Medicine, Northumbria Healthcare NHS Foundation Trust, Newcastle, England (Bourke); Institute of Cellular Medicine, Newcastle University, Newcastle, England (Bourke); School of Aging and Chronic Disease, University of Liverpool, Liverpool, England (Calverley); Respiratory Medicine, Royal Wolverhampton NHS Trust, Wolverhampton, England (Dowson); Respiratory Medicine, Aintree University Hospital, Liverpool, England (Duffy); Respiratory Medicine, Newcastle University, Newcastle, England (Gibson); Respiratory Medicine, Plymouth Hospital NHS Trust, Plymouth, England (Hughes); Respiratory Medicine, University College London, Royal Free Campus, London, England (Hurst); Respiratory Medicine, Swansea University, Swansea, England (Lewis); Respiratory Medicine, Heart of England NHS Trust, Birmingham, England (Mukherjee); Oxford NIHR Biomedical Research Centre, Oxford University and NHS Foundation Trust, Oxford, England (Nickol, Stradling); Respiratory Support and Centre, Papworth Hospital, Cambridge, England (Oscroft, Smith); Respiratory Medicine, Taunton and Somerset NHS Trust, Taunton, England (Pepperell); NIHR Respiratory Biomedical Research Unit, Royal Brompton and Harefield NHS Foundation Trust and Imperial College, London, England (Wedzicha, Polkey); Department of Respiratory Medicine, Leeds University Hospital, Leeds, England (Elliott).

**Author Contributions:** Drs Murphy and Hart had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
*Concept and design:* Murphy, Calverley, Crook, Hurst, Nickol, Oscroft, Smith, Stradling, Wedzicha, Polkey, Elliott, Hart.
*Acquisition, analysis, or interpretation of data:* Rehal, Arbane, Bourke, Crook, Dowson, Duffy, Gibson, Hughes, Hurst, Lewis, Mukherjee, Nickol, Oscroft, Patout, Pepperell, Smith, Polkey, Elliott, Hart.
*Drafting of the manuscript:* Murphy, Rehal, Duffy, Lewis, Polkey, Elliott, Hart.
*Critical revision of the manuscript for important intellectual content:* Murphy, Rehal, Arbane, Bourke, Calverley, Crook, Dowson, Gibson, Hughes, Hurst, Lewis, Mukherjee, Nickol, Oscroft, Patout, Pepperell, Smith, Stradling, Wedzicha, Polkey, Elliott, Hart.
*Statistical analysis:* Murphy, Rehal, Hart.
*Obtained funding:* Calverley, Hart.
*Administrative, technical, or material support:* Murphy, Arbane, Bourke, Hurst, Lewis, Oscroft, Patout, Pepperell, Smith, Hart.
*Supervision:* Crook, Dowson, Gibson, Hurst, Oscroft, Wedzicha, Polkey, Elliott, Hart.

**Conflict of Interest Disclosures:** The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. The Lane Fox Clinical Respiratory Physiology Research Centre has received unrestricted research grants from ResMed, Philips Respironics, Fisher & Paykel Healthcare, and B&D Electromedical. Dr Murphy reported receiving reimbursement for expenses for travel to conferences and lecture fees from Philips Respironics, ResMed, Fisher & Paykel, and B&D Electromedical. Dr Bourke reported receiving unrestricted research grant funding from Philips Respironics and Pfizer Open Air; and personal fees from Pfizer. Dr Hughes reported receiving reimbursement for travel expenses to scientific meetings from ResMed, Philips Respironics, and B&D Electromedical. Dr Lewis reported receiving speakers fees and institutional grant funding from Philips Respironics for an unrelated study. Dr Mukherjee reported receiving nonfinancial support from ResMed and Breas (before it was incorporated into B&D Electromedical). Dr Patout reported receiving personal fees from Fisher & Paykel and ResMed; nonfinancial support from Antadir; and grant funding from B&D Electromedical. Dr Pepperell reported receiving personal fees and nonfinancial support from ResMed for lecturing and serving on an advisory panel; and travel reimbursement and speakers fees from Philips Respironics, ResMed, Fisher & Paykel, B&D Electromedical, and Weinmann. Dr Smith reported receiving unrestricted research grant funding from B&D Electromedical. Dr Stradling reported receiving consultant fees from ResMed. Dr Wedzicha reported receiving personal fees from Novartis, GlaxoSmithKline, Pfizer, Takeda, AstraZeneca, Boehringer Ingelheim, Johnson & Johnson, Vifor Pharma, Bayer, Chiesi, and Napp; receiving grants from GlaxoSmithKline, Takeda, Johnson & Johnson, and Vifor Pharma; and receiving nonfinancial support from Novartis, GlaxoSmithKline, Takeda, AstraZeneca, and Boehringer Ingelheim. Dr Polkey reported receiving personal fees from Philips Respironics for serving as a consultant that were paid to his institution; and his institution is currently negotiating a consultancy position between Royal Brompton and Harefield Hospital Foundation Trust and Philips Respironics for which his trust will be remunerated. Dr Elliott reported receiving personal fees from ResMed, Philips Respironics, Curative Medical, and Agir a Dom. Dr Hart reported receiving personal fees from Fisher & Paykel; grant funding for other trials from Philips Respironics, ResMed, B&D Electromedical, and Fisher & Paykel; and having a patent pending for a myotrace technology. No other disclosures were reported.

**Funding/Support:** The study was supported by unrestricted educational grant funding from Philips Respironics, ResMed, the ResMed Foundation, and the Guy's and St Thomas' Charity. Philips Respironics provided the Harmony 2 ventilators and the Actiwatch spectrum devices used in the study. ResMed provided the VPAP IIISTa devices used in the study. The study was supported by Guy's and St Thomas' NHS Foundation Trust and King's College London, the National Institute of Health Research Comprehensive Biomedical Research Centre, and the NIHR Respiratory Disease Biomedical Research Unit at the Royal Brompton and Harefield NHS Foundation Trust and Imperial College London, which partly funded Dr Polkey's salary.

**Role of the Funder/Sponsor:** The funders were not involved in design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

**Disclaimer:** The views expressed in this publication are those of the authors and not necessarily those of the National Health Service, the National Institute for Health Research, or the Department of Health.

**Meeting Presentation:** Presented in part at the American Thoracic Society international conference; May 21, 2017; Washington, DC.

**Additional Contributions:** We acknowledge the uncompensated contributions to trial design and management made by Robert Davies, MD, who died before completion of the trial. We also acknowledge the efforts of all the research teams at the recruiting centers and in particular Michael Davies, MD (Respiratory Support and Sleep Center, Papworth Hospital, Cambridge, England), and Robert Angus, MD (Respiratory Medicine, Aintree University Hospital, Liverpool, England), who assisted with trial delivery and recruitment without remuneration.

## REFERENCES

1. Brochard L, Mancebo J, Wysocki M, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. *N Engl J Med*. 1995;333(13):817-822.

2. Bott J, Carroll MP, Conway JH, et al. Randomised controlled trial of nasal ventilation in acute ventilatory failure due to chronic obstructive airways disease. *Lancet*. 1993;341(8860):1555-1557.

3. Connors AF Jr, Dawson NV, Thomas C, et al; SUPPORT Investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments). Outcomes following acute exacerbation of severe chronic obstructive lung disease. *Am J Respir Crit Care Med*. 1996;154(4 pt 1):959-967.

4. Murray I, Paterson E, Thain G, Currie GP. Outcomes following non-invasive ventilation for hypercapnic exacerbations of chronic obstructive pulmonary disease. *Thorax*. 2011;66(9):825-826.

5. Chu CM, Chan VL, Lin AW, Wong IW, Leung WS, Lai CK. Readmission rates and life threatening events in COPD survivors treated with non-invasive ventilation for acute hypercapnic respiratory failure. *Thorax*. 2004;59(12):1020-1025.

6. Suh ES, Mandal S, Harding R, et al. Neural respiratory drive predicts clinical deterioration and safe discharge in exacerbations of COPD. *Thorax*. 2015;70(12):1123-1130.

7. Nickol AH, Hart N, Hopkinson NS, et al. Mechanisms of improvement of respiratory failure in patients with COPD treated with NIV. *Int J Chron Obstruct Pulmon Dis*. 2008;3(3):453-462.

8. Meecham Jones DJ, Paul EA, Jones PW, Wedzicha JA. Nasal pressure support ventilation plus oxygen compared with oxygen therapy alone in hypercapnic COPD. *Am J Respir Crit Care Med*. 1995;152(2):538-544.

9. Elliott MW, Mulvey DA, Moxham J, Green M, Branthwaite MA. Domiciliary nocturnal nasal intermittent positive pressure ventilation in COPD: mechanisms underlying changes in arterial blood gas tensions. *Eur Respir J*. 1991;4(9):1044-1052.

10. Lloyd-Owen SJ, Donaldson GC, Ambrosino N, et al. Patterns of home mechanical ventilation use in Europe: results from the Eurovent survey. *Eur Respir J*. 2005;25(6):1025-1031.

11. Clini E, Sturani C, Rossi A, et al; Rehabilitation and Chronic Care Study Group, Italian Association of Hospital Pulmonologists (AIPO). The Italian multicentre study on noninvasive ventilation in chronic obstructive pulmonary disease patients. *Eur Respir J*. 2002;20(3):529-538.

12. McEvoy RD, Pierce RJ, Hillman D, et al; Australian trial of non-invasive Ventilation in Chronic Airflow Limitation (AVCAL) Study Group. Nocturnal non-invasive nasal ventilation in stable hypercapnic COPD: a randomised controlled trial. *Thorax*. 2009;64(7):561-566.

13. Windisch W. Noninvasive positive pressure ventilation in COPD. *Breathe*. 2011;8(2):114-123.

14. Köhnlein T, Windisch W, Köhler D, et al. Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. *Lancet Respir Med*. 2014;2(9):698-705.

15. Struik FM, Sprooten RT, Kerstjens HA, et al. Nocturnal non-invasive ventilation in COPD patients with prolonged hypercapnia after ventilatory support for acute respiratory failure: a randomised, controlled, parallel-group study. *Thorax*. 2014;69(9):826-834.

16. Altman DG, Bland JM. Treatment allocation by minimisation. *BMJ*. 2005;330(7495):843.

17. Murphy PB, Brignall K, Moxham J, Polkey MI, Davidson AC, Hart N. High pressure versus high intensity noninvasive ventilation in stable hypercapnic chronic obstructive pulmonary disease: a randomized crossover trial. *Int J Chron Obstruct Pulmon Dis*. 2012;7:811-818.

18. National Institute for Health and Clinical Excellence (NICE). *Chronic Obstructive Pulmonary Disease in Over 16s: Diagnosis and Management [CG101]*. London, England: NICE; 2010.

19. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax*. 1999;54(7):581-586.

20. Ghosh D, Rzehak P, Elliott MW, Windisch W. Validation of the English Severe Respiratory Insufficiency Questionnaire. *Eur Respir J*. 2012;40(2):408-415.

21. Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. *Respir Med*. 1991;85(suppl B):25-31.

22. Jones PW. St George's Respiratory Questionnaire: MCID. *COPD*. 2005;2(1):75-79.

23. Kahan BC, Morris TP. Improper analysis of trials randomised using stratified blocks or minimisation. *Stat Med*. 2012;31(4):328-340.

24. Costello R, Deegan P, Fitzpatrick M, McNicholas WT. Reversible hypercapnia in chronic obstructive pulmonary disease: a distinct pattern of respiratory failure with a favorable prognosis. *Am J Med*. 1997;102(3):239-244.

25. Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 1998;157(5 pt 1):1418-1422.

26. De Backer L, Vos W, Dieriks B, et al. The effects of long-term noninvasive ventilation in hypercapnic COPD patients: a randomized controlled pilot study. *Int J Chron Obstruct Pulmon Dis*. 2011;6:615-624.

27. Gates KL, Howell HA, Nair A, et al. Hypercapnia impairs lung neutrophil function and increases mortality in murine pseudomonas pneumonia. *Am J Respir Cell Mol Biol*. 2013;49(5):821-828.

28. Pepperell JC, Ramdassingh-Dow S, Crosthwaite N, et al. Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised parallel trial. *Lancet*. 2002;359(9302):204-210.

29. Saatci E, Miller DM, Stell IM, Lee KC, Moxham J. Dynamic dead space in face masks used with noninvasive ventilators: a lung model study. *Eur Respir J*. 2004;23(1):129-135.

30. Rodway GW, Weaver TE, Mancini C, et al. Evaluation of sham-CPAP as a placebo in CPAP intervention studies. *Sleep*. 2010;33(2):260-266.

31. Djavadkhani Y, Marshall NS, D'Rozario AL, et al. Ethics, consent and blinding: lessons from a placebo/sham controlled CPAP crossover trial. *Thorax*. 2015;70(3):265-269.

32. Schwartz SW, Cimino CR, Anderson WM. CPAP or placebo-effect? *Sleep*. 2012;35(12):1585-1586.