CHAPTER 6A

Nocturnal non-invasive ventilation in COPD patients with prolonged hypercapnia after ventilatory support for acute respiratory failure: a randomized, controlled, parallel-group study

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Thorax. 2014 Sep;69(9):826-34.
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introduction: The effectiveness of non-invasive positive pressure ventilation (NIV) in COPD patients with prolonged hypercapnia after ventilatory support for acute respiratory failure (ARF) remains unclear. We investigated if nocturnal NIV in these patients prolongs the time to readmission for respiratory causes or death (primary endpoint) in the following 12 months.

Methods: Two hundred and one COPD patients admitted to hospital with ARF and prolonged hypercapnia >48 hours after termination of ventilatory support were randomised to NIV or standard treatment. Secondary outcomes were daytime arterial blood gasses, transcutaneous PCO\(_2\) during the night, lung function, health-related quality-of-life (HRQL), mood state, daily activities and dyspnoea.

Results: One year after discharge 65% vs. 64% of patients (NIV vs. standard treatment) were readmitted to hospital for respiratory causes or had died; time to event was not different (p=0.85). Daytime PaCO\(_2\) was significantly improved in NIV vs. standard treatment (PaCO\(_2\) 0.5 kPa (95% CI 0.04;0.90 p=0.03) as was transcutaneous PCO\(_2\) during the night. HRQL showed a trend (p=0.054 Severe Respiratory Insufficiency Questionnaire) in favor of NIV. Number of exacerbations, lung function, mood state, daily activity levels or dyspnoea were not significantly different.

Discussion: We could not demonstrate an improvement in time to readmission or death by adding NIV for one year in patients with prolonged hypercapnia after an episode of NIV for ARF. There is no reason to believe the NIV was not effective since daytime PaCO\(_2\) and nighttime PCO\(_2\) improved. The trend for improvement in HRQL favoring NIV, we believe nevertheless should be explored further.

What is the key question: What is the effect of nocturnal NIV alongside standard medical treatment in COPD patients with prolonged hypercapnia after ventilatory support for acute respiratory failure?

What is the bottom line: We could not demonstrate an improvement in time to readmission or death by adding NIV for one year in COPD patients with prolonged hypercapnia after an episode of NIV for acute respiratory failure.

Why read on? NIV did improve daytime PaCO\(_2\) and nighttime transcutaneous PCO\(_2\). This, and the trend for improvement in HRQL favoring NIV, should be explored further.
INTRODUCTION

Non-invasive positive pressure ventilation (NIV) has become an established treatment in patients with chronic obstructive pulmonary disease (COPD) who are admitted to hospital with acute respiratory failure (ARF) due to an exacerbation. As readmission and mortality rates in these patients are high, the application of long-term nocturnal NIV in stable hypercapnic COPD has been subject of several studies. However, in a meta-analysis no clear benefits were documented. Reasons for these negative results were: 1) insufficient ventilatory support; 2) lack of proper monitoring during the night; 3) baseline PaCO$_2$ too low; 4) low adherence to NIV. The two long-term RCTs comparing NIV in addition to long-term oxygen therapy (LTOT) showed conflicting results; one demonstrated small improvements in daytime arterial carbon dioxide tension (PaCO$_2$), dyspnoea and health-related quality-of-life (HRQL) in favor of NIV whereas the other found an improvement in survival but at the cost of worsening HRQL.

Two other studies investigated the effects of long-term NIV in the most severe subgroup of COPD patients; i.e. patients with acute-on-chronic respiratory failure. These indicated a benefit from long-term NIV in patients who previously required mechanical ventilation for treatment of ARF and who remained hypercapnic thereafter. Unfortunately, these were both small studies and given the huge impact of COPD on mortality and morbidity further studies are urgently needed.

We hypothesized that providing nocturnal NIV alongside standard medical treatment to patients who remain hypercapnic after ventilatory support during ARF, would prolong the time to readmission for respiratory causes or death. Therefore, we conducted a randomised controlled trial comparing nocturnal NIV with standard treatment for 1 year.
CHAPTER 6A

METHODS

The RESCUE trial (REspiratory Support in COPD after acUte Exacerbation) was a multi-centre, prospective, randomised, controlled study recruiting COPD patients who were admitted to hospital with ARF and treated with ventilatory support throughout the Netherlands between December 1, 2007 and July 1, 2012. Two hundred and one patients with severe COPD from in total 47 hospitals were enrolled by 3 Centers for Home Mechanical Ventilation (University Medical Center Groningen, Maastricht University Medical Center and the Erasmus Medical Center, Rotterdam) with a follow-up of 12 months. Inclusion criteria were: 1) Chronic Obstructive Pulmonary Disease (COPD), GOLD stage 3 and 4; 2) > 48 h independence from ventilatory support (invasive or non-invasive) for acute respiratory failure; 3) prolonged hypercapnia (PaCO₂ > 6.0 kPa) during daytime at rest without oxygen or ventilatory support. The study was approved by the local Medical Ethics Committee of the University Medical Centre Groningen, University of Groningen, patients gave informed consent to participate in the study and, the trial was registered at the Nederland’s Trial Register (NTR1100). For a more detailed description of the methods used, see Supplementary file.

Randomisation and intervention

Patients were randomised to nocturnal NIV or standard treatment by a computer with minimisation for FEV₁ (≤ 0.8 L or > 0.8 L), PaCO₂ (≤ 7.0 kPa or > 7.0 kPa), BMI (≤ 30 kg/m² or > 30 kg/m²), ventilatory support (invasive or noninvasive ventilation) and rehabilitation (yes/no). Standard treatment consisted of optimal medical treatment as usual, with long-term oxygen therapy (LTOT) in case of clinically stable patients with a PaO₂ < 8.0 kPa as indicated according to the Dutch Guideline.¹²

Nocturnal NIV was started by a highly experienced nurse practitioner from the nearest home mechanical ventilation centre who visited the hospital where the patient was admitted. NIV was initiated by BiPAP (Bi-level Positive Airway Pressure) in the Spontaneous/Timed mode (Synchrony, Respironics, INC, Murrysville, PA, USA) starting with a low back up frequency of 12/min with the aim to: 1) maximally support respiration and; 2) and achieve normocapnia. NIV was initiated with an IPAP (Inspiratory Positive Airway Pressure) of 14 cm H₂O and gradually increased during trials to a maximal tolerated level. EPAP (Expiratory Positive Airway Pressure) was started at 4 cm H₂O and increased if auto-PEEP was present or when patients used respiratory muscles to trigger the ventilator. Respiratory rate (RR) was set as close as possible to the RR of the patient, with adjustments if the patient triggered too much. Inspiration: expiration time was 1:3, with a short rise time and then titrated on comfort and effectiveness. All patients were initially given ventilation by means of a full-face mask and humidification to maximize comfort. Effectiveness with NIV during the night was observed by monitoring the transcutaneous O₂-saturation and PCO₂ (PtCO₂) with the TOSCA device (TOSCA 500, Linde Medical Sensors AG, Basel, Switzerland).¹³ Adherence to NIV was derived from time counters in the NIV device.
Non-invasive ventilation in hypercapnic COPD after acute respiratory failure

Measurements
At baseline, arterial and lung function measurements were performed just before randomization. Baseline Health-Related Quality-of-Life (HRQL) was assessed after randomization while transcutaneous measurements were performed during the night after patients were adjusted to NIV but before discharge of the initial admission for acute respiratory failure. Lung function and arterial blood gas measurements were repeated after 3, 6 and 12 months during visits to their regular pulmonologist. Arterial blood gases were taken while breathing room air; however when patients were unable to stop oxygen therapy even for short periods, measurements were taken with their usual oxygen flow rate. The nurse practitioner also visited all patients at home after 3, 6 and 12 months to collect survival, admission and exacerbation rates, HRQL and transcutaneous measurements, and if necessary to adjust NIV.

The long recruitment period enabled us to extend survival follow-up beyond 12 months to maximally 68 months for the first patients that entered the study.

HRQL was assessed by the Clinical COPD Questionnaire (CCQ),14 the Maugeri Respiratory Failure Questionnaire -28 (MRF-28)15 the Chronic Respiratory Questionnaire self-reported (CRQ),16 and the Severe Respiratory Insufficiency (SRI) questionnaire.17 We also measured mood state (Hospital Anxiety and Depression scale (HADS)),18 daily activity level (Groningen Activity and Restriction Scale (GARS)19 and dyspnoea (Medical Research Council (MRC)).20

Sample size calculations
Time to event (readmission for respiratory cause or death) as primary outcome was used to determine the sample size, based on the assumption of an event free survival of 20% in the standard treatment group2 after 12 months and 40% in the NIV group. With an alpha of 0.05 and a power of 80%, we needed 174 patients to detect the 20% difference in event free survival between groups. Estimating a maximum dropout rate of 15%, 200 patients were needed.

Statistical analysis
The primary outcome and survival analysis was based on intention-to-treat (ITT) using Kaplan-Meier estimates and the log-rank test. A complete case analysis was performed for the remaining secondary outcomes comparing data of the patients who completed the 12 months (completers) as the number of drop-outs was considerable due to progression of the disease and reluctance to adhere to study requirements. Arterial blood gas measurements could not always be performed under similar conditions for every patient. Therefore, data were analyzed in two ways; first regardless of oxygen use or the amount of oxygen and secondly only comparing baseline and 12 month data when either the measurements were both on room air or both on oxygen at the same flow rate (also see supplementary files).
As not all patients were compliant to NIV, either not using it every night or refusing treatment altogether, a per protocol analysis comparing patients in the NIV group who used ventilation > 5 hours/night with standard treatment was conducted based on results of a recent meta-analysis showing positive effects on change in arterial blood gases in this subgroup. All statistical calculations were performed using IBM SPSS Statistics version 20 (IBM, New York).

RESULTS

Patients
Two hundred and one patients met eligibility criteria, 101 were randomised to NIV and 100 to standard treatment (figure 1). At baseline, patient characteristics and demographics did not differ significantly between treatment groups for ITT as well as the completers (table 1) except for the total number of admission days in the previous year. Reasons for dropping-out of the study are listed in the supplementary files table s1. Four patients classified as drop-outs crossed from standard therapy over to the NIV treatment during the study. They remained in the standard treatment group for all ITT-analyses.

Figure 1. CONSORT flow diagram
Early drop-outs: When patients refused or were not able to continue the protocol (either NIV or standard treatment) within 10 days after inclusion. Completers: number of patients included in the complete case analysis.
Four patients classified as drop-outs crossed from standard therapy over to the NIV treatment during the study.
ITT: number of patients included in the intention-to-treat analysis; n, numbers for analysis; n†, number of patients who died within the drop-outs; NIV, noninvasive positive pressure ventilation; p-p, included in the per protocol analysis of patients who used ventilation > 5 hours/night.
Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>ITT NIV n=101</th>
<th>ITT Controls n=100</th>
<th>Completers NIV n=54</th>
<th>Completers Controls n=54</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.92 (8.6)</td>
<td>63.5 (7.9)</td>
<td>61.9 (7.9)</td>
<td>62.3 (7.9)</td>
</tr>
<tr>
<td>Gender, n (% female)</td>
<td>60 (59%)</td>
<td>58 (58%)</td>
<td>36 (67%)</td>
<td>34 (63%)</td>
</tr>
<tr>
<td>Pack years§</td>
<td>38 (0-140)</td>
<td>44 (0-125)</td>
<td>38 (0-125)</td>
<td>38 (0-125)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.6 (5.4)</td>
<td>24.8 (6.3)</td>
<td>24.7 (5.5)</td>
<td>24.2 (5.3)</td>
</tr>
<tr>
<td>LTOT, n (%)</td>
<td>76 (75%)</td>
<td>78 (78%)</td>
<td>38 (70%)</td>
<td>37 (69%)</td>
</tr>
<tr>
<td>Invasive, n (%) #</td>
<td>13 (13%)</td>
<td>12 (12%)</td>
<td>7 (13%)</td>
<td>10 (19%)</td>
</tr>
<tr>
<td>Duration ventilation¶ (days)</td>
<td>5.0 (1-19)</td>
<td>5.0 (1-24)</td>
<td>5.5 (2-19)</td>
<td>5.0 (1-23)</td>
</tr>
<tr>
<td>Admissions§ (yr⁻¹)</td>
<td>2.0 (1-9)</td>
<td>2.0 (1-10)</td>
<td>2.0 (1-9)</td>
<td>1.0 (1-6)</td>
</tr>
<tr>
<td>Total admission days/patient¶ (yr⁻¹)</td>
<td>28.5 (8-108)</td>
<td>22.0 (6-115)*</td>
<td>29.0 (8-100)</td>
<td>20.0 (7-115)*</td>
</tr>
<tr>
<td>Rehabilitation, n (%)</td>
<td>50 (50%)</td>
<td>51 (51%)</td>
<td>25 (46%)</td>
<td>30 (56%)</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>0.67 (0.23)</td>
<td>0.65 (0.23)</td>
<td>0.70 (0.24)</td>
<td>0.70 (0.25)</td>
</tr>
<tr>
<td>FEV₁ (% pred)</td>
<td>25.6 (7.8)</td>
<td>25.7 (8.6)</td>
<td>26.9 (7.7)</td>
<td>27.6 (8.6)</td>
</tr>
<tr>
<td>FVC (% pred)</td>
<td>64.3 (19.8)</td>
<td>63.6 (17.0)</td>
<td>65.7 (18.4)</td>
<td>67.8 (17.1)</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>32.5 (9.0)</td>
<td>33.0 (9.5)</td>
<td>33.9 (9.6)</td>
<td>33.8 (9.7)</td>
</tr>
<tr>
<td>PaCO₂ (kPa)</td>
<td>7.9 (1.2)</td>
<td>7.7 (1.3)</td>
<td>8.0 (1.2)</td>
<td>7.5 (1.0)</td>
</tr>
<tr>
<td>PaO₂ (kPa)</td>
<td>7.9 (2.1)</td>
<td>7.5 (1.7)</td>
<td>8.3 (1.6)</td>
<td>7.9 (1.8)</td>
</tr>
<tr>
<td>Medication, n (%)</td>
<td></td>
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<tr>
<td>Inhaled corticosteroid</td>
<td>86 (85%)</td>
<td>84 (84%)</td>
<td>43 (81%)</td>
<td>48 (89%)</td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>53 (53%)</td>
<td>38 (38%)</td>
<td>27 (50%)</td>
<td>17 (32%)</td>
</tr>
<tr>
<td>Beta agonists</td>
<td>98 (97%)</td>
<td>97 (97%)</td>
<td>52 (98%)</td>
<td>53 (98%)</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>94 (93%)</td>
<td>94 (94%)</td>
<td>49 (93%)</td>
<td>52 (96%)</td>
</tr>
<tr>
<td>Theophylline</td>
<td>37 (37%)</td>
<td>27 (27%)</td>
<td>20 (38%)</td>
<td>16 (30%)</td>
</tr>
</tbody>
</table>

Data presented as mean (SD) unless otherwise stated.

Abbreviations: BMI, body mass index; Controls, standard treatment; FEV₁, forced expiratory volume in one second; % pred, % predicted; FVC, forced vital capacity; ITT, intention-to-treat; LTOT, long-term oxygen therapy; n, numbers for analysis; NIV, noninvasive positive pressure ventilation; PaCO₂, arterial carbon dioxide pressure; PaO₂, arterial oxygen pressure.

§, pack years, duration ventilation and admissions for respiratory causes including index admission in median (range).

¶, while breathing room air, (in both groups blood samples from 21 patients were taken with oxygen as they were not able to come of oxygen).

*p<0.05 significant difference compared to NIV.
NIV settings + treatment adherence
Patients randomised for NIV were discharged with a mean ± sd IPAP of 19.2 ± 3.4, and EPAP of 4.8 ± 1.0 cm H₂O respectively, mean respiratory rate on NIV of 15 ± 3 breaths/minute, an inspiration time of 1.1 ± 0.3 seconds and a rise time of 0.2 ± 0.11 seconds. Settings were not different between the completers and the drop-outs. Sixty-eight % received oxygen combined with NIV during the night. Nearly all patients were ventilated through a full-face mask, one using a total face mask. Minor adjustments were made during the study to improve adherence, blood gasses and/or comfort. After 1 year the remaining 54 patients were ventilated with a mean IPAP of 21.0 ± 3.4 and an EPAP of 5.2 ± 1.2 cm H₂O. Two additional patients switched to a total face mask.

Mean duration of NIV use per night until death or last follow-up was 6.3 ± 2.4 hours/night in the total group and 6.9 ± 2.1 in the completers. Patients included in the per protocol analysis (NIV >5 hours) reached an average of 7.7 ± 1.5 hours/night (n=43).

Time to Event
One year after discharge 65% vs. 64% of patients (NIV vs. standard treatment) were either readmitted to hospital for COPD or had died. Figure 2 shows the ITT event-free survival of both groups in the first year, which was not significantly different (mean number of days to event was 192 and 198 for the NIV and standard treatment group respectively, p=0.85).

![Figure 2. Kaplan-Meier plot of time to event (readmission for respiratory cause or death) in patients randomised to non-invasive positive pressure ventilation (NIV) and standard treatment.](image-url)
Hospital admissions
After one year, readmission to hospital for respiratory causes occurred in 56 vs. 57% in the NIV and the standard treatment group, respectively. The median (range) number of readmissions during the 12 months of follow-up did not differ significantly between groups, (1.0 (0-9) in NIV vs. 1.0 (0-6) in the standard treatment group p=0.23), nor did the median number of total days spent in hospital (7.0 (0-107) in NIV vs. 3.5 (0-77) for standard treatment) (p=0.087)).

Survival
The number of deaths after 1 year was 30 and 29 in the NIV and standard treatment group respectively with a mean number of survival days of 299 for NIV and 291 days for the standard treatment group (p=0.99) (see supplementary files for causes of death table s2). Long-term survival is shown in figure 3, with 63 deaths in the NIV group vs. 58 in the standard treatment group.

Figure 3. Kaplan-Meier plot of long term survival curves of patients randomised to non-invasive positive pressure ventilation (NIV) and standard treatment. Because of small numbers of patients followed up after 3 years the right-hand end of the survival plots remain uncertain.
Table 2. Changes in daytime arterial blood gases

<table>
<thead>
<tr>
<th></th>
<th>ITT Baseline</th>
<th>n</th>
<th>Completers Baseline</th>
<th>n</th>
<th>Completers 12 months</th>
<th>n</th>
<th>Change over 1 year</th>
<th>n</th>
<th>Change over 1 year Similar circumstances</th>
<th>n</th>
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<tr>
<td><strong>pH</strong></td>
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<tr>
<td>NIV</td>
<td>7.38 ± 0.04</td>
<td>93</td>
<td>7.38 ± 0.04</td>
<td>46</td>
<td>7.40 ± 0.04</td>
<td>46</td>
<td>0.026 (0.010; 0.042)</td>
<td>46</td>
<td>0.022 (0.005; 0.039)</td>
<td>37</td>
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<tr>
<td>Controls</td>
<td>7.39 ± 0.04</td>
<td>99</td>
<td>7.39 ± 0.04</td>
<td>48</td>
<td>7.39 ± 0.03</td>
<td>48</td>
<td>-0.005 (-0.016; 0.006)</td>
<td>48</td>
<td>-0.005 (-0.020; 0.010)</td>
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<tr>
<td><strong>Treatment effect</strong></td>
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<td>0.03 (0.012; 0.050)</td>
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<td><strong>PaCO₂ (kPa)</strong></td>
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<tr>
<td>NIV</td>
<td>7.9 ± 1.2</td>
<td>100</td>
<td>7.7 ± 1.1</td>
<td>50</td>
<td>6.4 ± 1.0</td>
<td>50</td>
<td>-1.3 (-1.6; -0.9)</td>
<td>50</td>
<td>-1.0 (-1.4; -0.7)</td>
<td>38</td>
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<tr>
<td>Controls</td>
<td>7.7 ± 1.3</td>
<td>99</td>
<td>7.4 ± 0.9</td>
<td>48</td>
<td>6.6 ± 1.0</td>
<td>48</td>
<td>-0.8 (-1.1; -0.5)</td>
<td>48</td>
<td>-0.9 (-1.2; -0.5)</td>
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<td><strong>Treatment effect</strong></td>
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<td>-0.5 (-0.9; -0.04)</td>
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<td>-0.2 (-0.6; 0.3)</td>
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<td><strong>PaO₂ (kPa)</strong></td>
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<tr>
<td>NIV</td>
<td>7.9 ± 2.1</td>
<td>93</td>
<td>8.3 ± 1.6</td>
<td>45</td>
<td>8.3 ± 1.6</td>
<td>45</td>
<td>0 (-0.6; 0.6)</td>
<td>45</td>
<td>0.3 (-0.3; 0.9)</td>
<td>35</td>
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<tr>
<td>Controls</td>
<td>7.5 ± 1.6</td>
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<td>7.9 ± 1.9</td>
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<td>8.4 ± 1.4</td>
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<td>0.6 (-0.1; 1.2)</td>
<td>48</td>
<td>0.6 (-0.1; 1.3)</td>
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<td><strong>Treatment effect</strong></td>
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<td></td>
<td></td>
<td>0.6 (-1.4; 0.2)</td>
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<td>-0.3 (-1.2; 0.6)</td>
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<tr>
<td><strong>HCO₃⁻ (mmol/L)</strong></td>
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<tr>
<td>NIV</td>
<td>33.7 ± 4.6</td>
<td>94</td>
<td>33.0 ± 4.5</td>
<td>47</td>
<td>29.3 ± 3.5</td>
<td>47</td>
<td>-3.7 (-5.2; -2.1)</td>
<td>47</td>
<td>-3.0 (-4.8; -1.2)</td>
<td>36</td>
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<tr>
<td>Controls</td>
<td>33.6 ± 4.8</td>
<td>98</td>
<td>32.6 ± 4.1</td>
<td>48</td>
<td>28.8 ± 4.2</td>
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<td>-3.8 (-5.0; -2.6)</td>
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<td>-4.1 (-5.5; -2.7)</td>
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<tr>
<td><strong>Treatment effect</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>0.1 (-1.8; 2.1)</td>
<td></td>
<td>1.0 (-1.2; 3.3)</td>
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### BE

<table>
<thead>
<tr>
<th></th>
<th>NIV</th>
<th>Controls</th>
<th>Treatment effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BE</strong></td>
<td>7.8 ± 4.8</td>
<td>7.7 ± 3.8</td>
<td>0.5 (-1.1; 2.0)</td>
</tr>
<tr>
<td><strong>Sat (%)</strong></td>
<td>87.4 ± 6.4</td>
<td>88.4 ± 6.6</td>
<td>1.6 (-4.6; 1.3)</td>
</tr>
</tbody>
</table>

**Data presented as means (± standard deviation) and mean change (95% confidence intervals).**

Controls, standard treatment; ITT, intention-to-treat; n, numbers for analysis; NIV, noninvasive positive pressure ventilation; PaCO₂, arterial carbon dioxide pressure (kPa); PaO₂, arterial oxygen pressure (kPa); HCO₃⁻, bicarbonate (mmol/L); BE, base excess; Sat, saturation (%).

¹ Measurement performed regardless of oxygen use.

² Only comparing baseline and 12 month data when the measurements were both on room air or both on oxygen at the same flow rate. N=37 (out of 38 NIV) and n=35 (out of 37 controls) for which both measurements were performed on room air.

³ p<0.05 significant change after 12 months within the group.

⁴ p<0.05 significant difference in change after 12 months between the groups (treatment effect).
Exacerbations
No difference was observed between the annual median (range) number of exacerbations at home: 1.0 (0-9) for the NIV and 2.0 (0-14) for the standard treatment group (p=0.26).

Daytime arterial blood gases
After 12 months, daytime PaCO\textsubscript{2} improved significantly more in the NIV group compared to standard treatment (table 2, figure 4).

*Change in PaCO\textsubscript{2} was significantly better in the NIV group after 12 months (p<0.05).
Nocturnal gas exchange measurements
The mean nocturnal PtcCO\textsubscript{2} measured during the night before discharge out of hospital in the ITT group was significantly better in patients on NIV compared to standard treatment (mean difference -0.8 kPa (95% CI -1.3 to -0.4; p<0.01)). In the completers, this effect was not found at baseline but was present after 12 months; mean nocturnal PtcCO\textsubscript{2} was significantly better in the NIV group compared to standard treatment (mean difference -0.6 kPa (95% CI -1.1 to -0.1; p=0.03)).

Lung function
Mean FEV\textsubscript{1} and VC did not change significantly after 12 months within the NIV group or standard treatment group nor was there a significant change between groups (table 3).

Table 3. Changes in lung function

<table>
<thead>
<tr>
<th></th>
<th>ITT Baseline</th>
<th></th>
<th>Completers Baseline</th>
<th></th>
<th>Completers 12 months</th>
<th></th>
<th>Change over 1 year</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV\textsubscript{1} (litres)</td>
<td>NIV</td>
<td>0.67 (0.23)</td>
<td>99</td>
<td>0.70 (0.24)</td>
<td>48</td>
<td>0.71 (0.30)</td>
<td>48</td>
<td>0.01 (-0.05; 0.08)</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>0.65 (0.23)</td>
<td>95</td>
<td>0.72 (0.26)</td>
<td>46</td>
<td>0.76 (0.32)</td>
<td>46</td>
<td>0.04 (-0.03; 0.11)</td>
</tr>
<tr>
<td>Treatment effect</td>
<td></td>
<td>-0.024 (-0.12; 0.07)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>VC (litres)</td>
<td>NIV</td>
<td>2.1 (0.7)</td>
<td>98</td>
<td>2.1 (0.70)</td>
<td>49</td>
<td>2.2 (0.78)</td>
<td>49</td>
<td>0.09 (-0.09; 0.27)</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>2.3 (0.8)</td>
<td>95</td>
<td>2.3 (0.75)</td>
<td>46</td>
<td>2.4 (0.74)</td>
<td>46</td>
<td>0.13 (-0.08; 0.34)</td>
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<tr>
<td>Treatment effect</td>
<td></td>
<td>-0.036 (-0.31; 0.23)</td>
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</table>

Data presented as means (± standard deviation) and mean change (95% confidence intervals). Controls, standard treatment; FEV\textsubscript{1}, forced expiratory volume in one second, post-bronchodilator; ITT, intention-to-treat; n, numbers for analysis; NIV, noninvasive positive pressure ventilation; VC, vital capacity.

* p<0.05 significant change after 12 months within the group.
** p<0.05 significant difference in change after 12 months between the groups (treatment effect).

Health related quality of life
HRQL, ADL, anxiety/depression scores and dyspnoea improved in both groups but there was no significant difference between the groups (table 4 and supplementary files s3-s7). HRQL measured by the SRI total score showed a clear trend (p=0.054) with additionally significant differences between groups on the sub domains ‘attendant symptoms and sleep’ and ‘social relationships’ in favor of the NIV group (see supplementary files).
Table 4. Changes in Health-Related Quality-of-life measurements

<table>
<thead>
<tr>
<th></th>
<th>ITT Baseline</th>
<th>Completers Baseline</th>
<th>Completers 12 months</th>
<th>Change over 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td><strong>CCQ-Total</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIV</td>
<td>3.37 ± 1.2</td>
<td>3.4 ± 1.2</td>
<td>2.9 ± 1.1</td>
<td>-0.5 (-0.2; -0.8)</td>
</tr>
<tr>
<td>Controls</td>
<td>3.31 ± 1.06</td>
<td>3.2 ± 1.0</td>
<td>2.8 ± 1.1</td>
<td>-0.5 (-0.8; -0.1)</td>
</tr>
<tr>
<td><strong>Treatment effect</strong></td>
<td>-0.04 (-0.5; 0.4)</td>
<td></td>
<td></td>
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<tr>
<td><strong>MRF-28-Total</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>NIV</td>
<td>60.88 ± 23.60</td>
<td>58.3 ± 24.3</td>
<td>51.0 ± 24.8</td>
<td>-7.3 (-12.5; 2.1)</td>
</tr>
<tr>
<td>Controls</td>
<td>60.28 ± 23.89</td>
<td>55.3 ± 24.2</td>
<td>49.4 ± 24.2</td>
<td>-5.8 (-10.8; -0.8)</td>
</tr>
<tr>
<td><strong>Treatment effect</strong></td>
<td>-1.5 (-6.6; 5.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CRQ-Total</strong></td>
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<td></td>
</tr>
<tr>
<td>NIV</td>
<td>3.47 ± 1.10</td>
<td>3.5 ± 1.1</td>
<td>4.2 ± 1.2</td>
<td>0.7 (0.4; 1.1)</td>
</tr>
<tr>
<td>Controls</td>
<td>3.59 ± 1.08</td>
<td>3.6 ± 1.1</td>
<td>4.4 ± 1.1</td>
<td>0.7 (0.5; 1.0)</td>
</tr>
<tr>
<td><strong>Treatment effect</strong></td>
<td>0.01 (-0.4; 0.4)</td>
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<tr>
<td><strong>SRI-Total</strong></td>
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<tr>
<td>NIV</td>
<td>48.14 ± 14.97</td>
<td>47.9 ± 15.1</td>
<td>55.0 ± 15.4</td>
<td>7.0 (3.4; 10.7)</td>
</tr>
<tr>
<td>Controls</td>
<td>51.33 ± 15.87</td>
<td>53.6 ± 16.9</td>
<td>55.8 ± 16.3</td>
<td>2.2 (-1.2; 5.6)</td>
</tr>
<tr>
<td><strong>Treatment effect</strong></td>
<td>4.8 (-0.1; 9.7)</td>
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<td><strong>GARS-Total</strong></td>
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<td></td>
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<tr>
<td>NIV</td>
<td>36.66 ± 7.50</td>
<td>36.3 ± 9.4</td>
<td>34.6 ± 9.4</td>
<td>-1.6 (-3.3; 0.1)</td>
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<tr>
<td>Controls</td>
<td>36.76 ± 8.54</td>
<td>34.7 ± 8.8</td>
<td>32.7 ± 8.2</td>
<td>-2.0 (-4.1; 0.1)</td>
</tr>
<tr>
<td><strong>Treatment effect</strong></td>
<td>0.4 (-2.3; 3.0)</td>
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</table>
### ADS-Total

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<tr>
<td>NIV</td>
<td>15.88 ± 9.24</td>
</tr>
<tr>
<td>Controls</td>
<td>14.48 ± 8.83</td>
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</tbody>
</table>

### Treatment effect

-1.3 (-4.1 ; 1.6)

### MRC

<table>
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</thead>
<tbody>
<tr>
<td>NIV</td>
<td>3.9 ± 1.0</td>
</tr>
<tr>
<td>Controls</td>
<td>3.8 ± 1.0</td>
</tr>
</tbody>
</table>

### Treatment effect

-0.05 (-0.6 ; 0.5)

Data presented as means (± standard deviation) and mean change (95% confidence intervals).

CCQ, Clinical COPD Questionnaire; Controls, standard treatment; CRQ, Chronic Respiratory Questionnaire; GARS, Groningen Activity and Restriction Scale; HADS, Hospital Anxiety and Depression Scale (separate scores for anxiety and depression domain); MRC, Medical Research Council dyspnoea scale; MRF-28, Maugeri Respiratory Failure-28 questionnaire; n, numbers for analysis; NIV, noninvasive positive pressure ventilation; SRI, Severe Respiratory Insufficiency questionnaire.

* p<0.05 significant change after 12 months within the group.

** p<0.05 significant difference in change after 12 months between the groups (treatment effect).

Scores represent: CCQ and MRF-28↓=HRQL↑; CRQ and SRI↑ =HRQL↑; GARS↓=ADL↑; HADS↓=mood↑; MRC↓=dyspnoea↓.
Per protocol analysis
All results were similar in the per protocol analysis comparing patients with NIV > 5 hours/night with standard treatment.

DISCUSSION
Thus far, this is the largest randomised, controlled multicenter study reporting on the effects of NIV in COPD patients with prolonged hypercapnia after an episode of NIV for ARF. It showed that nocturnal NIV does not prolong the time to readmission for respiratory causes or death in COPD patients who remain hypercapnic after ventilatory support during ARF. Compared to standard treatment alone, NIV improves daytime PaCO$_2$ and nocturnal transcutaneous PCO$_2$ but does not improve survival, number of respiratory readmissions, exacerbations, lung function, HRQL, mood state, daily activity levels or dyspnoea.

In this large study, the design was practical and executed as in ‘real-life’, which make outcomes more broadly applicable (patients remained in their own hospital and blood gas and lung function measurements were performed during their regular visits to their own pulmonologist), but does make it difficult to compare our outcomes with previous studies in this field and therefore necessitates further discussion and comparison.

First, Funck et al $^{10}$ reported positive results in an RCT including similar patients (COPD patients remaining hypercapnic after ARF requiring mechanical ventilation), showing a higher probability of clinical worsening in the control (withdrawal) group compared to the NIV group. A crucial difference in trial designs is that all patients first received NIV for 6 months after which one group was randomised to stop NIV (withdrawal group). Clinical worsening was defined as 1) an intensive care unit admission for treatment of acute-on-chronic respiratory failure requiring mechanical ventilation, but for the withdrawal group escalation additionally comprised of 2) voluntary resumption of NIV due to severe dyspnoea and 3) re-institution of NIV due to progressive hypercapnia. A pitfall of this approach was, as the authors also note themselves, that by definition the achievable endpoints depended on the group allocation of the patient as the NIV group could only qualify for the first endpoint. Results after 12 months follow-up, showed that ten patients in the withdrawal group versus two in the NIV group experienced clinical worsening ($p=0.0018$). But upon looking more closely and, comparing only the endpoint which was achievable for both groups, only three out of the initial ten patients in the withdrawal group (vs. two) were admitted to the ICU for acute-on-chronic respiratory failure. Other positive outcomes in favor of NIV were a significant difference in 6-min walking distance after 3 months and a slightly lower resting daytime pH in the withdrawal group after 12 months. Our data show a higher daytime pH in the NIV group, but we did not consider this improvement clinically relevant (as patients were not acidic at baseline). We could not perform the 6-minute walking test since most patients were too weak to perform this test adequately and safely, raising ethical concerns.
Second, in a randomised pilot trial by Cheung and colleagues² with similar inclusion criteria as in our study, chronic home NIV was compared to placebo NIV (CPAP of 5 cm H₂O). In this study primary outcome was recurrent severe COPD exacerbation with acute hypercapnic respiratory failure (AHRF), resulting in NIV, intubation or death within the following year. The proportion of patients developing this condition in 1 year was 38.5% in the NIV vs. 60.2% in the placebo group (p=0.039). Compared to our study these patients were older (mean age 70) and had a lower mean BMI (19.2) suggesting a group of patients in worse condition than in the present study. Authors point out that ethical concerns led them to be prudent and to act upon severe enough exacerbations by instituting NIV, which could indicate a bias towards earlier conversion to NIV in the CPAP group and a possible explanation for the difference in proportions between groups. Furthermore, this trial did not find a difference in survival, arterial blood gasses and adverse events between groups.

Third, our power analysis was based on the study by Chu,¹ who found that 80% of COPD patients with AHRF and who were successfully treated by NIV were readmitted to hospital for respiratory problems within the following year. Our primary outcome consisted of readmission for respiratory causes but also death, probably leading to higher percentages of patients in which ‘the event’ would occur. Ideally, it would be more appropriate to power on pilot data from our own country or a similar European Healthcare system but as this was the only study at that time we had to work with these numbers. We hypothesized that in our study the NIV group would have a 20% lower prevalence of readmission for respiratory causes than the standard treatment group (i.e. 60% prevalence of re-admission). However, our study shows a much lower prevalence of re-admission in both the NIV and the standard treatment group (56 and 57 %, respectively). A possible explanation could be that patients recruited in the study by Chu were older (mean age 73.2) and had a lower BMI (20.2), indicating a worse physical condition. Our results do show similarities with a Spanish study² which was published during our inclusion phase, reporting readmission rates of 66% due to respiratory complications in COPD patients who survived an acute exacerbation with ARF that required NIV.

As patients were included during an admission for ARF, we anticipated blood gasses to improve in the first months after discharge from hospital in both groups. Although PaCO₂ was better in the NIV group after 12 months, we did not expect to see the same level of improvement in PaCO₂ in the standard treatment group in the first 3 months (figure 4). If we assume that the improvement in the control group is the natural recovery of the disease, one might conclude, that the included patients might not be the right target group for chronic NIV. The patients in this trial are possibly a mixed cohort of acute-on-chronic respiratory failure and acute respiratory failure, and therefore a subgroup analysis might be interesting. However, the hypothesis tested in this study is still legitimate as hypercapnia persisting post exacerbation is an increasingly common reason for initiation of NIV in patients with COPD.
Another possible subgroup analyses for the future concerns the need for supplementary oxygen. This subgroup is likely to indicate a more severe disease state and this would be a group expected to have greater therapeutic benefit with chronic NIV.

In a subgroup analysis from a recent meta-analysis on the effects of NIV in stable COPD, a significant change in PaCO$_2$ after 3 months within the NIV group was found for patients with a baseline PaCO$_2$ of at least 7.3 kPa (55 mmHg), for patients who used NIV for at least 5 hours per night as well as for patients ventilated with IPAP levels of at least 18 cm H$_2$O, when compared to patients with lower IPAP levels, lower adherence or lower levels of hypercapnia. In the current study, baseline PaCO$_2$ and change in PaCO$_2$ after 12 months of ventilation were significantly correlated ($r = -0.6$, $p<0.001$). Levels of IPAP and the number of hours of NIV/night were not correlated with change in PaCO$_2$ (data not shown). Our data show that 26% of all patients in the standard treatment group had become eucapnic after 3 months time. If we extrapolate that number to the NIV group, this proportion of patients is less likely to benefit from chronic NIV. This failure to demonstrate a dose-response in number of hours and change in PaCO$_2$ is therefore likely due to the ‘dilution’ of the prolonged hypercapnic patient cohort by patients who recover and improve and become eucapnic over a longer timeframe (>48 hours in the current trial) after an acute decompensated exacerbation i.e. patients that did not have acute-on-chronic respiratory failure but acute hypercapnic respiratory failure. Possibly, in future studies, selection of patients should be based on the level of hypercapnia after 3 months of recovering at home, before initiating home NIV. However, data from within the EU has demonstrated the high mortality of this patient group in the months following an AE requiring ventilatory support and although this trial may have evaluated patients too earlier the optimum timing remains to be proven.

A limitation in our study was our inability to obtain blood gasses on patient’s standard oxygen level, as patients were reluctant to undergo testing twice. Although our aim was to only obtain samples on room air, a portion of patients refused to stop their oxygen, making comparison of data difficult. Nevertheless, patients on NIV were adequately ventilated during the night as their mean nocturnal PtCO$_2$ was significantly better compared to standard treatment.

In an RCT on NIV in stable COPD, Clini et al did not find a difference in PaCO$_2$ between NIV and the control group (LTOT) during room air breathing, whereas they did show a significant difference when measured on patients’ usual oxygen regimen.

Also, long-term oral corticosteroid treatment is suggested to negatively impact on readmission rates and outcome. Since NIV-patients more frequently received oral corticosteroids (ITT: 53% versus 38%), this could also have affected the results.
Unique is the fact we were able to obtain extensive data on HRQL. During our study, we published an article in which reliability and validity of the CCQ, CRQ, MRF-28 and SRI questionnaires was assessed and compared from our patients at baseline. Although, all four questionnaires were feasible in these type of patients, the SRI scored tested most appropriate. This is reflected in our data after 12 months which show a clear trend towards improved HRQL as measured by the SRI total score. Two out of the seven sub domains were significantly improved in the NIV group compared to standard treatment. The very opposite was reported in the RCT by McEvoy et al who demonstrated a survival advantage of chronic NIV in hypercapnic stable COPD but accompanied by a deterioration in HRQL (measured by the more general St. Georges Respiratory Questionnaire). We believe this emphasizes the need to consistently use severity-specific HRQL questionnaires like the SRI and MRF-28 to further explore the possible benefits of NIV in future research, for instance also the supportive role of NIV in advanced care planning.

CONCLUSION

We could not demonstrate an improvement in time to readmission or death by adding NIV for one year in COPD patients who remained hypercapnic after an episode of NIV for ARF. There is no reason to believe the NIV was not effective since daytime PaCO$_2$ and nighttime PCO$_2$ improved. The trend for improvement in HRQL favoring NIV, we believe nevertheless should be explored further.

ACKNOWLEDGEMENTS

We would like to thank all patients who participated in the study. Furthermore, we especially would like to thank all HMV nurse practitioners involved in patient recruitment; M. Coolen, A. Kroos, L Wijnands, P Heijnen, D. van den Assem and all participating pulmonologists and respiratory nurses who contributed to the study. Lastly, we want to thank the Dutch Lung Foundation and Stichting Astma Bestrijding.
REFERENCES


SUPPLEMENTARY FILES

METHODS

Patients
Exclusion criteria were: 1) age < 18 or => 80 years; 2) significant bronchiectasis with recurrent infections; 3) significant heart failure; 4) kyphoscoliosis; 5) neuromuscular disease; 6) obstructive sleep apnea (Apnea Hypopnea Index: AHI >15 /hr); 7) current use of Continuous Positive Airway Pressure (CPAP) or Bi-level Positive Airway Pressure (BiPAP); 8) insufficient motivation for chronic ventilatory support; 9) social circumstances making chronic ventilatory support at home impossible; 10) other diagnoses limiting life expectations.

Home Mechanical Ventilation Center
In The Netherlands we have 4 legitimated and highly experienced Home Mechanical Ventilation Centers. Patients requiring chronic ventilation at home are sent in from all hospitals in the country to be established on mechanical ventilation by these centers. The nurse practitioners are allowed to establish long-term NIV also in external hospitals and deliver care at home. For this trial as a form of quality assurance, we set up a standardized protocol for establishment and NIV set up and organized a start up meeting to make sure everybody worked according to the same standard and regulations. Also, all centers worked with the same machines.

Intervention
Patients were instructed to use NIV during the night whilst asleep and, were advised to use NIV during the day/nap times if desired.

Measurements
An overnight polygraphy or Polysomnography was performed in patients with a body mass index \( \geq 30 \text{ kg/m}^2 \), or in patients with complaints of excessive snoring, disrupted sleep or morning headache to exclude Obstructive Sleep Apnea Syndrome.

Survival, respiratory admission rates and days in hospital were checked in hospital registers and with patients general practitioner. Exacerbations at home were registered in a diary by the patient themselves.

An exacerbation was defined using a modified version of the definition of Rodriguez-Roisin, as an event in the natural course of the disease characterized by a change in the patient’s baseline dyspnoea, cough, and/or sputum that is beyond day-to-day variations, is acute in onset, and treated with antibiotics and/or prednisolone in patients with COPD.¹
Lung function
Lung function measurements included routine spirometry by means of a pneumotachograph and according to ERS criteria. Absolute values and % pred. according to normal values.

Transcutaneous measurement
Transcutaneous monitoring during the night was performed using the TOSCA to measure skin-surface PO$_2$ and PCO$_2$ to provide estimates of arterial partial pressure of oxygen and carbon dioxide (PaO$_2$ and PaCO$_2$) and saturation. The device induces hyperperfusion by local heating of the skin of the earlobe and measures the partial pressure of oxygen and carbon dioxide electrochemically. The mean nocturnal PtcCO$_2$ was measured during the night before discharge out of hospital to see if patients were adequately adjusted to NIV. Patients in the standard treatment did not receive NIV during this measurement.

Health related quality of life questionnaires
Patients completed the following questionnaires concerning health related quality of life; the Clinical COPD Questionnaire (CCQ), the Chronic Respiratory Questionnaire self reported (CRQ), the Maugeri Respiratory Failure Questionnaire -28 (MRF-28) and the Severe Respiratory Insufficiency (SRI) questionnaire. The CCQ is a self-administered, 10-item questionnaire which can be divided into three domains: symptom, functional state and mental state. Scores range from 0 to 6 with high scores indicating extremely poor health status. The CRQ (self reported) contains 20 items and measures physical function and emotional function, divided into four domains: dyspnoea, fatigue, emotion and mastery. Scores range from 1 (worse) to 7 (best). The MRF-28 contains 28 items which are divided into 3 domains; daily activity, cognitive function and invalidity. The scores range from 0 (best) to 100 (worse). The SRI contains seven domains covering 49 items: respiratory complaints, physical functioning, attendant symptoms and sleep, social relationships, anxiety, psychological well-being and social functioning. Scoring ranges between 0-100, with high scores representing better HRQL.

Other measurements
The Groningen Activity and Restriction Scale (GARS) assesses activity and disability of daily living and consists of 18 items. The Hospital Anxiety and Depression Scale (HADS) was used to determine levels of depression and anxiety. It consists of 14 questions from which seven are on detection of anxiety and seven on depression (two subscales). Dyspnoea was measured using the Medical Research Council scale (MRC).

We could not perform the 6-minute walking test since most patients were too weak to perform this test adequately and safely, raising ethical concerns. Our alternative of measuring walking distance with a pedometer also fell short, as we noticed that in the patients who barely walk, shuffling occurs leading to an underestimation as the pedometer does not always detect their effort and thus real number of steps per day.
CHAPTER 6A

Statistical analysis
Continuous variables were summarized as means and standard deviations, or medians and ranges depending on their distribution. Changes within groups were compared using the paired sample T-test. Between group comparisons of continuous variables were performed using the independent samples T-test for variables with a normal distribution or the Mann-Whitney U test for variables with a non-normal distribution. Difference in change within groups and treatment effect between groups are shown as means with associated 95% confidence intervals (C.I.) and p-value (p<0.05 was considered statistically significant).

Supplementary file Table S1. Reasons for dropping out of study

<table>
<thead>
<tr>
<th>Reason for dropping out</th>
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<th>Standard treatment n=24</th>
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<tbody>
<tr>
<td>Lack of motivation</td>
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<td>14</td>
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<tr>
<td>Unable to come for testing</td>
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<td>6</td>
</tr>
<tr>
<td>Discomfort associated with treatment</td>
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<td>-</td>
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<tr>
<td>Critical intercurrent illness:</td>
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<tr>
<td>- Dementia</td>
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</tr>
<tr>
<td>- CVA</td>
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<td>0</td>
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<tr>
<td>Switch to NIV</td>
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CVA cerebrovasculair accident; n, numbers for analysis; NIV, noninvasive positive pressure ventilation.

Supplementary file Table S2. Causes of death

<table>
<thead>
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<th>Cause</th>
<th>ITT NIV n=30</th>
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<th>Non-drop outs Standard treatment n=22</th>
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<tbody>
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<td>15</td>
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<td>1</td>
</tr>
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<td>Cardiac disease</td>
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<tr>
<td>Lung carcinoma</td>
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</table>

ITT, intention-to-treat; n, numbers for analysis; NIV, noninvasive positive pressure ventilation.
Supplementary file Table S3. Changes in the Clinical COPD Questionnaire (CCQ) sub domains

<table>
<thead>
<tr>
<th></th>
<th>ITT Baseline n</th>
<th>Completers Baseline n</th>
<th>Completers 12 months n</th>
<th>Change over 1 year n</th>
<th>n</th>
</tr>
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<tbody>
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<td><strong>CCQ-Total</strong></td>
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<tr>
<td>NIV</td>
<td>3.4 ± 1.2</td>
<td>3.4 ± 1.2</td>
<td>2.9 ± 1.1</td>
<td>-0.5 (-0.2; -0.8) ³</td>
<td>48</td>
</tr>
<tr>
<td>Controls</td>
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<td>2.8 ± 1.1</td>
<td>-0.5 (-0.8; -0.1) ³</td>
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<tr>
<td><strong>Treatment effect</strong></td>
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<td>-0.04 (-0.5; 0.4)</td>
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<td>3.1 ± 1.2</td>
<td>3.0 ± 1.2</td>
<td>2.7 ± 1.2</td>
<td>-0.3 (-0.6; 0.1)</td>
<td>51</td>
</tr>
<tr>
<td>Controls</td>
<td>3.1 ± 1.2</td>
<td>3.2 ± 1.1</td>
<td>2.8 ± 1.1</td>
<td>-0.4 (-0.7; -0.04) ³</td>
<td>51</td>
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<td><strong>Treatment effect</strong></td>
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<td>4.1 ± 1.5</td>
<td>3.5 ± 1.5</td>
<td>-0.5 (-0.9; -0.2) ³</td>
<td>49</td>
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<tr>
<td>Controls</td>
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<td>3.4 ± 1.4</td>
<td>-0.5 (-0.9; -0.1) ³</td>
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<td>-0.07 (-0.6; 0.5)</td>
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<td>NIV</td>
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<td>1.7 ± 1.3</td>
<td>-1.0 (-1.4; -0.6) ³</td>
<td>50</td>
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<tr>
<td>Controls</td>
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<td>2.2 ± 1.6</td>
<td>1.6 ± 1.5</td>
<td>-0.6 (-1.0; -0.2) ³</td>
<td>51</td>
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<tr>
<td><strong>Treatment effect</strong></td>
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<td>-0.40 (-1.0; 0.2)</td>
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</tr>
</tbody>
</table>

Data presented as means (± standard deviation) and mean change (95% confidence intervals).
CCQ, Clinical COPD Questionnaire; ITT, intention-to-treat; n, numbers for analysis; NIV, non-invasive positive pressure ventilation.
³p<0.05 significant change after 12 months within the group.
*p<0.05 significant difference in change after 12 months between the groups (treatment effect).
Low CCQ scores indicate high quality of life. A negative treatment effect signifies a bigger improvement after 12 months for the NIV group compared to standard treatment.
### Supplementary file Table S4. Changes in the Maugeri Respiratory Questionnaire-28 (MRF-28) sub domains

<table>
<thead>
<tr>
<th></th>
<th>ITT Baseline</th>
<th>Completers Baseline</th>
<th>Completers 12 months</th>
<th>Change over 1 year</th>
<th>n</th>
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<tbody>
<tr>
<td><strong>MRF-28-Total</strong></td>
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<tr>
<td>NIV</td>
<td>60.9 ± 23.6</td>
<td>58.3 ± 24.3</td>
<td>51.0 ± 24.8</td>
<td>-7.3 (-12.5; -2.1)</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Controls</td>
<td>60.3 ± 23.9</td>
<td>55.3 ± 24.2</td>
<td>49.4 ± 25.0</td>
<td>-5.8 (-10.8; -0.8)</td>
<td>51</td>
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<tr>
<td>Treatment effect</td>
<td></td>
<td></td>
<td></td>
<td>-1.5 (-8.6; 5.7)</td>
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<tr>
<td><strong>Daily activities</strong></td>
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<td>NIV</td>
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<td>62.0 ± 29.9</td>
<td>54.5 ± 35.4</td>
<td>-7.5 (-15.0; 0.03)</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Controls</td>
<td>61.7 ± 30.5</td>
<td>55.6 ± 30.7</td>
<td>46.3 ± 29.2</td>
<td>-9.3 (-16.1; -2.4)</td>
<td>51</td>
<td>51</td>
</tr>
<tr>
<td>Treatment effect</td>
<td></td>
<td></td>
<td></td>
<td>1.7 (-8.4; 11.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cognition</strong></td>
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</tr>
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<td>NIV</td>
<td>48.5 ± 41.0</td>
<td>44.5 ± 40.8</td>
<td>33.7 ± 36.3</td>
<td>-10.8 (-22.5; 0.8)</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Controls</td>
<td>43.3 ± 35.9</td>
<td>39.7 ± 35.4</td>
<td>36.3 ± 35.5</td>
<td>-3.4 (-12.7; 5.8)</td>
<td>51</td>
<td>51</td>
</tr>
<tr>
<td>Treatment effect</td>
<td></td>
<td></td>
<td></td>
<td>-7.4 (-22.0; 7.2)</td>
<td></td>
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<tr>
<td><strong>Invalidity</strong></td>
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<td>NIV</td>
<td>74.2 ± 31.2</td>
<td>70.6 ± 34.0</td>
<td>69.5 ± 34.8</td>
<td>-1.1 (-9.4; 7.2)</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Controls</td>
<td>68.7 ± 33.5</td>
<td>59.2 ± 37.7</td>
<td>57.3 ± 39.4</td>
<td>-2.0 (-10.0; 6.1)</td>
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<tr>
<td>Treatment effect</td>
<td></td>
<td></td>
<td></td>
<td>0.9 (-10.6; 12.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data presented as means (± standard deviation) and mean change (95% confidence intervals).

ITT, intention-to-treat; MRF-28, Maugeri Respiratory Questionnaire-28; n, numbers for analysis; NIV, noninvasive positive pressure ventilation.

1 p<0.05 significant change after 12 months within the group.

*p<0.05 significant difference in change after 12 months between the groups (treatment effect).

Low MRF-28 scores indicate high quality of life. A negative treatment effect signifies a bigger improvement after 12 months for the NIV group compared to standard treatment.
### Table S5: Changes in the Clinical Respiratory Questionnaire (CRQ) sub domains

<table>
<thead>
<tr>
<th></th>
<th>ITT Baseline</th>
<th>Completers Baseline</th>
<th>Completers 12 months</th>
<th>Change score 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CRQ-Total</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>NIV</td>
<td>3.5 ± 1.1</td>
<td>3.5 ± 1.1</td>
<td>4.2 ± 1.2</td>
<td>0.7 (0.4; 1.1) *</td>
</tr>
<tr>
<td>Controls</td>
<td>3.6 ± 1.1</td>
<td>3.6 ± 1.1</td>
<td>4.4 ± 1.2</td>
<td>0.7 (0.4; 1.0) *</td>
</tr>
<tr>
<td><strong>Treatment effect</strong></td>
<td>0.01 (-0.4; 0.4)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Dyspnoea</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>NIV</td>
<td>3.0 ± 2.7</td>
<td>3.1 ± 1.6</td>
<td>3.5 ± 1.7</td>
<td>0.4 (0.03; 0.8) *</td>
</tr>
<tr>
<td>Controls</td>
<td>3.25 ± 1.4</td>
<td>3.4 ± 1.5</td>
<td>3.9 ± 1.5</td>
<td>0.5 (-0.002; 0.9)</td>
</tr>
<tr>
<td><strong>Treatment effect</strong></td>
<td>-0.02 (-0.6; 0.6)</td>
<td></td>
<td></td>
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<tr>
<td><strong>Fatigue</strong></td>
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<tr>
<td>NIV</td>
<td>2.70 ± 1.3</td>
<td>2.8 ± 1.3</td>
<td>3.8 ± 1.5</td>
<td>1.0 (0.5; 1.4) *</td>
</tr>
<tr>
<td>Controls</td>
<td>2.62 ± 1.2</td>
<td>2.5 ± 1.0</td>
<td>3.7 ± 1.3</td>
<td>1.1 (0.8; 1.5) *</td>
</tr>
<tr>
<td><strong>Treatment effect</strong></td>
<td>-0.2 (-0.7; 0.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Emotion</strong></td>
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<tr>
<td>NIV</td>
<td>3.93 ± 1.3</td>
<td>3.9 ± 1.3</td>
<td>4.6 ± 1.3</td>
<td>0.7 (0.3; 1.1) *</td>
</tr>
<tr>
<td>Controls</td>
<td>4.09 ± 1.2</td>
<td>4.1 ± 1.3</td>
<td>4.7 ± 1.4</td>
<td>0.6 (0.3; 0.9) *</td>
</tr>
<tr>
<td><strong>Treatment effect</strong></td>
<td>0.1 (-0.4; 0.6)</td>
<td></td>
<td></td>
<td></td>
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<td><strong>Mastery</strong></td>
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<tr>
<td>NIV</td>
<td>3.86 ± 1.4</td>
<td>3.8 ± 1.4</td>
<td>4.6 ± 1.4</td>
<td>0.8 (0.4; 1.2) *</td>
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<tr>
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<td>4.0 ± 1.4</td>
<td>5.0 ± 1.4</td>
<td>0.9 (0.5; 1.3) *</td>
</tr>
<tr>
<td><strong>Treatment effect</strong></td>
<td>-0.1 (-0.7; 0.4)</td>
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</tbody>
</table>

Data presented as means (± standard deviation) and mean change (95% confidence intervals).

CRQ, Clinical Respiratory Questionnaire; ITT, intention-to-treat; n, numbers for analysis; NIV, noninvasive positive pressure ventilation.

* p<0.05 significant change after 12 months within the group.

**p<0.05 significant difference in change after 12 months between the groups (treatment effect).

High CRQ scores indicate high quality of life. A positive treatment effect signifies a bigger improvement after 12 months for the NIV group compared to standard treatment.
Supplementary file Table S6. Changes in the Severe Respiratory Insufficiency questionnaire (SRI) sub domains

<table>
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<tr>
<th></th>
<th>ITT Completers</th>
<th>Controls</th>
<th>Treatment effect</th>
<th>Change score 12 months</th>
<th>n</th>
<th>n</th>
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</thead>
<tbody>
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<td></td>
<td>Baseline</td>
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<td>Baseline</td>
<td>n</td>
<td>12 months</td>
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<td>SRI-Total</td>
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<td>NIV</td>
<td>48.1 ± 15.0</td>
<td>100</td>
<td>47.9 ± 15.1</td>
<td>50</td>
<td>55.0 ± 15.4</td>
<td>7.0 (3.4; 10.7)</td>
</tr>
<tr>
<td>Controls</td>
<td>51.3 ± 15.9</td>
<td>90</td>
<td>53.6 ± 16.9</td>
<td>51</td>
<td>55.8 ± 16.3</td>
<td>2.2 (-1.2; 5.6)</td>
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<td>NIV</td>
<td>47.9 ± 19.6</td>
<td>100</td>
<td>48.9 ± 21.2</td>
<td>50</td>
<td>55.6 ± 19.4</td>
<td>6.7 (2.1; 11.2)</td>
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<tr>
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<td>90</td>
<td>45.7 ± 18.5</td>
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<td>54.3 ± 16.7</td>
<td>8.6 (3.8; 13.5)</td>
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<td>36.5 ± 21.6</td>
<td>3.8 (-1.4; 9.0)</td>
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<tr>
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<td>90</td>
<td>37.3 ± 21.4</td>
<td>51</td>
<td>41.3 ± 21.6</td>
<td>4.1 (-1.7; 9.9)</td>
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<td>54.4 ± 17.9</td>
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<td>64.8 ± 18.0</td>
<td>10.4 (5.3; 15.5)</td>
</tr>
<tr>
<td>Controls</td>
<td>58.6 ± 20.0</td>
<td>90</td>
<td>59.9 ± 22.3</td>
<td>51</td>
<td>61.7 ± 18.4</td>
<td>1.7 (-2.9; 6.4)</td>
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<tr>
<td>NIV</td>
<td>58.3 ± 17.1</td>
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<td>56.3 ± 14.0</td>
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<td>60.9 ± 18.9</td>
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<tr>
<td>Controls</td>
<td>66.5 ± 17.1</td>
<td>90</td>
<td>68.2 ± 17.3</td>
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<td>64.3 ± 17.4</td>
<td>-3.9 (-7.7; 0.03)</td>
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<td></td>
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</tr>
<tr>
<td>Treatment effect</td>
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* p < 0.05
† p < 0.01
### Anxiety

<table>
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<th>Controls</th>
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<tr>
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<td>46.2 ± 22.5</td>
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<td>12.8 (7.1; 18.5)</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>90</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>47.0 ± 24.6</td>
<td>52.6 ± 26.3</td>
<td>5.7 (0.6; 10.7)</td>
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<tr>
<td></td>
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<td>50</td>
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<tr>
<td></td>
<td>59.8 ± 22.1</td>
<td>58.2 ± 23.0</td>
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### Well-being

<table>
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<th>Controls</th>
<th>Treatment effect</th>
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<tbody>
<tr>
<td></td>
<td>52.6 ± 20.1</td>
<td>59.3 ± 20.4</td>
<td>6.0 (-0.8; 12.8)</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>90</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>52.2 ± 19.1</td>
<td>60.4 ± 22.1</td>
<td>-0.1 (-4.7; 4.4)</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>51</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>58.1 ± 22.9</td>
<td>60.3 ± 21.3</td>
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</tr>
<tr>
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### Social functioning

<table>
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<th>Controls</th>
<th>Treatment effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>43.1 ± 40.6</td>
<td>48.0 ± 20.4</td>
<td>5.9 (-1.4; 13.2)</td>
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<td></td>
<td>100</td>
<td>90</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>44.0 ± 19.4</td>
<td>51.4 ± 21.6</td>
<td>-0.8 (-5.9; 4.4)</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>51</td>
<td>51</td>
</tr>
<tr>
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<td>49.1 ± 20.1</td>
<td>50.7 ± 23.1</td>
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<td>51</td>
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</tr>
</tbody>
</table>

Data presented as means (± standard deviation) and mean change (95% confidence intervals).

- Attendant symp+sleep, attendant symptoms and sleep sub domain; ITT, intention-to-treat; n, numbers for analysis; NIV, noninvasive positive pressure ventilation; SRI, Severe Respiratory Insufficiency questionnaire.
- \( ^* p<0.05 \) significant change after 12 months within the group.
- \( ^* p<0.05 \) significant difference in change after 12 months between the groups (treatment effect).

High SRI scores indicate high quality of life. A positive treatment effect signifies a bigger improvement after 12 months for the NIV group compared to standard treatment.
Supplementary file Table S7. Changes in the Groningen Activity and Restriction Scale (GARS), Hospital Anxiety and Depression Scale (HADS) and Medical Research Council (MRC) sub domains

<table>
<thead>
<tr>
<th></th>
<th>ITT Baseline</th>
<th>n Completers Baseline</th>
<th>n Completers 12 months</th>
<th>n</th>
<th>Change score 12 months</th>
<th>n</th>
</tr>
</thead>
<tbody>
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<td>34.6 ± 9.4</td>
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<tr>
<td>Controls</td>
<td>36.8 ± 8.5</td>
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<td>34.7 ± 1.2</td>
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<td>-1.3 (-4.1; 1.6)</td>
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Data presented as means (± standard deviation) and mean change (95% confidence intervals).

GARS, Groninger Activity Restriction Scale; HADS, Hospital Anxiety and Depression Scale; ITT, Intention-to-treat; n, numbers for analysis; NIV, noninvasive positive pressure ventilation; MRC, Medical Research Council dyspnoea scale.

* p<0.05 significant change after 12 months within the group.

**p<0.05 significant difference in change after 12 months between the groups (treatment effect).

Low GARS scores indicate better daily activity levels. Low HADS scores indicate better mood state. Lower MRC scores represent less dyspnoea. A negative treatment effect signifies a bigger improvement after 12 months for the NIV group compared to standard treatment.
REFERENCES SUPPLEMENTARY FILES

Response to: Domiciliary long term non-invasive ventilation in COPD: should we select subgroups with a better likelihood to respond to NIV in subsequent randomized controlled trials?

Struik FM
Wijkstra PJ


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Dear editor,

With great interest we read the letter of Borel as a response to the paper of Struik. Borel and colleagues suggest that future studies should focus on specific COPD subgroups that have better likelihood to response to chronic noninvasive ventilation (NIV). They recently showed that obese COPD patients respond better to NIV compared to non-obese patients. We completely agree with their suggestion about focusing on COPD subgroups for future studies and in fact we tried to do so as well. In our study we investigated the benefits of chronic NIV in COPD patients after they received ventilatory support due to acute respiratory failure. However, we focused on a more specific COPD group (in your letter called “respiratory COPD”) and as we expected chronic NIV to be more beneficial in those patients with obstructive sleep apnoea (OSA), we excluded the latter group. The mean BMI of our study population was 25 kg/m² suggesting that obesity/OSA was not the major factor in their respiratory failure. In short, we focused on a group with more pure COPD who were being treated for acute respiratory failure but who showed no response to chronic NIV. The outcome of our study is relevant as it means that COPD patients who need NIV in the acute setting are a priori not the best candidates for chronic NIV.

The 2nd comment of Borel is related to adherence and the number of hours usage of NIV. In our recent meta-analysis we found significant differences in change in PaCO₂ after 3 months in those patients who used NIV for at least 5 hours per night compared to those with less than 5 hours of usage per night. Based on this review we defined our per protocol analysis in the present study including only patients who used NIV for more than 5 hours per night. However, this did not lead to a better primary outcome.

Overall, we agree with Borel that based on their study it seems that chronic NIV is more effective in obese COPD patients, however, an RCT in this specific subgroup is lacking. In addition, we think that further subgroup analysis in our “respiratory COPD” group is needed as we believe that even in these patients responders to chronic NIV can be found.
REFERENCES


