THE THERAPEUTIC ADMINISTRATION OF OXYGEN.

By J. S. HALDANE, M.D., F.R.S.,
OXFORD.

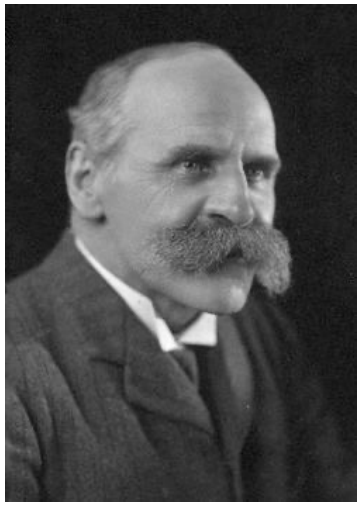
It is well known that the administration of oxygen often produces at least temporary benefit in cases of serious interference with the respiratory or circulatory functions; but sufficient attention has not hitherto been paid either to what precise benefit may be expected from the administration of oxygen, or to how it can best be administered. In the present paper I propose to discuss both these questions in the light of existing physiological knowledge, and to describe an apparatus designed for the clinical administration of oxygen.

Our knowledge of the physiology of respiration has advanced very rapidly within the last few years, and certain points which have been elucidated in this advance must first be referred to. Under normal conditions the breathing is so regulated as to keep the mean percentage of CO_2 in the air of the lung alveoli practically constant at a level which varies slightly for different individuals, but is about 5.6 per cent. The marvellous accuracy of this regulation was a revelation to physiology. A rise of about 0.2 per cent. in the mean alveolar CO_2 percentage doubles the amount of air taken into the lungs, while a fall of 0.2 per cent. produces apnoea. The rise in CO_2 acts through the blood on the respiratory centre in virtue of the very minute decrease in alkalinity which it causes; and the regulation of the blood alkalinity by the respiratory centre, kidneys, liver, and probably other organs, is so exact that no existing chemical or physical method of measuring variations in "reaction" (hydrogen ion concentration) can detect the more minute changes to which these organs are constantly reacting. For the present purpose it is, however, sufficient to remark that changes in the amount of air breathed are, under ordinary conditions, almost entirely dependent on the amount, not of oxygen, but of CO_2 in the blood leaving the lungs, and consequently passing to the respiratory centre. By reducing the CO_2 in the arterial blood apnoea can easily be produced in a person blue in the face from want of oxygen; and an animal from the blood of which sufficient CO_2 has been removed by forcible artificial respiration is not only apnoeic for a time, but will die from want of oxygen without drawing a single breath.

reaction (which is less readily produced in some persons than in others) the percentage, or rather the partial pressure, of oxygen in the alveolar air or blood supplying the respiratory centre must, however, fall below normal limits. At high altitudes, or in air with a greatly reduced oxygen percentage, the necessary reduction in the alveolar oxygen pressure occurs quite easily, and periodic breathing is a normal occurrence, which is stopped at once by increasing the oxygen percentage in the air breathed, just as Cheyne-Stokes breathing in a patient is stopped by administering oxygen. Periodic breathing, which is a sign of impending oxygen want, is simply the "hunting" of a too quickly acting respiratory governor, which is constantly overshooting the mark.

As already remarked, the initial hyperpnoea produced by rapid onset of oxygen want is soon relieved by the consequent washing out of CO_2 from the blood, provided that this washing out is free to occur. If not, the hyperpnoea will continue, even in spite of relief of the far more dangerous symptoms of oxygen want. Great hyperpnoea accompanied by oxygen want is characterized by marked rise in pulse-rate, palpitation, great rise in arterial blood pressure, and, what is still more remarkable, a simultaneous great rise in venous blood pressure. The latter phenomenon is indicated by distension of the lips, face, tongue, etc., with blue venous blood, distension of superficial veins in the neck and chest, and the other signs of "acute" cyanosis. The high venous blood pressure is very apt to lead to over-distension of the right side of the heart and consequent paralysis of the heart and death. For this reason, free venesection may be of the greatest service in conditions of acute cyanosis. The great and immediate benefit arising from free venesection in acute asphyxial conditions arising from irritant gas poisoning was, so far as I am aware, first pointed out by Drs. Irvine and Macaulay of Johannesburg, and was also independently observed by Dr. Hale White in a case brought to Guy's Hospital. In consequence of their experience, the utility of this mode of treatment in cases of acute cyanosis from chlorine poisoning was pointed out in France, and its success was recorded recently by Captain S. Hebblethwaite, R.A.M.C.[1]

If the washing out of CO_2 in the lungs is not interfered with, "acute" cyanosis and hyperpnoea do not occur at all, or are only temporary. The other effects of oxygen want then become more and more prominent. The lips become of a leaden or grey, rather than blue, colour, since they are not distended with blood. Sensibility, mental control, and memory begin to fail rapidly. At a further



1917:
John Scott Haldane descrive il potenziale terapeutico della somministrazione di ossigeno supplementare

Haldane JS. The therapeutic administration of oxygen. BMJ 1917;1:181–183.

Long-term oxygen therapy, the first intervention that was shown to improve survival in patients with both severe hypoxemia and chronic obstructive pulmonary disease (COPD), had an effect size so large that data from fewer than 300 patients were all that was needed to establish its efficacy.

N Engl J Med 391;11 nejm.org September 19, 2024

Evidence Supporting a Reduction in Mortality with Pharmacotherapy and Non-pharmacotherapy in COPD Patients

Figure 3.19

Therapy	RCT*	Treatment effect on mortality	Patient characteristics
Pharmacotherapy			
LABA+LAMA+ICS[1]	Yes	Single inhaler triple therapy compared to dual LABD therapy relative risk reduction: IMPACT: HR 0.72 (95% CI: 0.53, 0.99)[1a] ETHOS: HR 0.51 (95% CI: 0.33, 0.80)[1b]	Symptomatic people with a history of frequent and/or severe exacerbations
Non-pharmacological Therapy			
Smoking cessation[2]	Yes	HR for usual care group compared to intervention group (smoking cessation) HR 1.18 (95% CI: 1.02, 1.37)[2]	Asymptomatic or mildly symptomatic
Pulmonary rehabilitation[3#]	Yes	Old trials: RR 0.28 (95% CI 0.10, 0.84)[3a] New trials: RR 0.68 (95% CI 0.28, 1.67)[3b]	Hospitalized for exacerbations of COPD (during or ≤ 4 weeks after discharge)
Long-term oxygen therapy[4]	Yes	NOTT: ≥ 19 hours of continuous oxygen vs ≤ 13 hours: 50% reduction[4a] MRC: ≥ 15 hours vs no oxygen: 50% reduction[4b]	PaO_2 ≤ 55 mmHg or < 60 mmHg with *cor pulmonale* or secondary polycythemia
Noninvasive positive pressure ventilation[5]	Yes	12% in NPPV (high IPAP level) and 33% in control HR 0.24 (95% CI 0.11, 0.49)[5]	Stable COPD with marked hypercapnia
Lung volume reduction surgery[6]	Yes	0.07 deaths/person-year (LVRS) vs 0.15 deaths/person-year (UC) RR for death 0.47 (p = 0.005)[6]	Upper lobe emphysema and low exercise capacity

*RCT with pre-specified analysis of the mortality outcome (primary or secondary outcome); #Inconclusive results likely due to differences in pulmonary rehabilitation across a wide range of participants and settings.

1. a) IMPACT trial (Lipson et al. 2020) and b) ETHOS trials (Martinez et al. 2021); 2.Lung Health Study (Anthonisen et al. 2005); 3. a) Puhan et al. (2011) and b) Puhan et al. 2016; 4. a) NOTT (NOTT, 1980) and b) MRC (MRC, 1981); 5. Kohlein trial (Kohlein et al. 2014); 6. NETT trial (Fishman et al. 2003)

ICS: inhaled corticosteroid; IPAP: inspiratory positive airway pressure; LABA: long-acting beta$_2$-agonist; LABD: long-acting bronchodilator; LAMA: long-acting muscarinic antagonist; LTOT: long-term oxygen therapy; NPPV: noninvasive positive pressure ventilation; LVRS: lung volume reduction surgery; UC: usual treatment control group.

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… two small trials, performed more than 45 years ago, are the basis on which multiple professional societies and medical policy makers around the world recommend the use of long-term oxygen therapy for at least 15 hours per day in patients with severe resting hypoxemia.

N Engl J Med 391;11 nejm.org September 19, 2024

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.

In the **Nocturnal Oxygen Therapy Trial (NOTT)**, performed in North America, 203 patients with COPD and severe hypoxemia were randomly assigned to receive continuous oxygen supplementation (24 hours per day) or nocturnal oxygen therapy for 12 hours per day

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.

In another trial, which was conducted by the **U.K. Medical Research Council (MRC)**, 15 hours per day of oxygen therapy was compared with no supplemental oxygen in 87 such patients.

Table 1. Randomized Trials of Long-Term Oxygen Therapy in Chronic Obstructive Pulmonary Disease

Study	Inclusion Criteria	Intervention/Comparator	Primary Outcome	Main Results
Severe hypoxemia				
NOTT (3)	203 patients with COPD and Pa_{O_2} ≤55 mm Hg, or Pa_{O_2} ≤59 mm Hg with one of the following: *1*) edema, *2*) hematocrit ≥55%, or *3*) P pulmonale on ECG: 3 mm in leads II, III, aVF	Continuous oxygen ($n = 101$) vs. nocturnal oxygen ($n = 102$); frequent home and outpatient visits for both groups	Survival; adherence was monitored	At 2-yr follow-up, the overall mortality of those receiving continuous oxygen was 22.4%, whereas it was 40.8% among those receiving nocturnal oxygen ($P = 0.01$).
MRC (2)	87 patients <70 yr, FEV_1 <1.2 L, Pa_{O_2} between 40 and 60 mm Hg	Oxygen for ≥15 h/d ($n = 42$) vs. usual care ($n = 45$); some home visits and frequent outpatient visits in both groups	Survival; adherence was not monitored	At 5-yr follow-up, 19 (45%) of 42 patients receiving oxygen therapy had died, compared with 30 (66%) of the 45 control patients.

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Am J Respir Crit Care Med Vol 197, Iss 10, pp 1254–1264, May 15, 2018

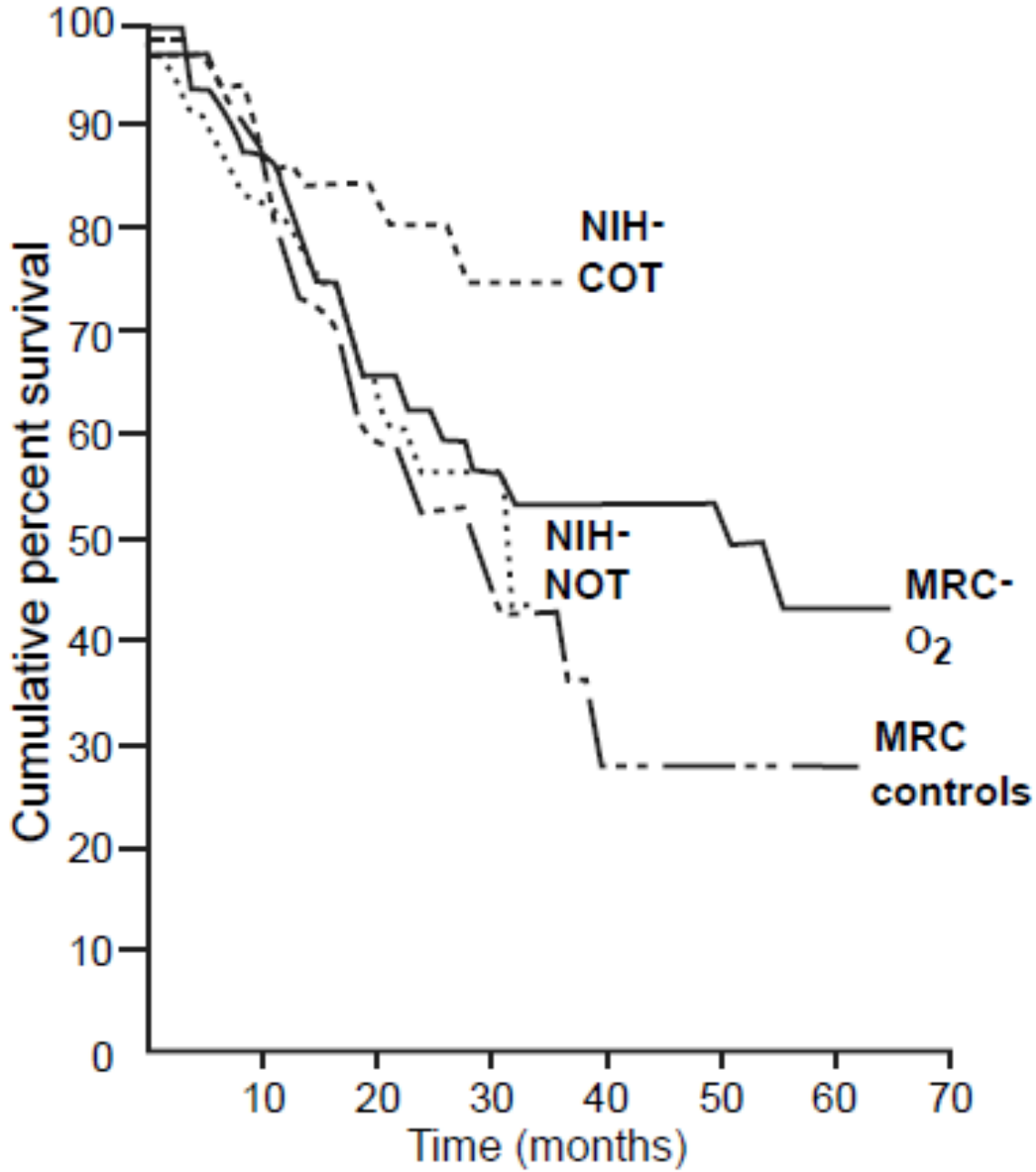
Cumulative percent survival
100
90
80
70
60
50
40
30
20
10
0
10
20
30
40
50
60
70
Time (months)
NIH-
COT
NIH-
NOT
MRC-
O2
MRC
controls

Table 1 Indications for LTOT in COPD (Cooper 1993)

UNITED STATES

$PaO_2 < 55$ mmHg or $SaO_2 < 88\%$ (room air)

PaO_2 56–59 mmHg or SaO_2 89%–90%, with (one or more)

Pulmonary hypertension

Evidence of cor pulmonale or edema due to heart failure

Elevated hematocrit (>56%)

UNITED KINGDOM

1. COPD ($FEV_1 < 1.5$ L, $FVC < 2.0$ L), hypoxemia ($PaO_2 < 55$ mmHg), hypercapnia ($PaCO_2 > 45$ mmHg), and edema. Stability demonstrated over 3 weeks
2. As in 1 but without edema or $PaCO_2 > 45$ mmHg
   Palliative therapy may be prescribed

EUROPE

1. $PaO_2 < 55$ mmHg, steady-state COPD
2. PaO_2 55–65 mmHg with (one or more)

Pulmonary hypertension

Evidence of cor pulmonale or edema due to heart failure

Elevated hematocrit (>56%)

Restrictive disease with $PaO_2 < 55$ mmHg

AUSTRALIA

1. $PaO_2 < 56$ mmHg, COPD, Right ventricular hypertrophy, polycythemia, and edema
2. Desaturation <90% on exercise
3. Refractory dyspnea associated with cardiac failure

International Journal of COPD 2008:3(2) 231–237

Terminology of Home Oxygen Therapy

Ambulatory oxygen: Oxygen delivered during exercise or activities of daily living when the individual is walking freely.

Continuous flow oxygen: Oxygen delivered at a constant rate, regardless of the respiratory rate. Continuous flow oxygen is in contrast to pulse-dose oxygen (*see below*).

Continuous oxygen: Oxygen prescribed for 24 h/d.

Home oxygen: Oxygen delivered in a home. Also known as *domiciliary oxygen*. It includes not only long-term oxygen but also short-term, nocturnal, palliative, ambulatory, and short-burst oxygen. It excludes oxygen use in healthcare and emergency settings.

Long-term oxygen: Oxygen delivered to patients with chronic hypoxemia, in most cases for the remainder of the patient's life. Long-term oxygen therapy is usually prescribed for at least 15–18 h/d.

Nocturnal oxygen: Oxygen delivered during sleep time only.

Palliative oxygen: Oxygen to relieve dyspnea. Palliative oxygen may be provided as continuous or nocturnal oxygen or during ambulation. Short-burst oxygen therapy falls into this category.

Portable oxygen: Oxygen delivered through systems that are light and can be carried by patients to allow them to leave their home (e.g., oxygen cylinders carried in trolleys or transportable concentrators).

Pulse-dose oxygen: Oxygen delivered during inspiration only in such a way that the quantity of oxygen administered is influenced by the respiratory rate. The delivery system is at rest while the patient is exhaling.

Short-burst oxygen: Brief and intermittent oxygen administration before and/or after exercise, generally used as needed, in the absence of known hypoxemia.

Short-term oxygen: Oxygen provided temporarily during a period of severe hypoxemia (e.g., during the course of and shortly after an exacerbation of chronic obstructive pulmonary disease).

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Home Oxygen Therapy for Adults with Chronic Lung Disease
An Official American Thoracic Society Clinical Practice Guideline
American Journal of Respiratory and Critical Care Medicine Volume 202 Number 10 | November 15 2020

British Thoracic Society guidelines for home oxygen use in adults

Maxine Hardinge,[1] Joe Annandale,[2] Simon Bourne,[3] Brendan Cooper,[4] Angela Evans,[5] Daryl Freeman,[6] Angela Green,[7] Sabrine Hippolyte,[8] Vikki Knowles,[9] William MacNee,[10] Lynn McDonnell,[11] Kathy Pye,[12] Jay Suntharalingam,[13] Vandana Vora,[14] Tom Wilkinson,[15] British Thoracic Society Home Oxygen Guideline Development Group, on behalf of the British Thoracic Society Standards of Care Committee

Thorax 2015;70:i1–i43.

AMERICAN THORACIC SOCIETY DOCUMENTS

Home Oxygen Therapy for Adults with Chronic Lung Disease

An Official American Thoracic Society Clinical Practice Guideline

Susan S. Jacobs, Jerry A. Krishnan, David J. Lederer, Marya Ghazipura, Tanzib Hossain, Ai-Yui M. Tan, Brian Carlin, M. Bradley Drummond, Magnus Ekström, Chris Garvey, Bridget A. Graney, Beverly Jackson, Thomas Kallstrom, Shandra L. Knight, Kathleen Lindell, Valentin Prieto-Centurion, Elisabetta A. Renzoni, Christopher J. Ryerson, Ann Schneidman, Jeffrey Swigris, Dona Upson, and Anne E. Holland; on behalf of the American Thoracic Society Assembly on Nursing

This official clinical practice guideline of the American Thoracic Society was approved September 2020

Am J Respir Crit Care Med Vol 202, Iss 10, pp e121–e141, Nov 15, 2020

Severe chronic resting room air hypoxemia

Severe resting hypoxemia was defined as a PaO2<55 mm Hg (7.3 kPa) or a PaO2<59 mm Hg (7.9 kPa) plus one of the following: edema, hematocrit>55%, or P pulmonale on ECG in the NOTT (Nocturnal Oxygen Therapy Trial) (Ann Intern Med 1980;93:391–398.);
or was defined as a PaO2 of 40–60 mm Hg (5.3–8.0 kPa) in patients with at least one prior episode of ankle edema in the MRC (Medical Research Council) study (Lancet 1981;1:681–686.).

In the pre- versus postintervention study, eligibility criteria were not reported; participants (n=6) had a PaO2 of 41.5–46.5 mm Hg (5.5–6.2 kPa) (Ann Intern Med 1967;66:639–650.).

The observational studies enrolled individuals with a PaO2<55 mm Hg (7.3 kPa) (Rehabil Nurs 2017;42:268–273., Monaldi Arch Chest Dis 1993;48:445–446.).

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Severe chronic resting room air hypoxemia

1) $PaO_2 \leq 55$ mm Hg (7.3 kPa) o $SpO_2 \leq 88\%$.

2) PaO2 = 56–59 mm Hg (7.5–7.9 kPa) or SpO_2 = 89% più una delle seguenti condizioni cliniche: edema, ematocrito ≥ 55%, o P pulmonale all'ECG.

Moderate chronic resting room air hypoxemia

E' così definita se presente una SpO_2 89–93%.

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Severe chronic resting room air hypoxemia

ATS recommendation.

In adults with COPD who have severe chronic resting room air hypoxemia, we recommend prescribing LTOT for at least 15 h/d (strong recommendation, moderate-quality evidence).

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Oxygen Therapy and Ventilatory Support in Stable COPD

Figure 3.17

Oxygen Therapy	• The long-term administration of oxygen increases survival in patients with severe chronic resting arterial hypoxemia **(Evidence A)** • In patients with stable COPD and moderate resting or exercise-induced arterial desaturation, prescription of long-term oxygen does not lengthen time to death or first hospitalization or provide sustained benefit in health status, lung function and 6-minute walk distance **(Evidence A)** • Sufficient resting oxygenation at sea level does not exclude the development of severe hypoxemia when traveling by air **(Evidence C)**
Ventilatory Support	• NPPV may improve hospitalization-free survival in selected patients after recent hospitalization, particularly in those with pronounced daytime persistent hypercapnia ($PaCO_2$ > 53 mmHg) **(Evidence B)** • In patients with severe chronic hypercapnia and a history of hospitalization for acute respiratory failure, long-term noninvasive ventilation may be considered **(Evidence B)**

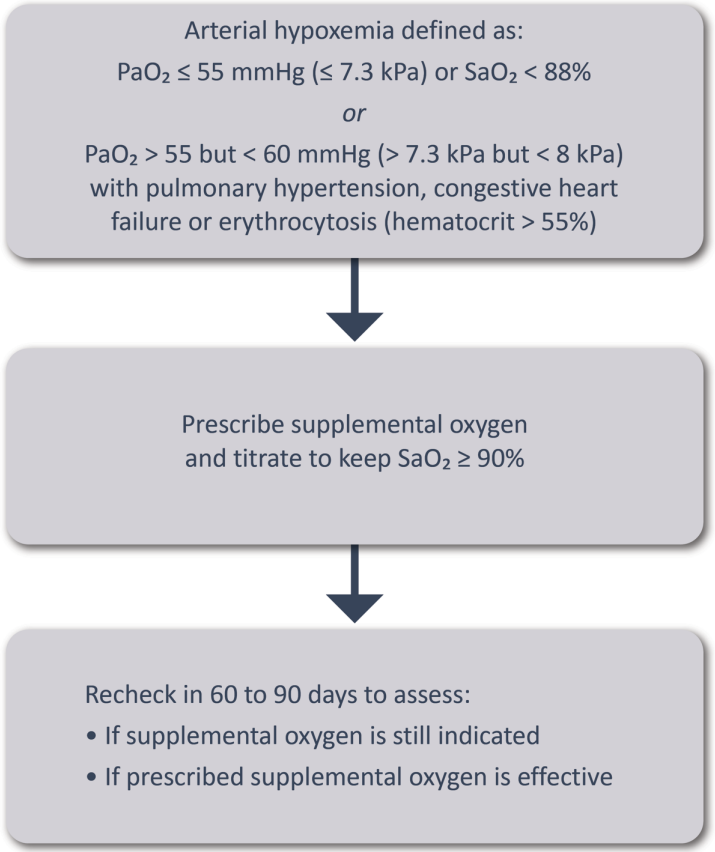
Proper reassessment of home oxygen needs

It is so important that it has been identified as one of the top five areas for further improvement in adult respiratory medicine.

Patients who commence LTOT after a COPD exacerbation should be reassessed 4–8 weeks after hospital discharge to ensure continued eligibility (Respirology 2016;21:76–78.).
In patients prescribed home oxygen for severe chronic resting room air hypoxemia, the GOLD initiative recommends reassessing the need for oxygen after 60–90 days; when home oxygen is started to treat severe hypoxemia after a COPD exacerbation, the GOLD initiative recommends reassessing the home oxygen requirement.
Ideally, reevaluation should occur at home to capture context and barriers to use.
Expert opinion suggests that patients should be monitored, at minimum, every 6 months to confirm continued oxygen use, a current oxygen prescription, and adequacy of the equipment used.

Prescription of Supplemental Oxygen to Patients with COPD

Figure 3.18



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Discharge Criteria and Recommendations for Follow-up

Figure 4.10

1. Full review of all clinical and laboratory data
2. Check maintenance therapy (see **Figure 3.9**, patients with elevated blood eosinophils should be discharged on LABA+LAMA+ICS)
3. Reassess inhaler technique
4. Ensure understanding of withdrawal of acute medications (steroids and/or antibiotics)
5. Assess need for continuing supplemental oxygen
6. Provide management plan
7. Follow-up comorbidities such as cardiovascular disease
8. Ensure follow-up arrangements: early follow-up < 4 weeks, and late follow-up > 12 weeks as indicated

1 – 4 Weeks Follow-up

- Evaluate ability to cope in his/her usual environment
- Review understanding of treatment regimen
- Reassessment of inhaler techniques
- Reassess need for long-term oxygen
- Document the capacity to do physical activity and consider patient eligibility to be enrolled in pulmonary rehabilitation
- Document symptoms: CAAT™ or mMRC
- Determine status of comorbidities

12 – 16 Weeks Follow-up

- Evaluate ability to cope in his/her usual environment
- Review understanding of treatment regimen
- Reassessment of inhaler techniques
- Reassess need for long-term oxygen
- Document the capacity to do physical activity and activities of daily living
- Measure spirometry: FEV1
- Document symptoms: CAAT™ or mMRC
- Determine status of comorbidities

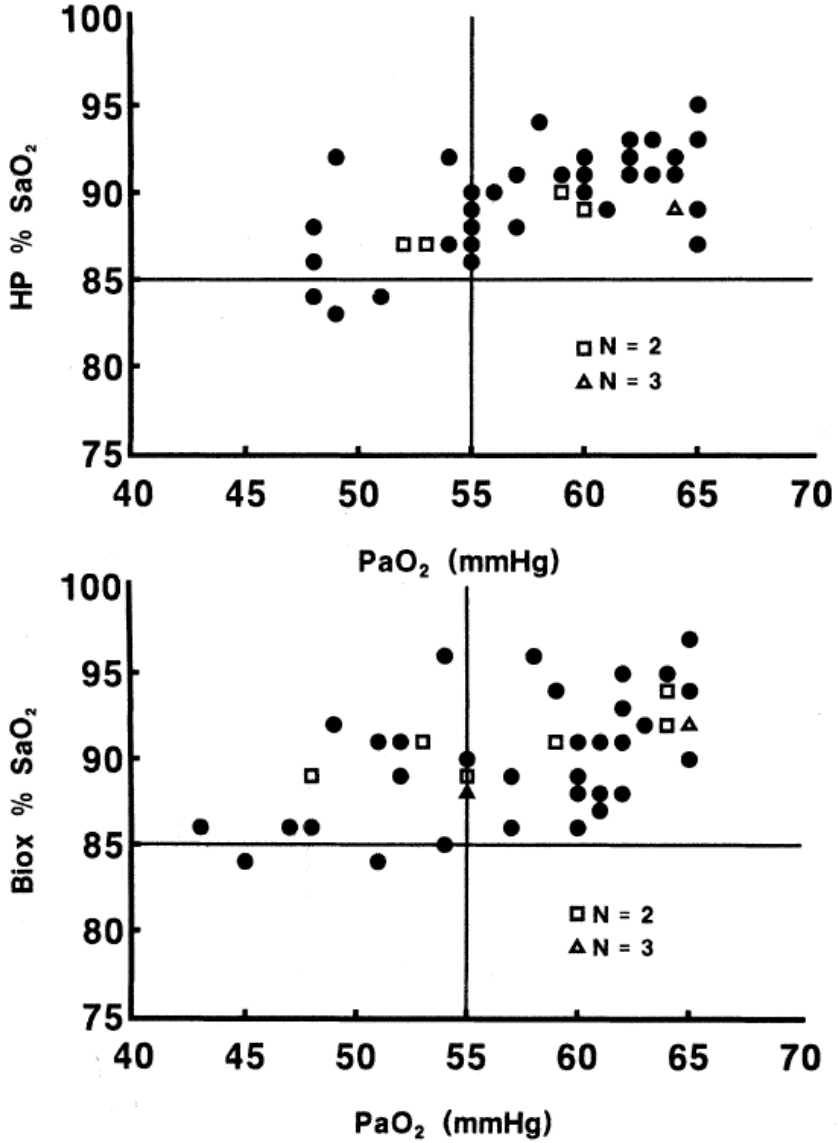

FIGURE. The relationship between resting arterial oxygen tension (PaO_2) and arterial oxygen saturation (SaO_2) measured by a Hewlett-Packard HP 47201A (top) or a Biox IIA (bottom) ear oximeter. *Solid lines* (PaO_2 7.33 kPa [55 mm Hg], SaO_2 85 percent) represent current Medicare criteria for long-term oxygen therapy prescription. ● = n = 1.

The Use of Cutaneous Oximetry in the Prescription of Long-term Oxygen Therapy*

Brian W. Carlin, M.D.;† Jack L. Clausen, M.D.; and Andrew L. Ries, M.D., F.C.C.P.

CHEST / 94 / 2 / AUGUST, 1988

In summary based on the results of this study, we conclude that cutaneous oximetry measurements currently cannot be substituted equivalently for measurements of Pa02 for decisions regarding initiation of long-term oxygen therapy.

Cutaneous oximetry may be useful for screening; if the Sa02 is less than 85 percent with the patient at rest, then the need for direct measurement of Pa02 is obviated. Additional studies are needed to explore the other potential roles for cutaneous oximetry in identifying patients likely to benefit from ambulatory oxygen therapy;

Eur Respir J 2008; 32: 1053–1059
DOI: 10.1183/09031936.00126507

Accuracy and reliability of pulse oximetry at different arterial carbon dioxide pressure levels

X. Muñoz*,#,¶,§, F. Torres+,§, G. Sampol*,¶, J. Rios+, S. Martí*,¶ and E. Escrich#

In conclusion,
in a heterogeneous group of patients with advanced respiratory disease, the present authors report that carbon dioxide arterial tension status can impair the agreement between arterial oxygen saturation and arterial oxygen saturation measured by pulse oximetry, particularly in patients with hypercapnia. In addition, the present results in a large number of paired samples show that agreement between arterial oxygen saturation and arterial oxygen saturation measure by pulse oximetry worsens as hypoxaemia values decrease. Therefore, it is likely that arterial oxygen saturation measured by oximetry may not be sufficiently accurate when assessing patients for long-term home oxygen therapy and should not substitute the gold standard arterial oxygen tension measured in arterial blood.

Eur Respir J 2008; 32: 1053–1059

Moderate chronic resting room air hypoxemia

The LOTT study defined moderate hypoxemia at rest on the basis of room air SpO2 of 89–93% (no PaO2 threshold specified) and desaturation only on exertion on the basis of SpO2>80% for >5 min and ,90% for >10 s during a 6-min-walk test .

Gorecka study (Thorax 1997;52:674–679) defined moderate hypoxemia on the basis of PaO2 of 56–65 mm Hg (no SpO2 thresholds specified)

Table 1. Randomized Trials of Long-Term Oxygen Therapy in Chronic Obstructive Pulmonary Disease

Study	Inclusion Criteria	Intervention/Comparator	Primary Outcome	Main Results
Moderate hypoxemia				
Górecka *et al.* (12)	135 patients aged 40–80 yr, Pa_{O_2} 56–65 mm Hg	Oxygen for ⩾17 h/d ($n = 68$) vs. usual care ($n = 67$)	Survival; adherence was monitored	Cumulative survival rates were 88%, 77%, and 66% at 1-, 2-, and 3-yr follow-up, respectively. No significant difference in survival rates was seen between those receiving LTOT and control subjects.
Haidl *et al.* (13)	28 patients with COPD and moderate hypoxemia (Pa_{O_2} at rest >55 mm Hg) and reversible hypercapnia during the course of an exacerbation (Pco_2 ⩽45 mm Hg at hospital discharge)	Oxygen for ⩾15 h/d ($n = 14$) vs. usual care ($n = 14$)	Endurance time (cycle ergometry); survival; adherence was monitored	At 1-yr follow-up, endurance time was improved among those receiving LTOT (7.1 vs. 4.9 min; $P = 0.04$); at 3 yr follow-up, four patients receiving LTOT had died, compared with three control subjects.
LOTT (14)	738 patients with COPD and moderate resting desaturation (Sp_{O_2}, 89–93%) or moderate exercise–induced desaturation (during 6MWT, Sp_{O_2} ⩾80% for ⩾5 min and <90% for ⩾10 s)	Continuous oxygen (or oxygen only during sleep and exercise in those with exercise-induced desaturation only) ($n = 368$) vs. usual care ($n = 370$)	Composite outcome of time to death or first hospitalization; compliance was monitored	Supplemental oxygen did not result in a longer time until death or first hospitalization than no long-term supplemental oxygen.

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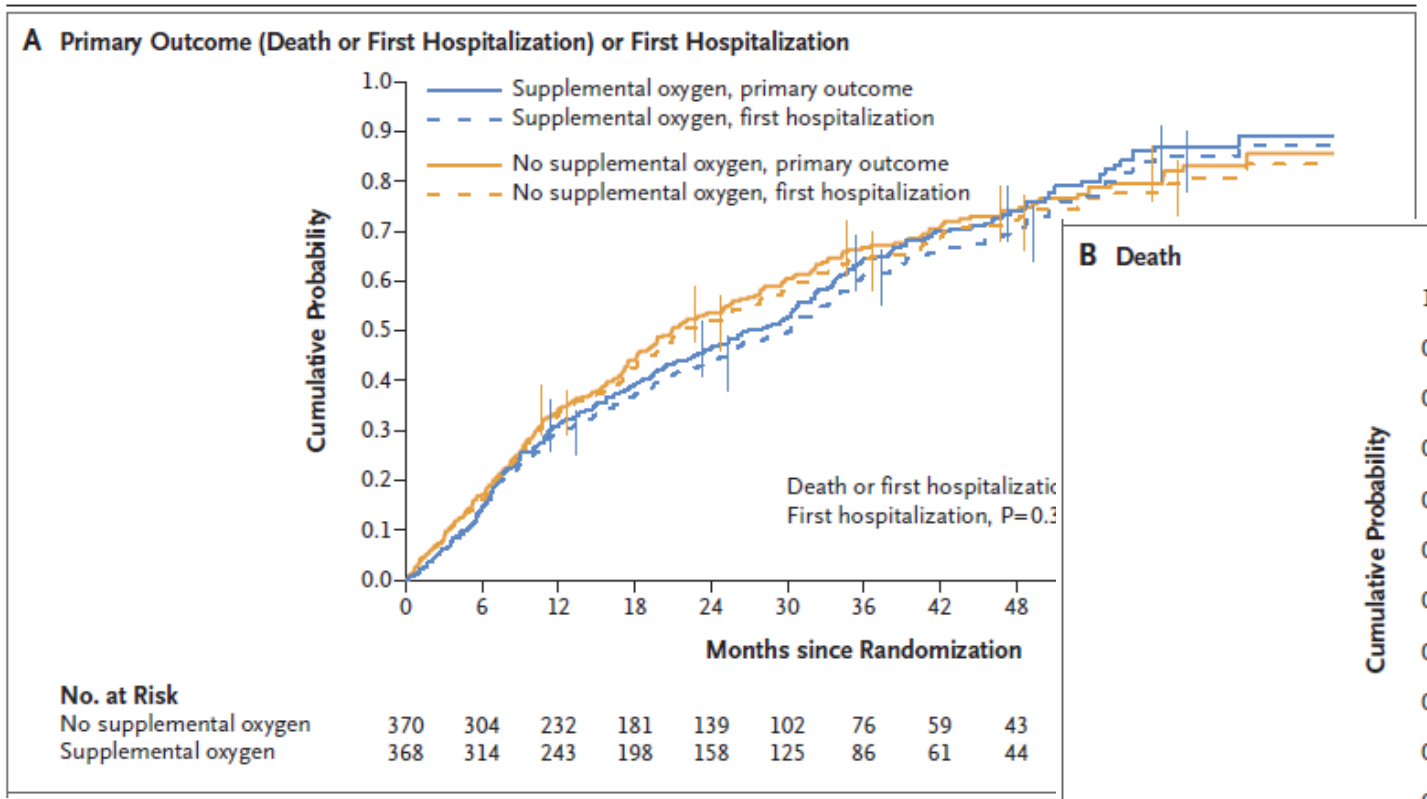
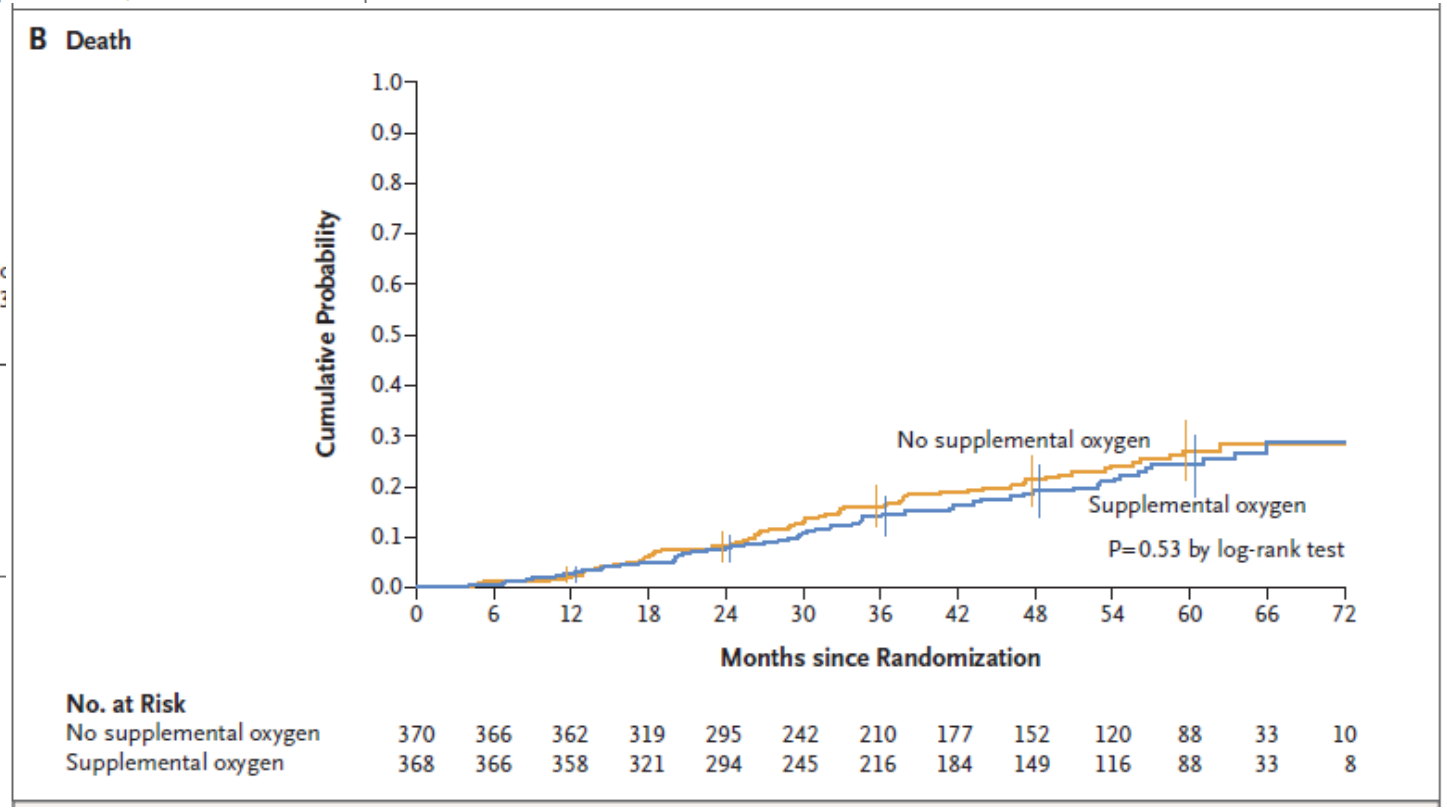
A Randomized Trial of Long-Term Oxygen for COPD with Moderate Desaturation

The Long-Term Oxygen Treatment Trial Research Group*

The Long-Term Oxygen Treatment Trial (LOTT)





N Engl J Med 2016;375:1617-27.

A Randomized Trial of Long-Term Oxygen for COPD with Moderate Desaturation

The Long-Term Oxygen Treatment Trial Research Group*

The Long-Term Oxygen Treatment Trial (LOTT)

Table 2. Primary Composite Outcome of Death or First Hospitalization for Any Cause and Composite Events in the Intention-to-Treat Population.*

Outcome	No Supplemental Oxygen (N=370)	Supplemental Oxygen (N=368)	Hazard Ratio (95% CI)	P Value
Primary outcome				
Death or first hospitalization for any cause			0.94 (0.79–1.12)	0.52
No. of events	250	248		
Composite rate per 100 person-yr	36.4	34.2		
Primary-outcome component events				
Death			0.90 (0.64–1.25)	0.53
No. of deaths	73	66		
Rate per 100 person-yr	5.7	5.2		
First hospitalization for any cause			0.92 (0.77–1.10)	0.37
No. of first hospitalizations	237	229		
Rate per 100 person-yr	34.5	31.6		

N Engl J Med 2016;375:1617-27.

Moderate chronic resting room air hypoxemia

ATS recommendation.

In adults with COPD who have moderate chronic resting room air hypoxemia, we suggest not prescribing LTOT (conditional recommendation, low-quality evidence).

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Oxygen Therapy and Ventilatory Support in Stable COPD

Figure 3.17

Oxygen Therapy	• The long-term administration of oxygen increases survival in patients with severe chronic resting arterial hypoxemia **(Evidence A)** • In patients with stable COPD and moderate resting or exercise-induced arterial desaturation, prescription of long-term oxygen does not lengthen time to death or first hospitalization or provide sustained benefit in health status, lung function and 6-minute walk distance **(Evidence A)** • Sufficient resting oxygenation at sea level does not exclude the development of severe hypoxemia when traveling by air **(Evidence C)**
Ventilatory Support	• NPPV may improve hospitalization-free survival in selected patients after recent hospitalization, particularly in those with pronounced daytime persistent hypercapnia ($PaCO_2$ > 53 mmHg) **(Evidence B)** • In patients with severe chronic hypercapnia and a history of hospitalization for acute respiratory failure, long-term noninvasive ventilation may be considered **(Evidence B)**

The NEW ENGLAND JOURNAL of MEDICINE

INOX ClinicalTrials

ORIGINAL ARTICLE

Randomized Trial of Nocturnal Oxygen in Chronic Obstructive Pulmonary Disease

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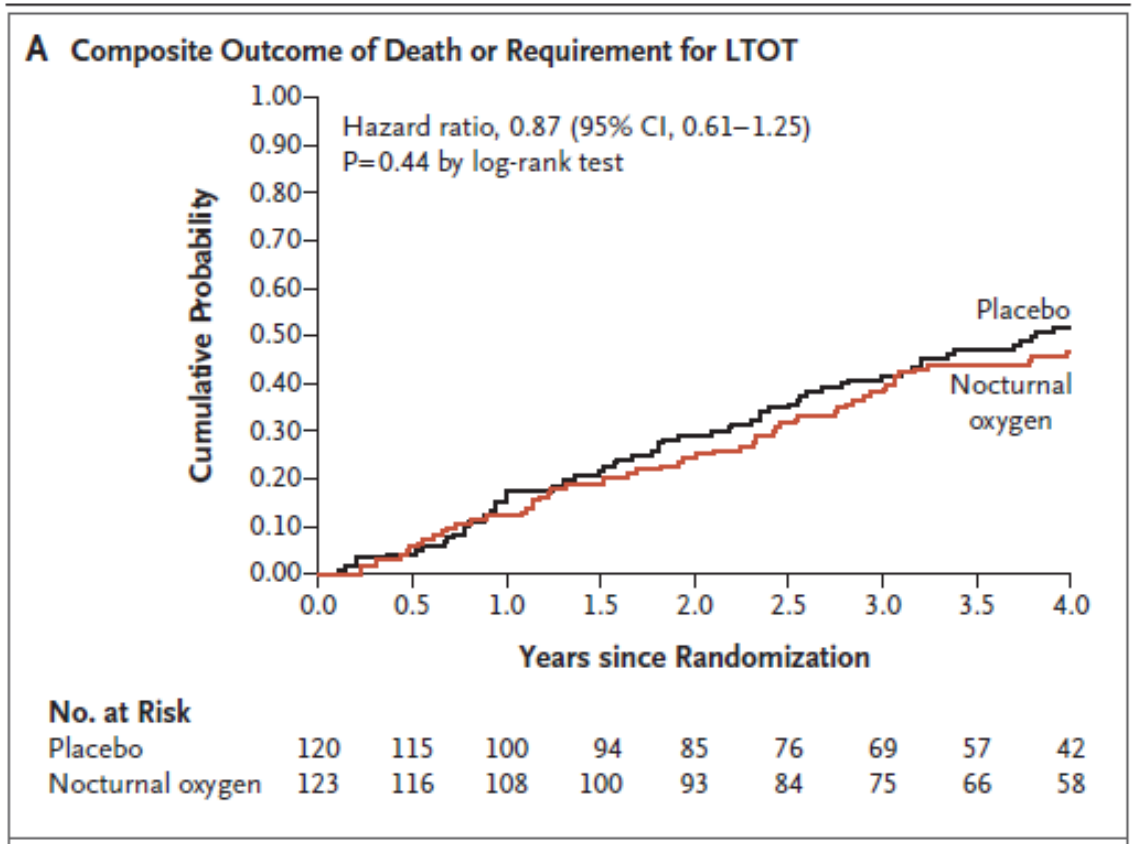

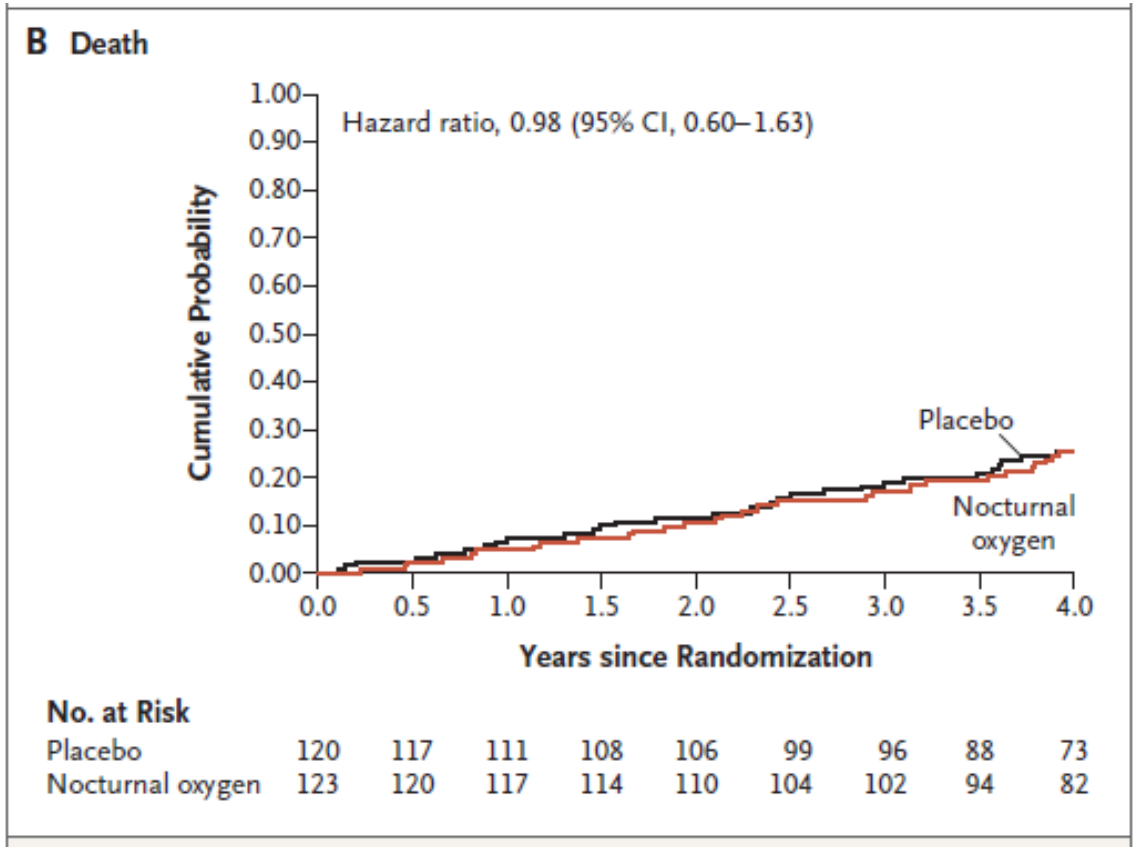

N Engl J Med 2020;383:1129-38.

The NEW ENGLAND JOURNAL of MEDICINE

INOX ClinicalTrials

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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)

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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.

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 19, 2024 VOL. 391 NO. 11

Long-Term Oxygen Therapy for 24 or 15 Hours per Day in Severe Hypoxemia

Magnus Ekström, M.D., Ph.D., Anders Andersson, M.D., Ph.D., Savvas Papadopoulos, M.D., Taivo Kipper, M.D., Bo Pedersen, M.D., Ozren Kricka, M.D., Pierre Sobrino, M.D., Michael Runold, M.D., Ph.D., Andreas Palm, M.D., Ph.D., Anders Blomberg, M.D., Ph.D., Ranjh Hamed, M.D., Eva Lindberg, M.D., Ph.D., Björn Sundberg, M.D., Nermin Hadziosmanovic, M.Sc., Filip Björklund, M.D., Christer Janson, M.D., Ph.D., Christine F. McDonald, M.D., Ph.D., David C. Currow, M.D., Ph.D., and Josefin Sundh, M.D., Ph.D., for the REDOX Collaborative Research Group*

The findings support that there is no clear disadvantage of supplemental oxygen use for 15 hours per day rather than 24 hours per day in terms of reducing the risk of hospitalization or death within 1 year. Therapy-free intervals up to 9 hours per day may substantially reduce the limitations and burdens of long-term oxygen therapy for many patients. This registry-based, randomized, controlled trial showed that among patients with severe hypoxemia, long-term oxygen therapy used 24 hours per day did not lead to a lower risk of hospitalization or death within 1 year than therapy for 15 hours per day.

The Registry-Based Treatment Duration and Mortality in Long-Term Oxygen Therapy (REDOX)

N Engl J Med 2024;391:977-88.

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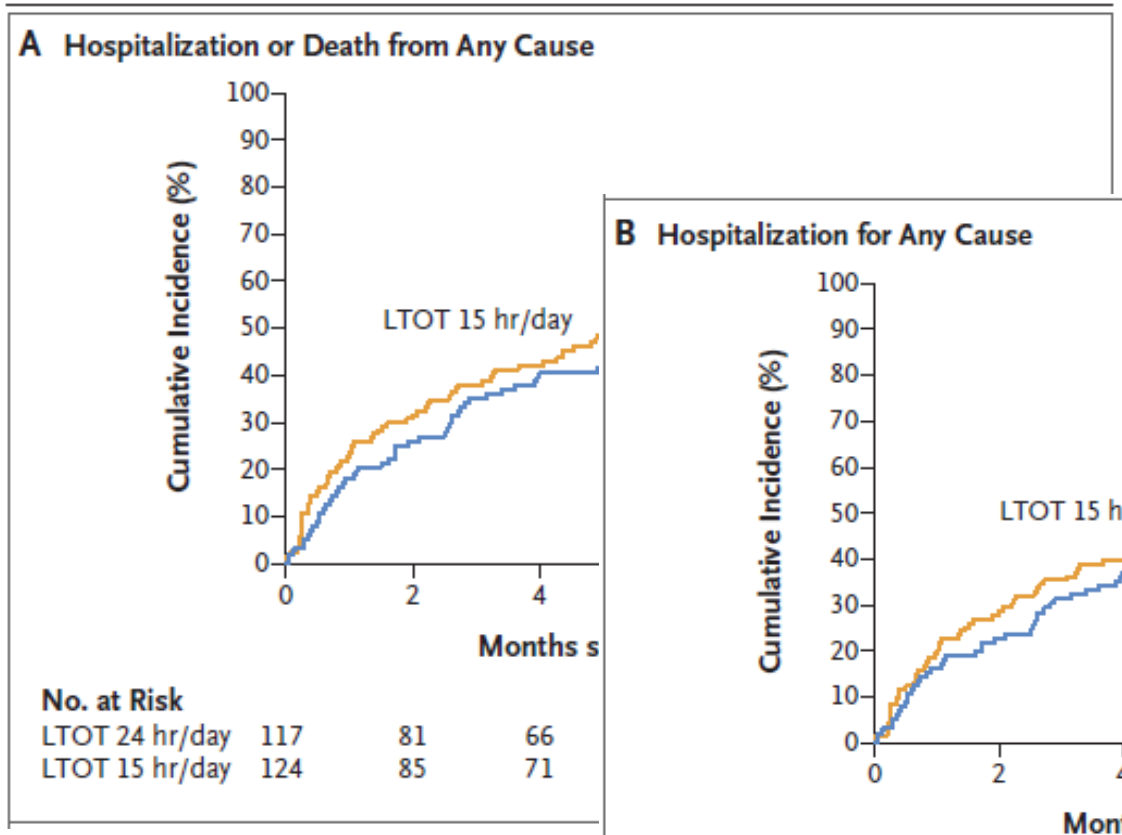

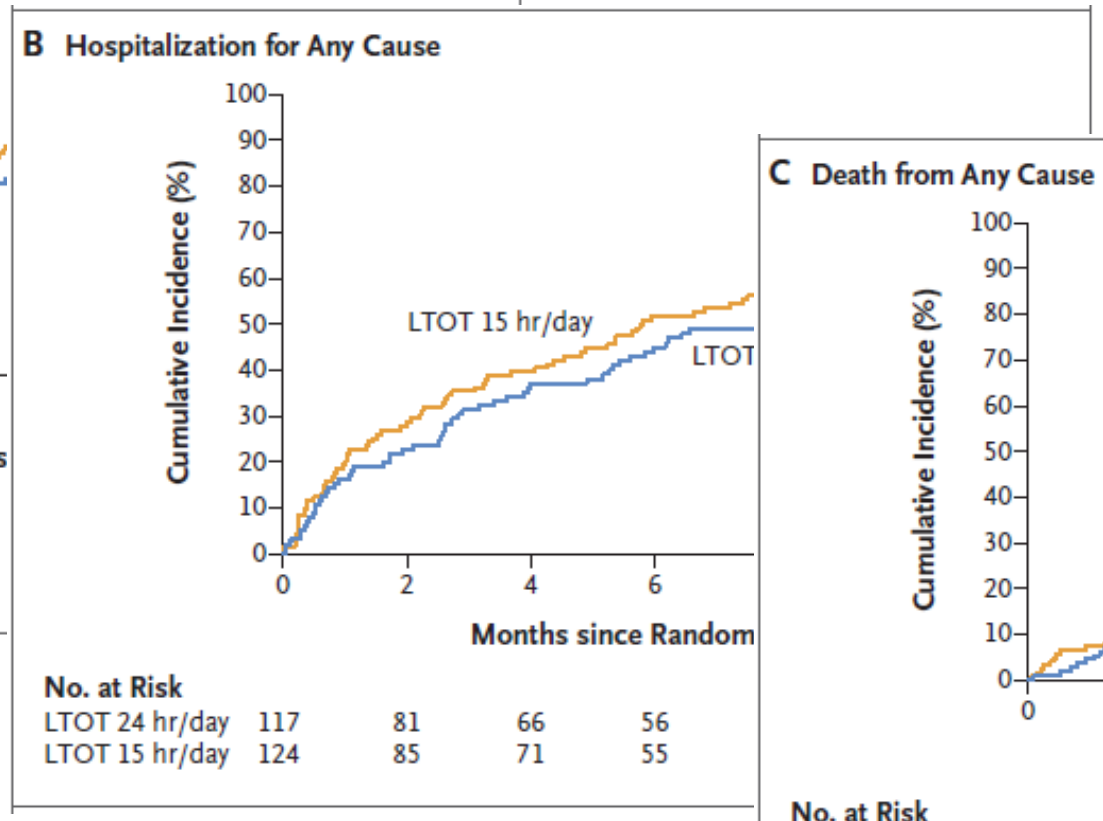

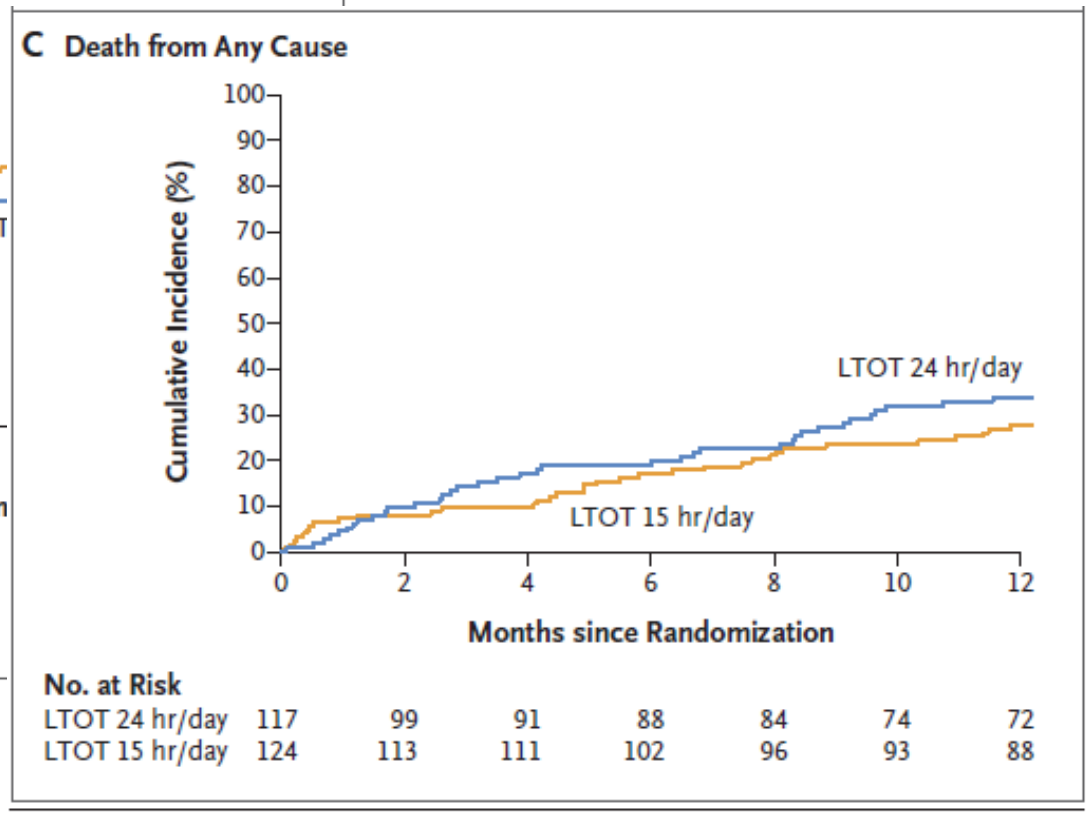

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Table 2. Trial Outcomes at 12 Months in the Intention-to-Treat Population.*

Outcome	LTOT 24 Hr/Day (N=117)	LTOT 15 Hr/Day (N=124)	Estimated Effect (95% CI), 24 vs. 15 Hr/Day†
Primary outcome			
Hospitalization or death from any cause — no. (%)	75 (64.1)	79 (63.7)	0.99 (0.72 to 1.36)
Secondary outcomes			
Death from any cause — no. (%)	37 (31.6)	34 (27.4)	1.26 (0.79 to 2.01)
Hospitalization for any cause — no. (%)	67 (57.3)	71 (57.3)	1.00 (0.72 to 1.40)
MDP A1 scale score for overall unpleasantness‡			
No. of patients assessed	46	59	
Mean score	4.46±2.65	4.05±2.85	0.41 (−0.67 to 1.48)
Median score (IQR)	5.0 (2.0 to 6.0)	4.0 (2.0 to 7.0)	
FACIT scale score for fatigue§			
No. of patients assessed	37	55	
Mean score	22.51±11.23	22.20±9.78	0.31 (−4.07 to 4.70)
Median score (IQR)	22.0 (13.0 to 29.0)	23.0 (16.0 to 29.0)	
CAT score for health status¶			
No. of patients assessed	43	57	
Mean score	21.56±5.34	18.82±7.28	2.73 (0.12 to 5.35)
Median score (IQR)	21.0 (18.0 to 25.0)	19.0 (14.0 to 23.0)	
EQ-5D VAS score for perceived overall well-being‖			
No. of patients assessed	47	58	
Mean score	46.70±22.75	46.98±22.54	−0.28 (−9.09 to 8.53)
Median score (IQR)	50.0 (30.0 to 60.0)	45.0 (30.0 to 60.0)	
Preferred daily duration of therapy — no./total no. (%)			
15 hr/day	18/41 (43.9)	37/54 (68.5)	0.36 (0.15 to 0.84)
24 hr/day	23/41 (56.1)	17/54 (31.5)	—

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Analysis Group	LTOT 24 Hr/Day	LTOT 15 Hr/Day	Hazard Ratio for Hospitalization or Death from Any Cause at 1 Year (95% CI)
	no. of patients with event/total no. of patients		
Intention-to-treat population	75/117	79/124	0.99 (0.72–1.36)
Per-protocol population	55/76	42/73	1.27 (0.85–1.90)
Subgroup with a baseline PaO_2 of <55 mm Hg	64/95	68/107	1.09 (0.77–1.53)
Subgroup with spirometry-verified COPD	38/56	40/66	1.11 (0.71–1.73)
Subgroup with condition other than COPD as the primary diagnosis	24/37	22/32	1.06 (0.59–1.89)

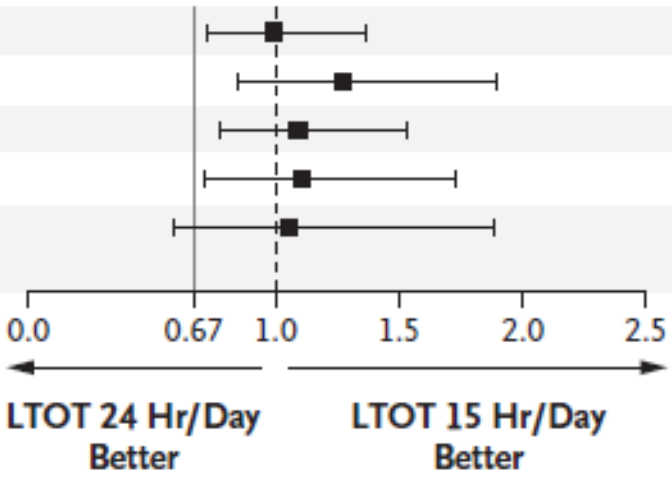

Figure 3. Intention-to-Treat, Per-Protocol, and Subgroup Analyses of the Primary Outcome.

The solid vertical line at 0.67 indicates the nonsuperiority margin, and the dashed line at 1.0 indicates no difference. The subgroup analyses were conducted in the intention-to-treat population. To convert the values for partial pressure of arterial oxygen (PaO_2, as measured with the patient breathing ambient air) to kilopascals, multiply by 0.1333. Patients with spirometry-verified chronic obstructive pulmonary disease (COPD) were those who had COPD as the primary diagnosis and a ratio of forced expiratory volume in 1 second to forced vital capacity of less than 0.70.

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The Registry-Based Treatment Duration and Mortality in Long-Term Oxygen Therapy (REDOX)

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INVITED REVIEW

Check for updates

Long-Term Oxygen Therapy in COPD Patients Who Do Not Meet the Actual Recommendations

Begum Ergan[a] and Stefano Nava[b]

[a]Department of Pulmonary and Critical Care, Faculty of Medicine, Dokuz Eylul University, Izmir, Turkey; [b]Department of Clinical, Integrated and Experimental Medicine (DIMES), Respiratory and Critical Care Unit, S. Orsola-Malpighi Hospital, Alma Mater University, Bologna, Italy

Table 1. Definitions.

Resting hypoxemia	Resting PaO_2 ≤55 mmHg or SaO_2 ≤88% OR Resting PaO_2 between 56-59 mmHg (or SaO_2 ≤88%) with evidence of either pulmonary hypertension, cor pulmonale or polycythemia (hematocrit >55%)
Moderate hypoxemia	Resting PaO_2 ranging between 56 and 69 mmHg
Nocturnal desaturation	Spending ≥30% sleep time with SaO_2 < 90% without evidence of associated sleep apnea OR A fall in SaO_2 below 90% for 5 minutes or more with a nadir SaO_2 below 85% during sleep
Exercise-induced desaturation	SaO_2 ≤ 88% during exercise OR A fall in SaO_2 ≥ 4% during exercise

COPD: JOURNAL OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE 2017, VOL. 14,NO. 3, 351–366

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Table 6. Summary of evidence for long-term oxygen use in in specific circumstances in COPD.

Moderate hypoxemia	Current evidence does not support the use of LTOT in COPD patients with moderate desaturation
Nocturnal desaturation	The benefit of LTOT for clinically relevant outcomes remains unclear due to the paucity of data
Exercise-induced desaturation	Oxygen administration causes less breathlessness and improves exercise capacity during exercise however the effectiveness of long term use of ambulatory oxygen on exercise capacity and mortality is not evident
Pulmonary rehabilitation and exercise training	There is insufficient evidence to confirm the benefits of supplemental oxygen during exercise training but oxygen administration may reduce breathlessness and improve exercise tolerance
Relief of dyspnea for palliation	Current evidence does not support the use of LTOT for the relief of dyspnea in non-hypoxemic COPD patients

COPD: JOURNAL OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE 2017, VOL. 14,NO. 3, 351–366

LTOT flow rates (BTS guidelines)

- Patients eligible for LTOT should be initiated on a flow rate of 1 L/min and titrated up in 1 L/min increments until SpO_2 >90%. An ABG should then be performed to confirm that a target PaO_2 ≥8 kPa (60 mm Hg) at rest has been achieved. (Grade B)

- Non-hypercapnic patients initiated on LTOT should increase their flow rate by 1 L/min during sleep in the absence of any contraindications. (Grade B)

- Patients initiated on LTOT who are active outdoors should receive an ambulatory oxygen assessment to assess whether their flow rate needs increasing during exercise. (Grade B)

Hardinge M, et al. Thorax 2015;70:i1–i43.
doi:10.1136/thoraxjnl-2015-206865

Ipossiemia cronica severa a riposo in aria ambiente in adulti con Malattia Interstiziale Polmonare (ILD)

Severa ipossiemia durante esercizio in aria ambiente in adulti con Malattia Interstiziale Polmonare (ILD)

Home Oxygen in Chronic Obstructive Pulmonary Disease
Yves Lacasse, et al.
Am J Respir Crit Care Med Vol 197, Iss 10, pp 1254–1264, May 15, 2018

Home Oxygen Therapy for Adults with Chronic Lung Disease
An Official American Thoracic Society Clinical Practice Guideline
American Journal of Respiratory and Critical Care Medicine Volume 202 Number 10 | November 15 2020

Figure 1. Examples of stationary and portable oxygen devices in the United States. Illustration by Patricia Ferrer Beals.

Contenitori Criogenici Base

Contenitori Criogenici Portatili Standard

BOMBOLA GASSOSO 3000 lt

Nella tabella di seguito, la durata di una bombola da 3000 lt in base al flusso erogato

Litri/minuto	DURATA
1 l/min	46h 40m
2 l/min	23h 20m
3 l/min	15h 33m
4 l/min	11h 40m
5 l/min	9h 20m
6 l/min	7h 46m
7 l/min	6h 40m
8 l/min	5h 50m
9 l/min	5h 11m
10 l/min	4h 40m
11 l/min	4h 14m
12 l/min	3h 53m
13 l/min	3h 35m
14 l/min	3h 20m
15 l/min	3h 6m

Concentratori ossigeno fissi

Concentratori ossigeno portatili

Grazie per l'attenzione