ORIGINAL ARTICLE

Randomized Trial of Nocturnal Oxygen in Chronic Obstructive Pulmonary Disease

Yves Lacasse, M.D., Frédéric Sériès, M.D., François Corbeil, M.D., Marc Baltzan, M.D., Bruno Paradis, M.D., Paula Simão, M.D., Araceli Abad Fernández, M.D., Cristóbal Esteban, M.D., Miguel Guimarães, M.D., Jean Bourbeau, M.D., Shawn D. Aaron, M.D., Sarah Bernard, M.Sc., and François Maltais, M.D., for the INOX Trial Group*

ABSTRACT

BACKGROUND

Long-term oxygen therapy improves survival in patients with chronic obstructive pulmonary disease (COPD) and chronic severe daytime hypoxemia. However, the efficacy of oxygen therapy for the management of isolated nocturnal hypoxemia is uncertain.

METHODS

We designed this double-blind, placebo-controlled, randomized trial to determine, in patients with COPD who have nocturnal arterial oxygen desaturation without qualifying for long-term oxygen therapy, whether nocturnal oxygen provided for a period of 3 to 4 years would decrease mortality or the worsening of disease such that patients meet current specifications for long-term oxygen therapy. Patients with an oxygen saturation of less than 90% for at least 30% of the recording time on nocturnal oximetry were assigned, in a 1:1 ratio, to receive either nocturnal oxygen or ambient air from a sham concentrator (placebo). The primary outcome was a composite of death from any cause or a requirement for long-term oxygen therapy as defined by the Nocturnal Oxygen Therapy Trial (NOTT) criteria in the intention-to-treat population.

RESULTS

Recruitment was stopped prematurely because of recruitment and retention difficulties after 243 patients, of a projected 600, had undergone randomization at 28 centers. At 3 years of follow-up, 39.0% of the patients assigned to nocturnal oxygen (48 of 123) and 42.0% of those assigned to placebo (50 of 119) met the NOTT-defined criteria for long-term oxygen therapy or had died (difference, −3.0 percentage points; 95% confidence interval, −15.1 to 9.1).

CONCLUSIONS

Our underpowered trial provides no indication that nocturnal oxygen has a positive or negative effect on survival or progression to long-term oxygen therapy in patients with COPD. (Funded by the Canadian Institutes of Health Research; INOX ClinicalTrials.gov number, NCT01044628.)

From Institut Universitaire de Cardiologie et de Pneumologie de Québec–Université Laval, Quebec, QC (Y.L., F.S., S.B., F.M.), Centre Hospitalier Affilié Universitaire de Trois-Rivières, Trois-Rivières, QC (F.C.), Mount Sinai Hospital, McGill University (M.B.), and Montreal Chest Institute, Research Institute of the McGill University Health Centre and McGill University (J.B.), Montreal, Centre Intégré de Santé et de Services Sociaux de Laval, Laval, QC (B.P.), and the Ottawa Hospital Research Institute, University of Ottawa, Ottawa (S.D.A.) — all in Canada; Hospital Pedro Hispano–Unidade Local de Saúde de Matosinhos, Matosinhos (P.S.), and Centro Hospitalar Vila Nova de Gaia–Espinho, Vila Nova de Gaia (M.G.) — both in Portugal; and Hospital Universitario de Getafe, Getafe (A.A.F.), and Hospital Galdakao, Servicio Vasco de Salud–Osakidetza, Bizkaia (C.E.) — both in Spain. Address reprint requests to Dr. Lacasse at Centre de Pneumologie, Institut Universitaire de Cardiologie et de Pneumologie de Québec, 2725 Chemin Sainte-Foy, Quebec, QC G1V 4G5, Canada, or at yves.lacasse@med.ulaval.ca.

*A complete list of the investigators in the INOX Trial Group is provided in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2020;383:1129-38.
DOI: 10.1056/NEJMoa2013219

A Quick Take is available at NEJM.org

Two landmark trials that were published in the early 1980s provided evidence that, under very specific circumstances, long-term oxygen therapy used for at least 15 to 18 hours per day improves survival in patients with chronic obstructive pulmonary disease (COPD).[1,2] These two trials targeted patients with COPD with severe chronic daytime hypoxemia documented by arterial blood gas measurement.

Sleep-related nonapneic oxygen desaturation often occurs in patients with COPD not qualifying for long-term oxygen therapy.[3,4] Alveolar hypoventilation (particularly during rapid-eye-movement [REM] sleep) and ventilation–perfusion mismatch are likely mechanisms.[5-7] This phenomenon is considered by many physicians as an indication for prescribing nocturnal oxygen because the progression of COPD to its end stages of severe hypoxemia, right heart failure, and death may result from the severity of desaturation occurring during sleep.[8,9] In addition, nocturnal oxygen desaturation in patients with COPD induces systemic inflammation that may also contribute to the pathogenesis of pulmonary hypertension and cardiovascular diseases.[10,11]

Three randomized trials directly addressed the issue of the effectiveness of nocturnal oxygen in patients not qualifying for long-term oxygen therapy who had desaturation overnight.[12-14] Only two trials examined the effect of nocturnal oxygen on survival and progression to long-term oxygen therapy at 3 years of follow-up; both trials had negative results but were underpowered, with only 38 patients undergoing randomization in one trial and 76 in the other trial.[12,13] Accordingly, the primary objective of the International Nocturnal Oxygen (INOX) trial was to determine, in patients with COPD with nocturnal arterial oxygen desaturation who do not qualify for long-term oxygen therapy because of the absence of severe daytime hypoxemia, whether nocturnal oxygen provided for a period of 3 to 4 years affects mortality or the progression of COPD such that patients meet current specifications for long-term oxygen therapy. Secondary objectives were to examine whether nocturnal oxygen changes disease-specific quality of life or modifies exacerbation and hospitalization rates.

Methods

Design and Oversight

The trial protocol has been published previously.[15] The trial was initially designed as a 3-year, multicenter, randomized, double-blind, placebo-controlled trial of nocturnal oxygen, evaluated in an intention-to-treat analysis. An independent data and safety monitoring board operated according to the terms of a charter that was developed from the recommendations of the DAMOCLES (Data Monitoring Committees: Lessons, Ethics, Statistics) Study Group.[16] The trial protocol and its amendments received approval from the ethics committee at each participating center. The authors assume responsibility for the accuracy and completeness of the data and for the adherence of the trial to the protocol, which is available with the full text of this article at NEJM.org. Authors' and investigators' contributions are listed in the Supplementary Appendix, available at NEJM.org. There was no commercial support for this trial.

Patients

The trial took place in 28 community or university-affiliated hospitals in Canada, Portugal, Spain, and France. Patients with a diagnosis of COPD (postbronchodilator forced expiratory volume in 1 second [FEV_1] of <70% of the predicted value, a ratio of the FEV_1 to the forced vital capacity [FVC] of <0.70, and a total lung capacity as measured by body plethysmography of >80% of the predicted value) who had a history of smoking were screened. All had had stable disease for at least 6 weeks before enrollment and had been nonsmokers for at least 6 months. We excluded patients with severe daytime hypoxemia who were already receiving long-term oxygen therapy and those likely to require long-term oxygen therapy at trial entry according to the Nocturnal Oxygen Therapy Trial (NOTT) criteria (a partial pressure of arterial oxygen [Pao_2] of ≤55 mm Hg while the patient was breathing ambient air, or a Pao_2 of 56 to 59 mm Hg with evidence of cor pulmonale or erythrocythemia).[1] We also excluded patients with sleep apnea (defined by an apnea–hypopnea index of ≥15 events per hour),[17] those currently using nocturnal oxygen, and those with known left heart failure, interstitial lung disease, bronchiectasis, lung carcinoma, severe obesity (body-mass index [the weight in kilograms divided by the square of the height in meters], ≥40), or any other disease that could influence survival.

Nocturnal desaturation was defined on the basis of a nocturnal home oximetry recording as at least 30% of the recording time (time in bed)

with an oxygen saturation (Spo_2) of less than 90%.[18] Continuous nocturnal saturation monitoring was performed with the PalmSAT 2500 oximeter (Nonin Medical). Only recordings with a duration of at least 4 hours were accepted. All the patients underwent two oximetry studies separated by no more than 2 weeks. Patients were eligible if desaturation was shown on either of two oximetry recordings. Those with an oximetry tracing suggestive of sleep apnea (i.e., cyclical changes in saturation in addition to desaturation) were excluded, unless sleep apnea could be ruled out on the basis of in-laboratory polysomnography performed off-protocol (Fig. S1 in the Supplementary Appendix).

TRIAL PROCEDURES

Patients were randomly assigned to receive, in a 1:1 ratio, either home nocturnal oxygen from an oxygen concentrator or ambient air from a sham concentrator (placebo). Randomization was performed with a centralized computer-generated random listing of the two intervention assignments blocked by variable blocks of four and six and stratified according to site. (Details are provided in the Supplementary Appendix.) Baseline clinical measurements included the Charlson comorbidity index[19] (scores range from 0 to 37, with higher scores indicating worse health status and increased risk of death within 1 year), spirometry, lung volumes measured by plethysmography, carbon monoxide diffusion capacity measured by the single-breath method, and arterial blood gas measurements (obtained while the patient was breathing ambient air at rest). Patients were contacted by telephone every 2 months in order to capture adverse events. On-site visits took place every 4 months for clinical assessment, including pulse oximetry. Arterial blood gas measurements were obtained every 12 months or during the intercurrent visits if daytime resting oxygen saturation was less than 92%. Details of the schedule of procedures are provided in Table S1.

INTERVENTIONS

Nocturnal oxygen was delivered overnight from an electrically powered oxygen concentrator (NewLife Intensity Oxygen Concentrator, AirSep) and was administered through nasal cannula. Patients were instructed to use supplemental oxygen throughout the night. After randomization, the oxygen flow rate to be used during the trial was determined with the goal of maintaining nocturnal oxygen saturation of more than 90% for at least 90% of the recording time. Adjustment of the oxygen flow rate was performed at home, starting with a flow rate of 2 liters per minute during a first test night and increased, if needed, by increments of 1 liter per minute per night, up to 4 liters per minute. Patients who were assigned to the control group received ambient air delivered through identical concentrators rendered ineffective by bypassing the sieve beds. To preserve blinding, patients in the control group underwent a sham flow-rate adjustment procedure that is described in Figure S2. Short-term oxygen therapy (i.e., daytime and nighttime oxygen provided temporarily to treat severe hypoxemia during the course of an exacerbation of COPD) was allowed. Patients were visited at home every 4 months for maintenance of the concentrator.

OUTCOMES

The primary outcome was a composite of death from any cause or a requirement for long-term oxygen therapy in the intention-to-treat population. We used the NOTT criteria to define a requirement for long-term oxygen therapy.[1] Secondary outcomes included adherence to the intervention, exacerbation and hospitalization rates, and quality of life. The duration of nighttime oxygen therapy (or placebo) was objectively determined from the concentrator's counter clock recording the number of hours of use. Only event-based exacerbations (i.e., those leading to treatment with antibiotics, systemic glucocorticoids, or both, with or without hospitalization) were recorded. Disease-specific and generic quality of life was measured every 12 months with the use of the St. George's Respiratory Questionnaire[20] (SGRQ; scores range from 0 to 100, with higher scores indicating worse quality of life; minimal clinically important difference, 4 points) and the 36-Item Short-Form Health Survey[21] (SF-36; scores range from 0 to 100, with higher scores indicating better quality of life; minimal clinically important difference, 10 points), respectively.

INTERIM ANALYSIS AND TRIAL TERMINATION

The sample size was calculated with the assumption that 3-year mortality in the control group would be 20% and that a further 20% of the patients would have progression to long-term oxygen therapy.[13] We targeted an absolute differ-

ence in the percentage of patients with a composite outcome event of 12 percentage points (i.e., 40% in the control group and 28% in the active-treatment group), which is consistent with the minimal clinically important difference perceived by Canadian pulmonologists in a national survey that we conducted before the trial.[22] In relative terms, this translates to a 30% relative difference in risk. We computed a sample size of 300 patients per group, assuming a trial power of 90% (two-sided alpha error, 5%).

Recruitment started in November 2010. The data and safety monitoring board intervened on two separate occasions during the trial. First, because the trial rarely met its monthly recruitment targets, the steering committee and the data and safety monitoring board agreed in June 2013 to extend follow-up from 3 years to 4 years in order to enhance the capture of events, without any other protocol modification. Recruitment strategies were also reviewed. Second, because recruitment failed to improve, the data and safety monitoring board requested in November 2014 that an interim analysis be conducted. From this analysis, the data and safety monitoring board recommended that enrollment into the trial be halted because of recruitment and retention difficulties (not for therapeutic futility) and that the 4-year follow-up of patients who had already undergone randomization be continued. The steering committee concurred with this plan and remained unaware of the results of the interim analysis.

STATISTICAL ANALYSIS

The primary outcome was assessed in the intention-to-treat population according to the assigned intervention. For both groups, we constructed survival curves using Kaplan–Meier estimates and used the log-rank test for between-group comparisons. A Fine–Gray model was used to account for death as a competing risk event for a requirement for long-term oxygen therapy.[23] Hazard ratios and 95% confidence intervals for the composite of death or a requirement for long-term oxygen therapy and its separate components were estimated with the use of Cox regression models. We tested the assumption of proportional hazards by using cumulative sums of Martingale residual plots and Kolmogorov-type supremum tests.[24] Daily exposure to oxygen or placebo was calculated from the total number of hours recorded on the concentrator counter clock (from initiation of the intervention to its discontinuation) divided by the number of days with receipt of the intervention, with exclusion of the number of days in the hospital or with receipt of short-term oxygen. The mean numbers of exacerbation and hospitalization events per patient-year were compared between groups with the use of a Poisson distribution with overdispersion correction.[25] Linear mixed models were used to examine the effect of the intervention, time, and their interaction on quality-of-life scores. Prespecified subgroup analyses were limited to the examination of the effect of nocturnal oxygen at various thresholds of mean nocturnal saturation. Finally, in a post hoc, per-protocol analysis, we assessed the effect of adherence to nocturnal oxygen therapy using inverse-probability weighting.[26] In this analysis, we estimated a sequential propensity score to reweight patients according to their total time of exposure to oxygen (hours) during the trial. No method of adjustment for multiple comparisons was specified in the protocol. Accordingly, all P values that are reported in the primary analyses are nominal and two-sided. The report of secondary outcomes is limited to point estimates of treatment effects with 95% confidence intervals. The width of the intervals was not adjusted for multiple comparisons.

RESULTS

PATIENTS

From November 2010 through January 2015, a total of 243 patients were enrolled; 123 were randomly assigned to receive nocturnal oxygen and 120 to receive placebo (Fig. 1). Of the 243 patients, 192 (79.0%) met our case definition for nocturnal desaturation on the two oximetry studies obtained at trial entry. No significant between-group differences were observed with respect to baseline characteristics (Table 1 and Table S2). One patient was lost to follow-up after 2.5 years of receiving placebo, and 11 withdrew from the trial during the fourth year and did not consent to final outcome assessment. The primary composite outcome could therefore be ascertained in 242 patients at the 3-year follow-up and in 231 patients (95.1%) at the 4-year follow-

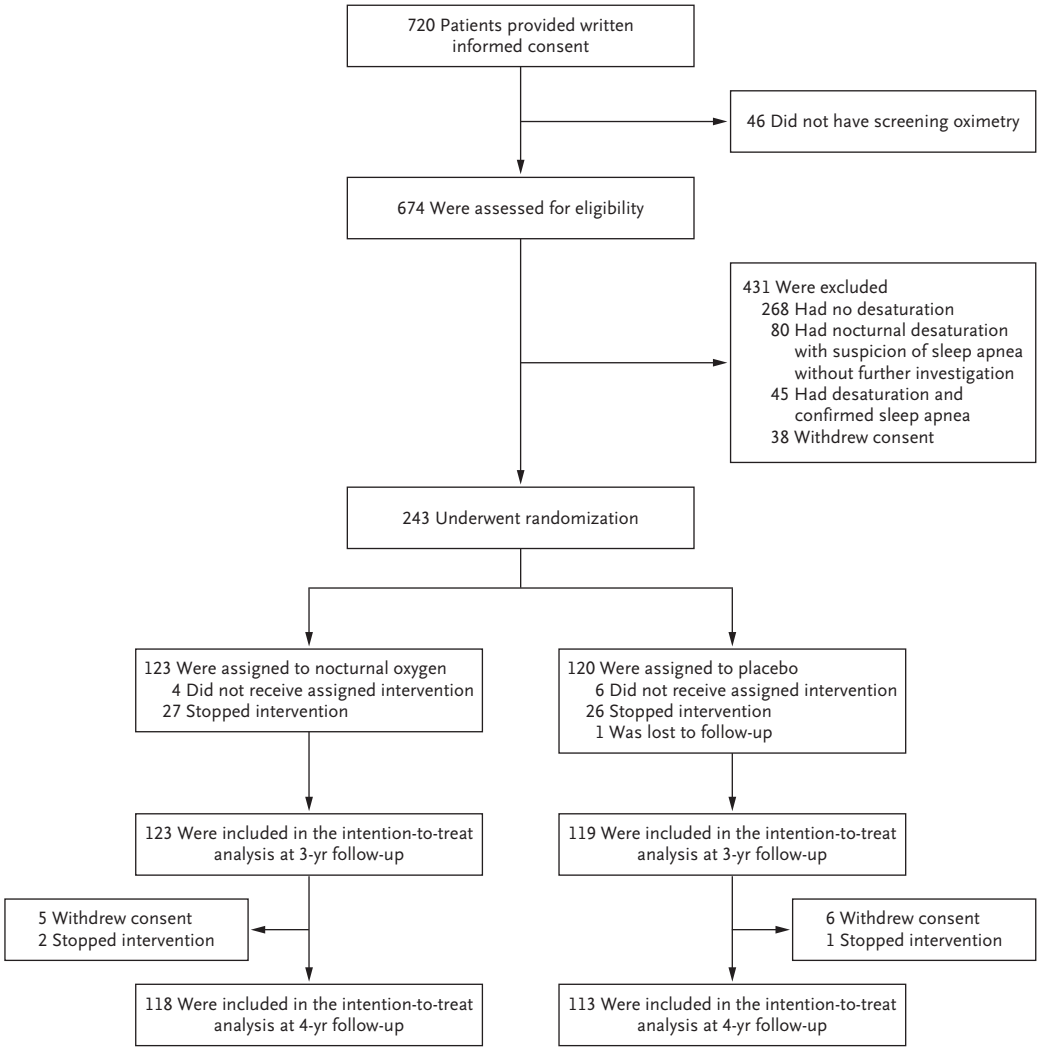

Figure 1. Screening, Randomization, and Follow-up.

up. In accordance with the protocol, none of the patients was a current smoker at trial entry; 12 resumed smoking during the trial (7 in the active-treatment group and 5 in the control group) and were allowed to continue.

OXYGEN FLOW RATE

A total of 10 patients did not receive the assigned intervention (4 in the active-treatment group and 6 in the control group). After adjustment of the oxygen flow rate, 116 of the 119 patients (97.5%) who received oxygen had nocturnal saturation during treatment within the target flow rate; 93 patients (78.2%) were given oxygen at a flow rate of 2 liters per minute (Table S3).

ADHERENCE TO THE INTERVENTION

A total of 53 patients (27 receiving nocturnal oxygen and 26 receiving placebo) discontinued the intervention during the first 3 years of follow-up; 3 additional patients (2 receiving nocturnal oxygen and 1 receiving placebo) discontinued the intervention during the fourth year. While receiving the intervention, patients who were assigned to nocturnal oxygen used their concentrator a mean (±SD) of 7.0±3.5 hours per night,

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Nocturnal Oxygen (N=123)	Placebo (N=120)
Male sex — no. (%)	81 (65.9)	77 (64.2)
Age — yr	69±8	69±9
Body-mass index	26±5	27±6
Charlson comorbidity index†	1.4±0.7	1.4±1.0
Smoking history — pack-yr	58±35	63±39
MRC dyspnea scale score‡	3.3±1.2	3.2±1.0
Lung function		
Postbronchodilator FEV_1 — liters	0.99±0.42	1.04±0.38
FEV_1 — % of predicted value	41±15	42±14
Ratio of FEV_1 to FVC	0.41±0.12	0.42±0.11
DLco — ml/min/mm Hg	12.3±7.8	12.0±7.8
DLco — % of predicted value	57±39	55±32
Inhaled medication — no. (%)		
LABA, LAMA, or both	16 (13.0)	14 (11.7)
Either LABA + glucocorticoid or LAMA + glucocorticoid	6 (4.9)	14 (11.7)
LABA + LAMA + glucocorticoid	101 (82.1)	92 (76.7)
Oral medication — no. (%)		
Glucocorticoid	8 (6.5)	4 (3.3)
Beta-blocker	19 (15.4)	10 (8.3)
Theophylline	13 (10.6)	12 (10.0)
Prophylactic antibiotic	10 (8.1)	10 (8.3)
Arterial blood gas and nocturnal oximetry		
pH	7.42±0.03	7.42±0.03
Pao_2 — mm Hg	67±7	67±7
$Paco_2$ — mm Hg	42±7	41±6
Spo_2 — %	93±2	93±2
Mean nocturnal Spo_2 — %§	89±2	89±2
Percentage of time with nocturnal Spo_2 of <90%	75±23	73±24
Quality of life		
SGRQ total score¶	52±17	52±19
SF-36 score: physical component‖	31±10	32±11
SF-36 score: mental component‖	45±13	45±13

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. DLco denotes diffusing capacity of the lung for carbon monoxide, FEV_1 forced expiratory volume in 1 second, FVC forced vital capacity, LABA long-acting beta-agonist, LAMA long-acting muscarinic antagonist, $Paco_2$ partial pressure of arterial carbon dioxide, Pao_2 partial pressure of arterial oxygen, and Spo_2 oxygen saturation as measured by pulse oximetry.

† The score on the Charlson comorbidity index reflects a weighted sum of 17 medical conditions; scores range from 0 to 37, with higher scores indicating a greater burden of illness and an increased risk of death within 1 year.

‡ Medical Research Council (MRC) dyspnea scale scores range from 1 to 5, with higher scores indicating worse dyspnea.

§ The mean Spo_2 during the recording time (time in bed) was calculated for each patient. Shown here is the mean of the individual means.

¶ Scores on the St. George's Respiratory Questionnaire (SGRQ) range from 0 to 100, with higher scores indicating worse quality of life. The minimal clinically important difference is 4 units. Baseline scores in each of three domains are shown in Table S2 in the Supplementary Appendix.

‖ Scores on the 36-Item Short-Form Health Survey (SF-36) range from 0 to 100, with higher scores indicating better quality of life. The minimal clinically important difference is 10 units. For both the physical component and the mental component, baseline scores in each of four domains are shown in Table S2.

Table 2. Primary Composite Outcome of Death or Requirement for Long-Term Oxygen Therapy (LTOT) and Its Separate Components.*

Outcome	Nocturnal Oxygen	Placebo	Difference (95% CI)†	Hazard Ratio (95% CI)†
			percentage points	
Composite outcome: death or requirement for LTOT‡				
Event at 3 yr of follow-up — no./total no. (%)	48/123 (39.0)	50/119 (42.0)	−3.0 (−15.1 to 9.1)	
Rate per 100 person-yr	16.0	17.8		
Event at 4 yr of follow-up — no./total no. (%)	57/120 (47.5)§	61/113 (54.0)	−6.5 (−18.9 to 5.9)	0.87 (0.61 to 1.25)
Rate per 100 person-yr	15.6	18.1		
Death				
Event at 3 yr of follow-up — no./total no. (%)	21/123 (17.1)	23/119 (19.3)	−2.3 (−11.7 to 7.2)	
Rate per 100 person-yr	6.2	7.1		
Event at 4 yr of follow-up — no./total no. (%)	31/118 (26.3)§	30/113 (26.5)	−0.3 (−11.6 to 11.1)	0.98 (0.60 to 1.63)
Rate per 100 person-yr	7.2	7.3		
Requirement for LTOT				
Event at 3 yr of follow-up — no./total no. (%)	33/123 (26.8)	34/119 (28.6)	−1.7 (−12.8 to 9.4)	
Rate per 100 person-yr	11.0	12.1		
Event at 4 yr of follow-up — no./total no. (%)	40/120 (33.3)§	44/113 (38.9)	−5.6 (−17.5 to 6.2)	0.87 (0.57 to 1.34)
Rate per 100 person-yr	10.9	13.0		

* The total 3-year follow-up was 339.6 person-years in the nocturnal-oxygen group and 323.3 person-years in the placebo group; the total 4-year follow-up was 432.4 person-years and 410.2 person-years in the respective groups. A requirement for LTOT was defined according to the Nocturnal Oxygen Therapy Trial criteria (a Pao_2 of ≤55 mm Hg while the patient was breathing ambient air, or a Pao_2 of 56 to 59 mm Hg with evidence of cor pulmonale or erythrocythemia).
† Confidence intervals were not adjusted for multiple comparisons.
‡ For the composite outcome, any patient who required LTOT and then died was counted only once.
§ Two of the five patients in the nocturnal-oxygen group who withdrew consent after 3 years of follow-up had received LTOT before withdrawal; only their vital status was unknown at 4 years of follow-up.

whereas those who were assigned to placebo used it 6.1±3.2 hours per night (Table S4).

PRIMARY OUTCOME

In the intention-to-treat population at 3 years of follow-up, 39.0% of the patients assigned to nocturnal oxygen (48 of 123) and 42.0% of those assigned to placebo (50 of 119) met the NOTT-defined criteria for long-term oxygen therapy or had died (difference, −3.0 percentage points; 95% confidence interval [CI], −15.1 to 9.1; P=0.64). At 3 years and 4 years of follow-up, the absolute differences between the two trial groups in the percentage of patients with a primary outcome event, the separate component of death, or the separate component of a requirement for long-term oxygen therapy were all no more than 6.5 percentage points (Table 2). Time-to-event analyses indicated no evidence of a significant difference between nocturnal oxygen and placebo in the composite outcome (hazard ratio, 0.87; 95% CI, 0.61 to 1.25; P=0.44) or its separate components of death (hazard ratio, 0.98; 95% CI, 0.60 to 1.63) and a requirement for long-term oxygen therapy (hazard ratio, 0.87; 95% CI, 0.57 to 1.34) (Table 2, Fig. 2, and Fig. S3).

SECONDARY OUTCOMES

We found no evidence of a significant difference between the two groups in the rates of exacerbation and hospitalization (Table 3 and Table S5). We also found no evidence of a significant between-group difference in the change in SGRQ and SF-36 scores over time (Fig. S4 and Tables S6 and S7).

OTHER ANALYSES AND ADVERSE EVENTS

Mean nocturnal oxygen saturation showed little dispersion in the whole sample (Table 1), and clinically meaningful subgroups could not be

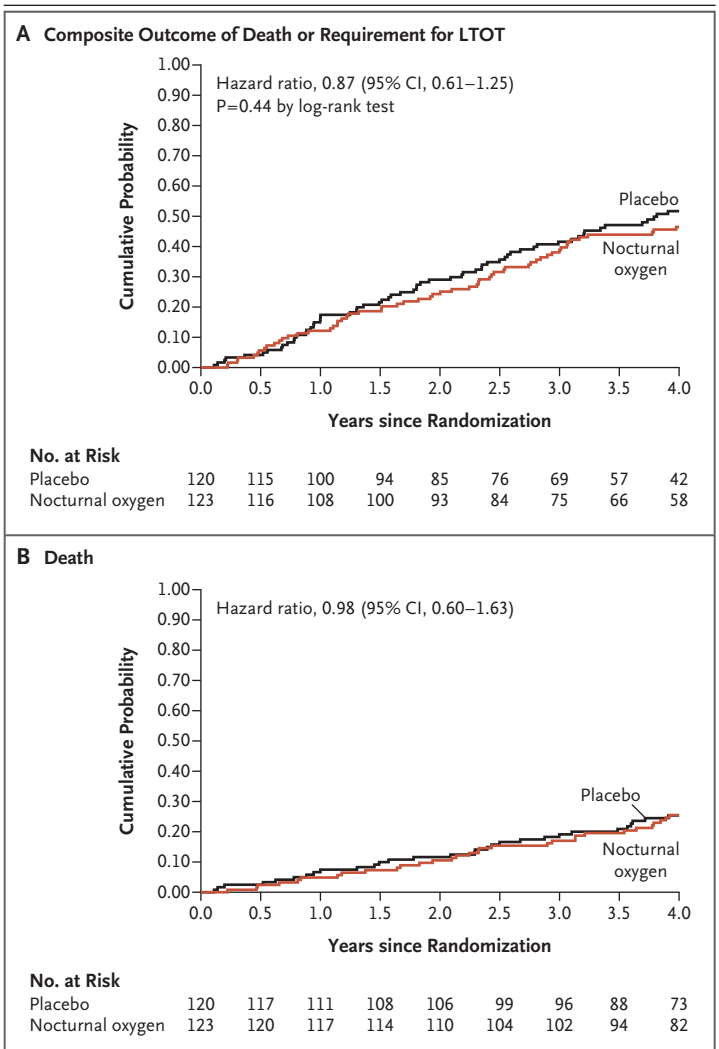

Figure 2. Kaplan–Meier Analyses of the Primary Outcome in the Intention-to-Treat Population.

Panel A shows the results for the composite outcome of death from any cause or a requirement for long-term oxygen therapy (LTOT) according to the Nocturnal Oxygen Therapy Trial criteria. Panel B shows the results for the separate component of death. Data were censored at the date of discontinuation of the intervention or last visit. The results for the separate component of a requirement for LTOT are shown in Figure S3 in the Supplementary Appendix.

defined. Consequently, we did not proceed with the prespecified subgroup analysis according to the severity of nocturnal desaturation. In the per-protocol analysis, the total time of exposure to nocturnal oxygen during the trial did not modify the overall treatment effect on the primary composite outcome (adjusted hazard ratio, 1.02; 95% CI, 0.79 to 1.31). No serious adverse event that was directly attributable to the intervention (including fires or burns) was reported during the trial.

DISCUSSION

Our trial did not show evidence of an effect of nocturnal oxygen therapy on survival or progression to long-term oxygen therapy in patients with COPD with isolated nocturnal oxygen desaturation. Because enrollment in the trial was stopped before we had reached our proposed sample size, the trial was underpowered, with the consequence of a wide confidence interval around the point estimate of the absolute difference in risk between the trial groups at 3 years of follow-up. The data that were accrued could not rule out benefit or harm from nocturnal oxygen and included the minimal clinically important difference determined before the trial. However, nocturnal oxygen had no observed effect on secondary outcomes, including exacerbation and hospitalization rates and quality of life. Furthermore, the duration of exposure to nocturnal oxygen did not modify the overall effect of therapy.

Because our trial did not reach full enrollment, it makes sense to view our results in the context of other results in the field. A systematic review of the effect of home oxygen therapy in patients with COPD with isolated nocturnal desaturation identified two published trials that examined the effect of nocturnal oxygen on survival and progression to long-term oxygen therapy.[27] One was placebo-controlled and used as an enrollment criterion episodic oxygen desaturation; this was associated mainly with REM sleep.[12] The other trial was open-label and defined nocturnal desaturation as we did, as at least 30% of the recording time with an Spo_2 of less than 90%.[13] Both definitions of nocturnal desaturation are associated with increased mortality among patients with COPD.[8] Neither of the two previous trials nor their meta-analysis published in 2005[27] showed evidence of a survival benefit from nocturnal oxygen. We recently updated and complemented this meta-analysis to consider the composite outcome of death or progression to long-term oxygen therapy. Apart from the two studies included in the 2005 meta-

Table 3. Exacerbation and Hospitalization Rates.

Variable	Nocturnal Oxygen	Placebo	Rate Ratio (95% CI)
Total person-yr of follow-up	366.1	340.3	
Acute exacerbations treated at home			
No. of events	473	396	
Rate per person-yr (95% CI)	1.29 (1.07–1.56)	1.16 (0.94–1.43)	1.11 (0.84–1.47)
Hospitalizations for any cause			
No. of events	144	156	
Rate per person-yr (95% CI)	0.39 (0.31–0.50)	0.46 (0.36–0.58)	0.86 (0.61–1.21)
Hospitalizations for respiratory conditions			
No. of events	104	104	
Rate per person-yr (95% CI)	0.28 (0.21–0.37)	0.31 (0.23–0.40)	0.93 (0.64–1.36)

analysis and the INOX trial, we did not uncover any additional published, unpublished, or ongoing trials. When we combined the results of the two previously published trials with those of the INOX trial at 3 years of follow-up, the point estimate was close to null (relative risk, 1.04). However, the 95% confidence interval, 0.81 to 1.34, was still wide. The lower limit of the 95% confidence interval around the pooled measure of effect excluded what we would consider as the minimal clinically important difference. Full details of this updated meta-analysis are provided in the Supplementary Appendix. The consistency of the findings of the INOX trial added to those of the previous trials does not provide evidence to suggest benefit from the use of nocturnal oxygen in patients with COPD and isolated nighttime oxygen desaturation.

These results must also be interpreted in light of recent external evidence. The Long-Term Oxygen Treatment Trial (LOTT) sought to determine whether long-term supplemental oxygen would result in a longer time to death or first hospitalization than no oxygen in patients with moderate resting desaturation or moderate desaturation with exertion only.[28] The intervention in the LOTT did not result in any benefit as indicated by the analysis of the primary composite outcome, its separate components, or any secondary outcomes (including quality of life). Taken together, the INOX trial, the previous trials of nocturnal oxygen for COPD, and the LOTT suggest that a clinically significant benefit from nocturnal oxygen in patients with COPD who do not meet current criteria from long-term oxygen therapy is unlikely.

Our trial has several limitations. The most obvious is that recruitment was terminated prematurely. A second limitation is that adherence to therapy was suboptimal (<100%), thus favoring the null hypothesis in the intention-to-treat population. Nevertheless, post hoc analyses indicated that increased time of exposure to nocturnal oxygen was not associated with better outcomes. Third, our interpretation of the clinical significance of the trial is based on the results of a survey of Canadian pulmonologists.[22] Uncertainty therefore exists in the judgment of the minimal clinically important difference. Fourth, we did not explore the reasons for nonadherence to nocturnal oxygen at the individual level, which limits our understanding and capacity to overcome this problem in the event of future trials.

Home oxygen therapy comes in second place (only after hospitalizations) as the most expensive health care expenditure associated with clinical care for COPD in developed countries.[29] Although the wide confidence intervals around the data do not preclude a benefit of oxygen treatment, the INOX trial and the previous trials considered alone or together do not show the presence of a clear clinical benefit of nocturnal oxygen.

Supported by the Canadian Institutes of Health Research (grant MCT-99512).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

REFERENCES

1. Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Ann Intern Med 1980;93:391-8.
2. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema: report of the Medical Research Council Working Party. Lancet 1981;1:681-6.
3. Chaouat A, Weitzenblum E, Kessler R, et al. Sleep-related O2 desaturation and daytime pulmonary haemodynamics in COPD patients with mild hypoxaemia. Eur Respir J 1997;10:1730-5.
4. Lacasse Y, Sériès F, Vujovic-Zotovic N, et al. Evaluating nocturnal oxygen desaturation in COPD — revised. Respir Med 2011;105:1331-7.
5. Catterall JR, Calverley PM, MacNee W, et al. Mechanism of transient nocturnal hypoxemia in hypoxic chronic bronchitis and emphysema. J Appl Physiol (1985) 1985;59:1698-703.
6. Hudgel DW, Martin RJ, Capehart M, Johnson B, Hill P. Contribution of hypoventilation to sleep oxygen desaturation in chronic obstructive pulmonary disease. J Appl Physiol Respir Environ Exerc Physiol 1983;55:669-77.
7. Becker HF, Piper AJ, Flynn WE, et al. Breathing during sleep in patients with nocturnal desaturation. Am J Respir Crit Care Med 1999;159:112-8.
8. Fletcher EC, Donner CF, Midgren B, et al. Survival in COPD patients with a daytime PaO2 greater than 60 mm Hg with and without nocturnal oxyhemoglobin desaturation. Chest 1992;101:649-55.
9. Sergi M, Rizzi M, Andreoli A, Pecis M, Bruschi C, Fanfulla F. Are COPD patients with nocturnal REM sleep-related desaturations more prone to developing chronic respiratory failure requiring long-term oxygen therapy? Respiration 2002;69:117-22.
10. Macrea MM, Owens RL, Martin T, Smith D, Oursler KK, Malhotra A. The effect of isolated nocturnal oxygen desaturations on serum hs-CRP and IL-6 in patients with chronic obstructive pulmonary disease. Clin Respir J 2019;13:120-4.
11. Joppa P, Petrasova D, Stancak B, Tkacova R. Systemic inflammation in patients with COPD and pulmonary hypertension. Chest 2006;130:326-33.
12. Fletcher EC, Luckett RA, Goodnight-White S, Miller CC, Qian W, Costarangos-Galarza C. A double-blind trial of nocturnal supplemental oxygen for sleep desaturation in patients with chronic obstructive pulmonary disease and a daytime PaO2 above 60 mm Hg. Am Rev Respir Dis 1992;145:1070-6.
13. Chaouat A, Weitzenblum E, Kessler R, et al. A randomized trial of nocturnal oxygen therapy in chronic obstructive pulmonary disease patients. Eur Respir J 1999;14:1002-8.
14. Orth M, Walther JW, Yalzin S, et al. Influence of nocturnal oxygen therapy on quality of life in patients with COPD and isolated sleep-related hypoxemia: a prospective, placebo-controlled cross-over trial. Pneumologie 2008;62:11-6. (In German.)
15. Lacasse Y, Bernard S, Sériès F, et al. Multi-center, randomized, placebo-controlled trial of nocturnal oxygen therapy in chronic obstructive pulmonary disease: a study protocol for the INOX trial. BMC Pulm Med 2017;17:8.
16. DAMOCLES Study Group, NHS Health Technology Assessment Programme. A proposed charter for clinical trial data monitoring committees: helping them to do their job well. Lancet 2005;365:711-22.
17. Hosselet J, Ayappa I, Norman RG, Krieger AC, Rapoport DM. Classification of sleep-disordered breathing. Am J Respir Crit Care Med 2001;163:398-405.
18. Levi-Valensi P, Weitzenblum E, Rida Z, et al. Sleep-related oxygen desaturation and daytime pulmonary haemodynamics in COPD patients. Eur Respir J 1992;5:301-7.
19. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83.
20. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation: the St. George's Respiratory Questionnaire. Am Rev Respir Dis 1992;145:1321-7.
21. McHorney CA, Ware JE Jr, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care 1993;31:247-63.
22. Lacasse Y, Sériès F, Martin S, Maltais F. Nocturnal oxygen therapy in patients with chronic obstructive pulmonary disease: a survey of Canadian respirologists. Can Respir J 2007;14:343-8.
23. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496-509.
24. Lin DY, Wei IJ, Ying Z. Checking the Cox model with cumulative sums of martingale-based residuals. Biometrika 1993;80:557-72.
25. Aaron SD, Fergusson D, Marks GB, et al. Counting, analysing and reporting exacerbations of COPD in randomised controlled trials. Thorax 2008;63:122-8.
26. Hernán MA, Robins JM. Per-protocol analyses of pragmatic trials. N Engl J Med 2017;377:1391-8.
27. Cranston JM, Crockett AJ, Moss JR, Alpers JH. Domiciliary oxygen for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2005;4:CD001744.
28. The Long-Term Oxygen Treatment Trial Research Group. A randomized trial of long-term oxygen for COPD with moderate desaturation. N Engl J Med 2016;375:1617-27.
29. Foo J, Landis SH, Maskell J, et al. Continuing to confront COPD international patient survey: economic impact of COPD in 12 countries. PLoS One 2016;11(4):e0152618.