

## Journal Club

# Journal Club: Non-invasive Mechanical Ventilation in Stable COPD

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**Abbreviations:** non-invasive mechanical ventilation, **NIV**; acute hypercapnia respiratory failure, **AHRF**; acute exacerbation of COPD, **AECOPD**; forced expiratory volume in 1 second, **FEV<sub>1</sub>**; health-related quality of life, **HRQL**; randomized controlled trials, **RCTs**; Global initiative for chronic Obstructive Lung Disease, **GOLD**; partial pressure of carbon dioxide, **PaCO<sub>2</sub>**; St George's Respiratory Questionnaire, **SGRQ**; Respiratory Support in COPD after Acute Exacerbations study, **RESCUE**; Home Mechanical Ventilation Versus Home Oxygen Therapy in COPD, **HMV-HOT-UK**; American Thoracic Society, **ATS**

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### Keywords

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## Introduction

The burden of chronic obstructive pulmonary disease (COPD) continues to grow worldwide and outpaces the development of effective treatment modalities.<sup>1</sup> The exploration of non-invasive ventilator support as a therapy for COPD dates back to the 1960s, where negative pressure ventilation was unsuccessfully used with the intent of increasing respiratory muscle strength in patients with COPD.<sup>2</sup> In the past 3 decades, with the advent of positive pressure ventilation, there has been a dramatic rise in the use of non-invasive mechanical ventilation (NIV) for several indications due to promising clinical trial data.<sup>3-5</sup> For COPD patients, the utility of NIV in acute hypercapnic respiratory failure (AHRF) has been well supported by robust evidence of benefit since the early to mid-1990s.<sup>6,7</sup> The role of long-term NIV in stable COPD, however, is not as established. In the setting of AHRF, NIV has been demonstrated to reduce the rate of

endotracheal intubation, hospital length of stay, and in-hospital mortality.<sup>7-10</sup> Unlike for AHRF, there have been conflicting data on the role of NIV as therapy in stable COPD and contradictory reports on the effect on important outcomes such as frequency of acute exacerbations of COPD (AECOPD) and impact on mortality.

The investigation into whether NIV is beneficial for patients with severe COPD outside of AECOPD or AHRF has been the goal of several clinical studies beginning in the late 1990s. The importance of this question was reinforced when it was documented that in patients with severe COPD and hypoxemia, hypercapnia is a significant negative prognostic factor associated with mortality.<sup>11</sup> NIV in severe but stable COPD is theorized to improve lung mechanics by improving inspiratory muscle function from resting chronically-fatigued respiratory muscles, increasing inspiratory flow rate, reducing the occurrence of hypoventilation, and improving sleep quantity and efficiency, as well as several thus far undefined mechanisms.<sup>12-14</sup> Additionally, several studies have shown stabilization of lung function as measured by forced expiratory volume in 1 second, (FEV<sub>1</sub>), although the mechanism for this is unclear.<sup>15,16</sup> Given the inconsistencies in the reported literature on the role of long-term NIV in stable COPD, there was a Cochrane review in 2002 with a subsequent update.<sup>17,18</sup> The summary of the 2013 update to the review concluded that overall, for long-term NIV for COPD, there was no evidence of significant benefit on gas exchange, exercise capacity, lung function,

or health-related quality of life (HRQL). The 2013 Cochrane update, however, showed that a subgroup that has severe hypercapnia were more likely to benefit.<sup>18</sup>

After the 2013 update to the Cochrane review on this topic, several well-done randomized controlled trials (RCTs) were performed that utilized high-intensity NIV (high inspiratory pressures), thus increasing the body of literature, with many showing potential benefits from long-term NIV use, to an extent that had not been shown before.<sup>19</sup> One such study was a large multicenter trial by Köhnlein and colleagues<sup>19</sup> that assessed 195 patients with severe COPD (Global initiative for chronic Obstructive Lung Disease [GOLD]<sup>20</sup> grade 4) and hypercapnia. Unlike many earlier trials, they utilized high-intensity NIV. In this trial, the NIV group had in-hospital NIV titration targeting a partial pressure of carbon dioxide (PaCO<sub>2</sub>) reduction of 20%, or below 48mmHg, and this was compared to standard COPD therapy.<sup>19</sup> They observed a significant reduction in 1-year mortality (12% versus 33%) in the NIV group compared to the control group ( $p=0.0004$ ) as well as significant improvement in St George's Respiratory Questionnaire scores (SGRQ). Other improved outcomes include improved PaCO<sub>2</sub>, pH, oxygen saturation, serum bicarbonate, and FEV<sub>1</sub> in the NIV group. The Respiratory Support in COPD after Acute Exacerbation (RESCUE) trial was less favorable.<sup>21</sup> This trial compared NIV with backup rate to standard treatment in 201 patients admitted with AECOPD requiring invasive or non-invasive mechanical ventilation. After 12 months, follow-up data showed improvement in daytime PaCO<sub>2</sub> with high-intensity NIV, a trend towards improvement in HQRL but no difference in mortality or time to readmission.<sup>21</sup> The Home Mechanical Ventilation versus Home Oxygen Therapy in COPD study (HMV-HOT-UK) then showed that in patients with persistent hypercapnia after a hospitalized AECOPD, the addition of long-term NIV compared to oxygen therapy alone prolonged the time to readmission or death within 12 months (4.3 months versus 1.4 months).<sup>22</sup> It has been suggested that the conflicting results in these studies are primarily due to patient selection. Despite the conflicting data, the use of high-intensity NIV with titration targeting a substantial PaCO<sub>2</sub> drop has become more prominent.

Given the potential impact of NIV on HRQL,

AECOPD outcomes, and mortality, NIV use continues to be promising; however, this treatment must be reserved for those who benefit. This, combined with the shortage of therapies that offer benefits in severe COPD, has given rise to the increased use of chronic NIV in treating people with severe stable COPD. The use has recently become even more established with the European Respiratory Society and American Thoracic Society (ATS) guidelines on long-term NIV in COPD.<sup>23,24</sup> Given the recent conflicting clinical trial data since the 2013 update and the growing rise of NIV use, there have been several analyses and reviews of the current literature to date.

In this Journal Club, we review the Cochrane intervention review, "Chronic Non-Invasive Ventilation for Chronic Obstructive Pulmonary Disease."<sup>25</sup> We will also review some of the most recent literature looking at the applications of chronic NIV in COPD patients.<sup>24-27</sup>

**Note: Abstracts are presented in their original, published format and have not been edited to match JCOPDF style.**

## Abstract 1 Chronic Non-Invasive Ventilation for Chronic Obstructive Pulmonary Disease

Raveling T, Vank J, Struik FM, et al. *Cochrane Database Syst Rev.* 2021;8:CD002878.

doi: <https://doi.org/10.1002/14651858.CD002878.pub3>

### Background:

Chronic non-invasive ventilation (NIV) is increasingly being used to treat people with COPD who have respiratory failure, but the evidence supporting this treatment has been conflicting.

### Objectives:

To assess the effects of chronic non-invasive ventilation at home via a facial mask in people with COPD, using a pooled analysis of IPD and meta-analysis.

### Search strategy:

We searched the Cochrane Airways Register of Trials, MEDLINE, Embase, PsycINFO, CINAHL, AMED,

proceedings of respiratory conferences, clinical trial registries and bibliographies of relevant studies. We conducted the latest search on 21 December 2020.

### Selection criteria:

We included randomised controlled trials (RCTs) comparing chronic NIV for at least five hours per night for three consecutive weeks or more (in addition to standard care) versus standard care alone, in people with COPD. Studies investigating people initiated on NIV in a stable phase and studies investigating NIV commenced after a severe COPD exacerbation were eligible, but we reported and analysed them separately. The primary outcomes were arterial blood gases, health-related quality of life (HRQL), exercise capacity (stable COPD) and admission-free survival (post-exacerbation COPD). Secondary outcomes for both populations were: lung function, COPD exacerbations and admissions, and all-cause mortality. For stable COPD, we also reported respiratory muscle strength, dyspnoea and sleep efficiency.

### Data collection and analysis:

We used standard methodological procedures expected by Cochrane. After inclusion of a study, we requested the IPD. We analysed continuous and time-to-event data using linear- and cox-regression mixed-effect models with a random effect on study level. We analysed dichotomous IPD using generalised estimating equations. We adjusted all models for age and sex. We assessed changes in outcomes after three and 12 months. We also conducted a meta-analysis on aggregated trial data.

### Main results:

We included 14 new RCTs in this review update, in addition to the seven previously included. Seventeen studies investigated chronic NIV in stable COPD and four studies investigated chronic NIV commenced after a severe COPD exacerbation. Three studies compared NIV to sham continuous positive airway pressure (2 to 4cm H<sub>2</sub>O). Seven studies used a nasal mask, one study used an oronasal mask and eight studies used both interfaces. Five studies did not report the interface. The majority of trials (20/21) were at high risk of performance bias due to an unblinded design. We considered 11 studies to have a low risk of selection bias and 13 to have a

low risk of attrition bias. We collected and analysed the IPD from 13 stable COPD studies (n=778, 68% of the participants included) and from three post-exacerbation studies (n=364, 96% of the participants included).

In the stable COPD group, NIV probably results in a minor benefit on the arterial partial pressure of oxygen (PaO<sub>2</sub>) after three months (adjusted mean difference (AMD) 0.27kPa, 95% CI 0.04 to 0.49; 9 studies, 271 participants; moderate-certainty evidence), but there was little to no benefit at 12 months (AMD 0.09kPa, 95% CI -0.23 to 0.42; 3 studies, 171 participants; low-certainty evidence). The arterial partial pressure of carbon dioxide (PaCO<sub>2</sub>) was reduced in participants allocated to NIV after three months (AMD -0.61kPa, 95% CI -0.77 to -0.45; 11 studies, 475 participants; high-certainty evidence) and persisted up to 12 months (AMD -0.42kPa, 95% CI -0.68 to -0.16; 4 studies, 232 participants; high-certainty evidence).

Exercise capacity was measured with the 6-minute walking distance (minimal clinical important difference: 26m). There was no clinically relevant effect of NIV on exercise capacity (3 months: AMD 15.5m, 95% CI -0.8 to 31.7; 8 studies, 330 participants; low-certainty evidence; 12 months: AMD 26.4m, 95% CI -7.6 to 60.5; 3 studies, 134 participants; very low-certainty evidence). HRQL was measured with the Severe Respiratory Insufficiency and the St. Georges's Respiratory Questionnaire and may be improved by NIV, but only after three months (3 months: standardised mean difference (SMD) 0.39, 95% CI 0.15 to 0.62; 5 studies, 259 participants; very low-certainty evidence; 12 months: SMD 0.15, 95% CI -0.13 to 0.43; 4 studies, 200 participants; very low-certainty evidence). Lastly, the risk for all-cause mortality is likely reduced by NIV (adjusted hazard ratio (AHR) 0.75, 95% CI 0.58 to 0.97; 3 studies, 405 participants; moderate-certainty evidence).

In the post-exacerbation COPD group, there was little to no benefit on the PaO<sub>2</sub> after three months, but there may be a slight decrease after 12 months (3 months: AMD -0.10kPa, 95% CI -0.65 to 0.45; 3 studies, 234 participants; low-certainty evidence; 12 months: -0.27kPa, 95% CI -0.86 to 0.32, 3 studies; 170 participants; low-certainty evidence). The PaCO<sub>2</sub> was reduced by NIV at both three months (AMD -0.40kPa, 95% CI -0.70 to -0.09; 3 studies, 241 participants; moderate-certainty evidence) and 12 months (AMD -0.52kPa, 95% CI -0.87 to -0.18; 3 studies, 175

participants; high-certainty evidence). NIV may have little to no benefit on HRQL (3 months: SMD 0.25, 95% CI -0.01 to 0.51; 2 studies, 219 participants; very low-certainty evidence; 12 months: SMD 0.25, 95% CI -0.06 to 0.55; 2 studies, 164 participants; very low-certainty evidence). Admission-free survival seems improved with NIV (AHR 0.71, 95% CI 0.54 to 0.94; 2 studies, 317 participants; low-certainty evidence), but the risk for all-cause mortality does not seem to improve (AHR 0.97, 95% CI 0.74 to 1.28; 2 studies, 317 participants; low-certainty evidence).

## Comments

This timely review assessed a total of 17 randomized controlled trials and data from 1264. As the use of chronic NIV in stable COPD grows, this meta-analysis assessed the potential treatment effect on blood gas analysis, exacerbation outcomes, mortality, and patient-centered outcomes such as quality of life, among others. This analysis was well done, balanced in the trial inclusion, and included all the pertinent trials since the 2013 update to this Cochrane review. Some key points from this review are: (1) chronic NIV improves daytime hypercapnia; (2) there is a short-term quality of life benefit that is not observed at longer follow-ups, even though there is a suggestive trend; and (3) despite the negative NIV results in COPD trials, the review suggests that with appropriate patient selection, chronic NIV may affect mortality and readmissions for exacerbation, particularly in people with hypercapnia. This meta-analysis highlighted that future clinical trials would advance the field further if the emphasis were on identifying predictors of success with NIV use in COPD instead of performing more clinical trials that compare NIV modalities to standard COPD treatment.

## Abstract 2 Long-Term Non-invasive Ventilation in Chronic Stable Hypercapnic Chronic Obstructive Pulmonary Disease. An Official American Thoracic Society Clinical Practice Guideline

Macrea M, Oczkowski S, Rochweg B, et al. *Am J Respir Crit Care Med.* 2020;202(4): e74-e87.  
doi: <https://doi.org/10.1164/rccm.202006-2382ST>

### Background:

Non-invasive ventilation (NIV) is used for patients with chronic obstructive pulmonary disease (COPD) and chronic hypercapnia. However, evidence for clinical efficacy and optimal management of therapy is limited.

### Target Audience:

Patients with COPD, clinicians who care for them, and policy makers.

### Methods:

We summarized evidence addressing five PICO (patients, intervention, comparator, and outcome) questions. The GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach was used to evaluate the certainty in evidence and generate actionable recommendations. Recommendations were formulated by a panel of pulmonary and sleep physicians, respiratory therapists, and methodologists using the Evidence-to-Decision framework.

### Recommendations:

1) We suggest the use of nocturnal NIV in addition to usual care for patients with chronic stable hypercapnic COPD (conditional recommendation, moderate certainty); 2) we suggest that patients with chronic stable hypercapnic COPD undergo screening for obstructive sleep apnea before initiation of long-term NIV (conditional recommendation, very low certainty); 3) we suggest not initiating long-term NIV during an admission for acute-on-chronic hypercapnic respiratory failure, favoring instead reassessment for NIV at 2–4 weeks after resolution (conditional recommendation, low certainty); 4) we suggest not using an in-laboratory overnight polysomnogram to titrate NIV in patients with chronic stable hypercapnic COPD who are initiating NIV (conditional recommendation, very low certainty); and 5) we suggest NIV with targeted normalization of PaCO<sub>2</sub> in patients with hypercapnic COPD on long-term NIV (conditional recommendation, low certainty).

### Conclusions:

This expert panel provides evidence-based

recommendations addressing the use of NIV in patients with COPD and chronic stable hypercapnic respiratory failure.

## Comments

There is growing use of NIV in stable COPD patients and an expanding population of people who would benefit from NIV use, however, misuse is also a significant challenge. Raveling and a multidisciplinary group of experts in this recently published clinical practice guideline provide insights into patient selection for those who would benefit while acknowledging that this is an area for further study. In these practice guidelines, the ATS expert panel conducts a thorough review of the literature to date and identifies issues and other pertinent challenges related to using NIV in this population. The authors offer practical recommendations on standardizing the NIV approach such that care with this modality is streamlined to those who would benefit most.

### Abstract 3 Day-to-Day Variability of Parameters Recorded by Home Noninvasive Positive Pressure Ventilation for Detection of Severe Acute Exacerbations in COPD

Jiang W, Chao Y, Wang X, Chen C, Zhou J, Song Y. *Int J Chron Obstruct Pulmon Dis*. 2021;16 (2021):727-737. doi: <https://doi.org/10.2147/COPD.S299819>

#### Background:

Home non-invasive positive pressure ventilation (NPPV) can be considered not only as an evidence-based treatment for stable hypercapnic chronic obstructive pulmonary disease (COPD) patients, but also as a predictor for detecting severe acute exacerbations of chronic obstructive pulmonary disease (AECOPD).

#### Methods:

In this retrospective observational study, we collected clinical exacerbations information and daily NPPV-related data in a cohort of COPD patients with home NPPV for 6 months. Daily changes in NPPV-related parameters' variability prior to AECOPD

were examined using two-way repeated measures ANOVA and individual abnormal values (>75th or <25th percentile of individual baseline parameters) were calculated during 7-day pre-AECOPD period. Multivariate logistic regression was used to identify the independent risk factors associated with AECOPD that then were incorporated into the nomogram.

#### Results:

Between January 1, 2018, and January 1, 2020, a total of 102 patients were included and 31 (30.4%) participants experienced hospitalization (AECOPD group) within 6 months. Respiratory rate changed significantly from baseline at 1, 2 or 3 days prior to admission ( $p < 0.001$ , respectively) in the AECOPD group. The number of days with abnormal values of daily usage, leaks, or tidal volume during the 7-day pre-AECOPD period in the AECOPD group was higher than in the stable group ( $p < 0.001$ , respectively). On multivariate analysis, 7-day mean respiratory rate (OR 1.756, 95% CI 1.249- 2.469), abnormal values of daily use (OR 1.918, 95% CI 1.253- 2.934) and tidal volume (OR 2.081, 95% CI 1.380- 3.140) within 7 days were independently associated with the risk of AECOPD. Incorporating these factors, the nomogram achieved good concordance indexes of 0.962.

#### Conclusion:

Seven-day mean respiratory rate, abnormal values of daily usage, leaks, and tidal volume within the 7-day pre-AECOPD period may be biomarkers for detection of AECOPD.

## Comments

While this is a single-center, retrospective cohort study with a relatively small sample size, this study uses information available from NIV. Thus far, most studies assessing NIV have prioritized understanding the role of NIV as a therapeutic intervention. In this study, the authors show that significant and clinically relevant information can be gleaned from NIV use and relevant patient parameters. They identify potential biomarkers that may be early identifiers of pending AECOPD and may offer information that can alter COPD management.

## Abstract 4

### Home Initiation of Chronic Non-Invasive Ventilation in COPD Patients With Chronic Hypercapnic Respiratory Failure: A Randomised Controlled Trial

Duiverman ML, Vonk JM, Bladder GM, et al. *Thorax*. 2020;75(3):244-252.

doi: <https://10.1136/thoraxjnl-2019-213303>

#### Introduction:

Chronic non-invasive ventilation (NIV) has become evidence-based care for stable hypercapnic COPD patients. While the number of patients increases, home initiation of NIV would greatly alleviate the healthcare burden. We hypothesise that home initiation of NIV with the use of telemedicine in stable hypercapnic COPD is non-inferior to in-hospital NIV initiation.

#### Methods:

Sixty-seven stable hypercapnic COPD patients were randomised to initiation of NIV in the hospital or at home using telemedicine. Primary outcome was daytime arterial carbon dioxide pressure (PaCO<sub>2</sub>) reduction after 6 months NIV, with a non-inferiority margin of 0.4kPa. Secondary outcomes were health-related quality of life (HRQoL) and costs.

#### Results:

Home NIV initiation was non-inferior to in-hospital initiation (adjusted mean difference in PaCO<sub>2</sub> change home vs in-hospital: 0.04kPa (95% CI -0.31 to 0.38kPa), with both groups showing a PaCO<sub>2</sub> reduction at 6 months compared with baseline (home: from 7.3±0.9 to 6.4±0.8kPa ( $p<0.001$ ) and in-hospital: from 7.4±1.0 to 6.4±0.6kPa ( $p<0.001$ )). In both groups, HRQoL improved without a difference in change between groups (Clinical COPD Questionnaire total score-adjusted mean difference 0.0 (95% CI -0.4 to 0.5)). Furthermore, home NIV initiation was significantly cheaper (home: median €3768 (IQR €3546-€4163) vs in-hospital: median €8537 (IQR €7540-€9175);  $p<0.001$ ).

#### Discussion:

This is the first study showing that home initiation of

chronic NIV in stable hypercapnic COPD patients, with the use of telemedicine, is non-inferior to in-hospital initiation, safe and reduces costs by over 50%.

## Comments

The use of telemedicine for sleep medicine care is growing; however, this study of the implementation of this technology has not been very well evaluated. This study shows that home initiation of NIV is non-inferior to current care for initiation of chronic NIV in stable COPD patients. As many areas around the globe have adopted in-hospital initiation and titration of NIV, this study suggests that home initiation is likely safe, feasible, and cost-effective. Many COPD patients under current U.S. guidelines would not qualify for in-home sleep monitoring. This publication provides relevant information especially given the current limitations to in-person physician visits with the current pandemic, and the potential expansion of telemedicine for sleep medicine expands the effective use of NIV to regions where patients would typically not have access to this level of care and support. As growing evidence accumulates for the use of telemedicine in the care of COPD patients, this study shows that telemedicine use in managing the initiation of chronic NIV can eliminate barriers to care such as lack of transportation problems, time off work, etc.<sup>28-30</sup>

## Bottom Line

With an estimated 300 million people worldwide suffering from COPD, the burden of symptoms from COPD is expanding.<sup>31</sup> For patients with severe COPD, very few therapies effectively improve symptoms and reduce hospitalizations and associated morbidity and mortality. Since the 1990s, there has been a dramatic rise in NIV for COPD and other cardio-respiratory etiologies, especially in the sickest of patients. The Cochrane review by Raveling et al showed a signal for a benefit from NIV use with patients with chronic hypercapnia receiving the most benefit. The lack of a more robust signal may be related to the heterogeneity of pathophysiological factors that impact COPD patients and the impact of patient selection. The pathophysiological factors likely impact the success of therapy; thus, a more targeted approach is likely to improve outcomes such as hospitalizations,

mortality, and the quality-of-life measures. The only way to identify these factors is to devote time and effort to studying these effects. Presently, tools such as polysomnography and blood gas analysis help to identify individuals who would benefit; however, these tools are not readily available, are time-intensive, and in some parts of the world, can be cost-prohibitive. The current data suggest that chronic NIV use may reduce hospitalizations for AECOPD, so it is crucial to find ways to maximize the availability of polysomnography and blood gas analysis to increase the number of COPD patients receiving this care, such as more robust utilization of telemedicine strategies. It is becoming more apparent that the benefits do not apply

to all patients with COPD. As the use of NIV becomes more widespread, more effort needs to be placed on identifying features that identify COPD patients who would receive the most benefit. Future efforts should be on restructuring future RCTs on NIV and creating novel methods of increasing the population who can safely be treated with NIV, as well as identifying methods to maximally utilize the information that can be gleaned from patients using chronic NIV for COPD. There is disagreement within the sleep medicine community about which mode of ventilation is optimal for stable COPD, but the role of NIV for COPD will likely continue to expand.

## References

1. Dransfield M, Stolz D, Kleinert S. Towards eradication of chronic obstructive pulmonary disease: a Lancet commission. *Lancet*. 2019;393(10183):1786-1788.  
doi: [https://doi.org/10.1016/S0140-6736\(19\)30950-X](https://doi.org/10.1016/S0140-6736(19)30950-X)
2. McClement JH, Christianson LC, Hubaytar RT, Simpson DG. The body-type respirator in the treatment of chronic obstructive pulmonary disease. *Ann NY Acad Sci*. 1965;121(3):746-750.  
doi: <https://doi.org/10.1111/j.1749-6632.1965.tb14243.x>
3. Sullivan DR, Kim H, Gozalo PL, Bunker J, Teno JM. Trends in noninvasive and invasive mechanical ventilation among Medicare beneficiaries at the end of life. *JAMA Intern Med*. 2021;181(1):93-102.  
doi: <https://doi.org/10.1001/jamainternmed.2020.5640>
4. Moran F, Bradley JM, Piper AJ. Non-invasive ventilation for cystic fibrosis. *Cochrane Database Syst Rev*. 2017;(2):CD002769.  
doi: <https://doi.org/10.1002/14651858.CD002769.pub5>
5. Dreher M, Ekkernkamp E, Schmoor C, Schoenheit-Kenn U, Winterkamp S, Kenn K. Pulmonary rehabilitation and noninvasive ventilation in patients with hypercapnic interstitial lung disease. *Respiration*. 2015;89(3):208-213.  
doi: <https://doi.org/10.1159/000369862>
6. 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.  
doi: [https://doi.org/10.1016/0140-6736\(93\)90696-E](https://doi.org/10.1016/0140-6736(93)90696-E)
7. Antonelli M, Conti G, Rocco M, et al. A comparison of noninvasive positive-pressure ventilation and conventional mechanical ventilation in patients with acute respiratory failure. *NEngl J Med*. 1998;339(7):429-435. doi: <https://doi.org/10.1056/NEJM199808133390703>
8. Osadnik CR, Tee VS, Carson-Chahhoud KV, Picot J, Wedzicha JA, Smith BJ. Non-invasive ventilation for the management of acute hypercapnic respiratory failure due to exacerbation of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2017;(7):CD004104.  
doi: <https://doi.org/10.1002/14651858.CD004104.pub4>
9. 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.  
doi: <https://doi.org/10.1056/NEJM199509283331301>
10. Plant P, Owen J, Elliott M. Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial. *Lancet*. 2000;355(9219):1931-1935.  
doi: [https://doi.org/10.1016/S0140-6736\(00\)02323-0](https://doi.org/10.1016/S0140-6736(00)02323-0)
11. Foucher P, Baudouin N, Merati M, et al. Relative survival analysis of 252 patients with COPD receiving long-term oxygen therapy. *Chest*. 1998;113(6):1580-1587.  
doi: <https://doi.org/10.1378/chest.113.6.1580>
12. Elliott M, Mulvey D, Moxham J, Green M, Branthwaite M. 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.  
doi: <https://pubmed.ncbi.nlm.nih.gov/1756837/>
13. Becker HF, Piper AJ, Flynn WE, et al. Breathing during sleep in patients with nocturnal desaturation. *Am J Respir Crit Care Med*. 1999;159(1):112-118.  
doi: <https://doi.org/10.1164/ajrccm.159.1.9803037>
14. Dreher M, Ekkernkamp E, Walterspacher S, et al. Noninvasive ventilation in COPD: impact of inspiratory pressure levels on sleep quality. *Chest*. 2011;140(4):939-945.  
doi: <https://doi.org/10.1378/chest.11-0253>
15. Dreher M, Storre JH, Schmoor C, Windisch W. High-intensity versus low-intensity non-invasive ventilation in patients with stable hypercapnic COPD: a randomised crossover trial. *Thorax*. 2010;65(4):303-308. doi: <https://doi.org/10.1136/thx.2009.124263>
16. Duiverman ML, Wempe JB, Bladder G, et al. Two-year home-based nocturnal noninvasive ventilation added to rehabilitation in chronic obstructive pulmonary disease patients: a randomized controlled trial. *Respir Res*. 2011;12(1):1-10.  
doi: <https://doi.org/10.1186/1465-9921-12-112>
17. Wijkstra PP, Lacasse Y, Guyatt GH, Goldstein R, Struik F. Nocturnal non-invasive positive pressure ventilation for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2002;(2):CD002878.  
doi: <https://doi.org/10.1002/14651858.CD002878>
18. Struik FM, Lacasse Y, Goldstein R, Kerstjens HA, Wijkstra PJ. Nocturnal non-invasive positive pressure ventilation for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2013;(6):CD002878.  
doi: <https://doi.org/10.1002/14651858.CD002878.pub2>
19. 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.  
doi: [https://doi.org/10.1016/S2213-2600\(14\)70153-5](https://doi.org/10.1016/S2213-2600(14)70153-5)
20. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for diagnosis, management, and prevention of COPD -2021. GOLD website. Accessed October 2021. Published December 2020. <https://goldcopd.org/>
21. Struik F, Sprooten R, Kerstjens H, 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.  
doi: <https://doi.org/10.1136/thoraxjnl-2014-205126>
22. Murphy PB, Rehal S, Arbane G, et al. 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. *JAMA*. 2017;317(21):2177-2186.  
doi: <https://doi.org/10.1001/jama.2017.4451>



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23. Ergan B, Oczkowski S, Rochweg B, et al. European Respiratory Society guidelines on long-term home non-invasive ventilation for management of COPD. *Eur Respir J*. 2019;54(3): 1901003. doi: <https://doi.org/10.1183/13993003.01003-2019>
- 
24. Macrea M, Oczkowski S, Rochweg B, et al. Long-term noninvasive ventilation in chronic stable hypercapnic chronic obstructive pulmonary disease. an official American Thoracic Society clinical practice guideline. *Am J Respir Crit Care Med*. 2020;202(4):e74-e87. doi: <https://doi.org/10.1164/rccm.202006-2382ST>
- 
25. Raveling T, Vonk J, Struik FM, et al. Chronic non-invasive ventilation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2021;(8):CD002878. doi: <https://doi.org/10.1002/14651858.CD002878.pub3>
- 
26. Jiang W, Chao Y, Wang X, Chen C, Zhou J, Song Y. Day-to-day variability of parameters recorded by home noninvasive positive pressure ventilation for detection of severe acute exacerbations in COPD. *Int J Chron Obstruct Pulmon Dis*. 2021;16:727-737. doi: <https://doi.org/10.2147/COPD.S299819>
- 
27. Duiverman ML, Vonk JM, Bladder G, et al. Home initiation of chronic non-invasive ventilation in COPD patients with chronic hypercapnic respiratory failure: a randomised controlled trial. *Thorax*. 2020;75(3):244-252. doi: <https://doi.org/10.1136/thoraxjnl-2019-213303>
- 
28. Cordova FC, Ciccolella D, Grabianowski C, et al. A telemedicine-based intervention reduces the frequency and severity of COPD exacerbation symptoms: a randomized, controlled trial. *Telemed J E Health*. 2016;22(2):114-122. doi: <https://doi.org/10.1089/tmj.2015.0035>
- 
29. Bhatt SP, Patel SB, Anderson EM, et al. Video telehealth pulmonary rehabilitation intervention in chronic obstructive pulmonary disease reduces 30-day readmissions. *Am J Respir Crit Care Med*. 2019;200(4):511-513. doi: <https://doi.org/10.1164/rccm.201902-0314LE>
- 
30. Alrajeh AM, Aldabayan YS, Aldhair AM, et al. Global use, utility, and methods of tele-health in COPD: a health care provider survey. *Int J Chron Obstruct Pulmon Dis*. 2019;14:1713. doi: <https://doi.org/10.2147/COPD.S202640>
- 
31. Soriano JB, Kendrick PJ, Paulson KR, et al. Prevalence and attributable health burden of chronic respiratory diseases, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Respir Med*. 2020;8(6):585-596. doi: [https://doi.org/10.1016/S2213-2600\(20\)30105-3](https://doi.org/10.1016/S2213-2600(20)30105-3)