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RESEARCH ARTICLE

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Long-term non-invasive ventilation for COPD patients following an exacerbation with acute hypercapnic respiratory failure: a randomized controlled trial

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ABSTRACT

Introduction: It remains unclear whether long-term non-invasive ventilation (LT-NIV) for patients with chronic obstructive pulmonary disease (COPD) improves survival and reduces admissions as results from randomized trials are inconsistent. We aim to determine whether LT-NIV initiated after an admission with acute hypercapnic respiratory failure (AHRF) can affect survival and admission rate in COPD patients.

Methods: A randomized controlled open-label trial, allocating patients with COPD to LT-NIV or standard of care immediately after an admission with AHRF treated with acute NIV. LT-NIV was aimed to normalize $PaCO_2$ using high-pressure NIV.

Results: The study was discontinued before full sample size due to slow recruitment. 28 patients were randomized to LT-NIV and 27 patients to standard of care. 42% of patients had a history of ≥ 2 admissions with AHRF. Median IPAP was 24 cmH_2O (IQR 20–28). The primary outcome, time to readmission with AHRF or death within 12 months, did not reach significance, hazard ratio 0.53 (95% CI 0.25–1.12) $p = 0.097$. In a competing risk analysis, adjusted for history of AHRF, the odds ratio for AHRF within 12 months was 0.30 (95% CI 0.11–0.87) $p = 0.024$. The LT-NIV group had less exacerbations (median 1 (0–1) vs 2 (1–4) $p = 0.021$) and readmissions with AHRF (median 0 (0–1) vs 1 (0–1) $p = 0.016$).

Conclusion: The risk of the primary outcome, time to readmission with AHRF or death within 12 months was numerically smaller in the LT-NIV group, however, did not reach significance. Nevertheless, several secondary outcome analyses like risk of AHRF, number of episodes of AHRF and exacerbations were all significantly reduced in favour of high-pressure LT-NIV, especially in patients with frequent AHRF.

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Introduction

In chronic obstructive pulmonary disease (COPD), domiciliary nocturnal long-term non-invasive ventilation (LT-NIV) is widely used treatment to reduce acute exacerbations (AECOPD) and mortality in highly selected patients with chronic respiratory hypercapnic failure [1]. In two randomized controlled trials (RCT), aiming to reduce arterial carbon dioxide pressure ($PaCO_2$) with high-pressure LT-NIV, using inspiratory positive airway pressure (IPAP) higher than 21 mm Hg, in patients with $PaCO_2$ above 7 kPa, mortality was significantly reduced [2,3]. The studies differ regarding patient AECOPD history, one study included stable patients with no AECOPD within 4 weeks before randomization [2], while the other investigated less stable patients with persistent

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hypercapnia 2–4 weeks after admission with acute hypercapnic respiratory failure (AHRF) [3]. Other RCTs have found inconsistent results regarding survival and admission rates which may be explained by the different approaches regarding timing of inclusion after AECOPD [4–6] and pressure settings [6–9]. Prospective observational studies providing LT-NIV to COPD patients with recurrent admission with AHRF found a significant reduction in AHRF frequency [10,11]. No RCTs have considered patients' history of AHRF before LT-NIV initiation.

The present trial was initiated in 2013 when data from RCTs on LT-NIV for COPD was sparse. The aim was to determine whether LT-NIV can affect admission rate and survival in COPD patients who have been admitted with AHRF. We hypothesized that patients admitted with AHRF once are at great risk of readmissions which can be prevented by self-treatment with LT-NIV every night or intermittently when having symptoms of AECOPD. The aim of the study was to determine whether LT-NIV initiated after an admission with AHRF can affect survival and admission rate in COPD patients.

Methods

In this multi-center open-label randomized controlled trial, patients were recruited from three hospitals in urban areas of greater Copenhagen: Copenhagen University Hospital Gentofte, Hvidovre and Bispebjerg.

The study protocol was published [12] and approved by the Regional Committee on Health Research Ethics and the Danish Patient Safety Authority.

Eligibility criteria

Inclusion criteria were a) COPD diagnosis according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2012 strategy (FEV1/FVC <0.7 after bronchodilator and chronic respiratory symptoms) [13], b) admission with AHRF, arterial blood gas: pH < 7.35 and $PaCO_2$ >6 kPa after 1 h of initial treatment and c) treatment with acute NIV. Exclusion criteria were a) respiratory rate < 12/min, b) severe hypoxia requiring >15 L O_2/min, c) standard bicarbonate <20 mmol/L, d) risk of aspiration, e) recent abdominal, facial or upper airway surgery, f) malignancy or life expectancy of less than 6 months due to diseases other than COPD, g) known obstructive sleep apnoea, h) lack of acceptance and cooperation of NIV, and i) previous LT-NIV.

Randomization

Patients were recruited before discharge of index admission and randomized 1:1 either to the intervention group with LT-NIV and standard of care (SOC) or control group with SOC alone. A computer-generated block-randomization for each site was used with individually sealed envelopes prepared. The intervention was unblinded to patients and clinicians. No sham NIV was used in the control group.

Intervention

LT-NIV was initiated during index admission. Patients were trained to handle the equipment before discharge. NIV settings were adjusted aiming to normalize $PaCO_2$ (≤6.0 kPa) and base excess (−2 to +2 mM), especially IPAP, expiratory positive airway pressure (EPAP) and back up rate or breath per minute (BPM). If necessary IPAP up to 30 cmH_2O was used. Spontaneous/timed mode (ST) ventilator setting was used during admission. Patients were offered to convert to average volume-assured pressure support (AVAPS) if judged appropriate in attempt to improve patient comfort and tolerance to higher pressure settings. The BiPAP A30 ventilator (Philips Respironics) was used. Patients were encouraged to use NIV for a minimum of 6 h per night. Training and setting adjustment were performed by experienced respiratory nurses in collaboration with the principal investigators.

At the 1-month visit, patients randomized to LT-NIV with no history of AHRF and with no subjective relief of LT-NIV were given the option to use NIV intermittently. Intermittent users were instructed to resume LT-NIV, with support from the respiratory team, if experiencing increased respiratory symptoms.

All patients received thorough optimization of COPD treatment according to the GOLD strategy [13]. This included consideration of triple bronchodilator treatment and prophylactic azithromycin if indicated. Patients were offered smoking cessation support and COPD rehabilitation courses.

As a study protocol safety criterion, patients randomised to the control group who experienced ≥ 2 admission with AHRF during follow-up were able to deviate from randomization, withdraw from the study and initiate LT-NIV as rescue treatment.

Measurements and data collection

During index admission arterial blood gases were collected upon admission, during NIV treatment and at discharge. Regular clinical lab works up included blood

count, infectious, liver and kidney parameters, electrocardiogram and chest X-ray. Patients performed spirometry and answered the health-related quality-of-life (HRQoL) questionnaires before discharge. Questionnaires included Medical Research Council's Dyspnoea scale (MRC), HRQoL measured by COPD Assessment Test (CAT) [14], Severe Respiratory Insufficiency Questionnaire (SRI) [15], and sleep quality measured by the Epworth Sleepiness Scale (ESS) [16].

Follow-up visits were performed at 1 week, 3, 6, 9, and 12 months after discharge in both groups. The 1 week visit was a home visit, all other visits were outpatient clinic visits. Arterial blood gas, spirometry, and HRQoL questionnaires were collected.

Outcomes

Primary outcome was time to event (TTE), readmission with AHRF or death of all causes, within 12-month follow-up. Secondary outcomes were 1-year mortality, admissions due to respiratory causes, readmissions with AHRF, AECOPD treated with oral corticosteroids or oral antibiotics, body mass index, forced expiratory volume in one second (FEV_1) with reference scale 'Løkke 2013' [17], MRC, HRQoL measured by CAT and SRI, and sleep quality measured by ESS.

Sample size considerations

Power calculation was based on the 63.3% one-year risk of death or repeated AHRF among COPD patients having survived an admission with NIV treatment of AHRF in the study by Chu et al. [18] and the proportion of patients in the LT-NIV group, 38.5%, who developed AHRF during the on-year follow-up in the RCT by Cheung et al. [6]. We accepted a 0.05 risk of type 1 error (α) and 0.2 of type 2 error (β). With a power (1-β) of 0.8, the needed sample size was 120. With expected dropout of 20%, we intended to include 150 patients, 75 in each arm.

Statistical analysis

The original statistical analysis plan was adjusted when a decision of early study termination before reaching full sample size was made. This was done before any member of the study group had knowledge of the results, and after consultation with an independent researcher without connection to the study.

The primary composite outcome of readmission with AHRF or death within 12-month follow-up, was analysed as TTE in an unadjusted Cox proportional hazards regression. Adjustment was performed for age, if ≥2 years age difference between the groups, and sex if > 10% difference. Kaplan-Meier estimator survival analysis and log-rank test were performed. Analyses were performed as Intention-To-Treat (ITT) and modified ITT (mITT) not including patients discontinuing early, before discharge of index admission.

Two exploratory outcome analyses were included to investigate the influence of patients' history of AHRF. First, an additive cox model of the primary TTE analysis was performed, adjusting for the potential confounder, history of ≥ 2 admissions with AHRF within the year before inclusion. Second, an analysis of AHRF, with mortality as a competing risk, was performed using the logit-link function for cause-specific cumulative incidence regression, adjusting for history of AHRF.

Secondary outcomes were analysed as treated in per protocol (PP) analyses. Mann-Whitney U test were used for the continuous variables and X^2-statistics for the dichotomous variables. For all-cause mortality, a Kaplan-Meier survival analysis and log rank test were performed.

For all comparisons, $p < 0.05$ was the level of significance. Analyses were performed in SAS Enterprise Guide 7.1 (SAS Institute, Cary, NC, USA) and plots made in RStudio V.1.2.5001.

Results

The study was initiated in May 2013, the last patient was randomized in March 2020 with follow-up completed in March 2021. The study was prematurely discontinued before reaching full sample size due to slow recruitment. No schedule date of closure was set in the study protocol but after seven years of slow recruitment, despite firm efforts, with no possibility to add further sites due to organizational challenges, continuation was assessed unviable when the COVID-19 pandemic emerged in early 2020. The decision was made by the primary investigator and the study group, blinded of the outcome data and study results. The funders were not involved in the decision. No interim analysis was performed before study termination.

Analysis population

In all 55 patients admitted with AHRF and receiving acute NIV in 2013–2020 were included: 5 patients at Bispebjerg hospital and 50 patients at Gentofte hospital. Further, a small number of patients ($n < 5$) were recruited at Hvidovre Hospital in 2013–2014. The case record forms of these patients were lost as hospital archives were relocated in 2020, and data could not be reconstructed, and the exact number of patients could not be identified. These patients were not

included in the analyses. In 2015, recruitment was centred at Gentofte Hospital due to organizational challenges.

Due to COVID restrictions, two patients had their final 12-month visit converted to phone consultations and did not include spirometry or blood sample.

Complete 1-year follow-up data on events and mortality were collected through electronic medical records on all randomized patients despite discontinuation. Outcomes are presented for the ITT, mITT populations, and PP with short-term follow-up (90 days) and long-term follow-up (365 days).

Randomization allocation and protocol adherence

As presented in the Consort flow diagram (Figure 1), 28 patients were randomized to the intervention LT-NIV group and 27 patients to the control standard of care group.

In the LT-NIV group, three patients discontinued early, before discharge of index admission, and were not included in the mITT analysis. During follow-up, three patients discontinued from the LT-NIV group and 18 from the control group. In the control group, 13 (48%) patients discontinued and were initiated on rescue LT-NIV due to recurrent AHRF. In the intervention group, eight patients (32%) chose to continue as intermittent LT-NIV users after 1-month follow-up. One participant was non-compliant within the first month of follow-up, using NIV less than 6 h per night, but continued with intermittent LT-NIV.

Baseline characteristics and data from the index admission are presented in Table 1. Overall randomization was well balanced, except for BMI, which was significantly lower in the control group, $p = 0.045$. Collectively, 42% of patients had a history of ≥ 2 admissions with AHRF within the year before study inclusion.

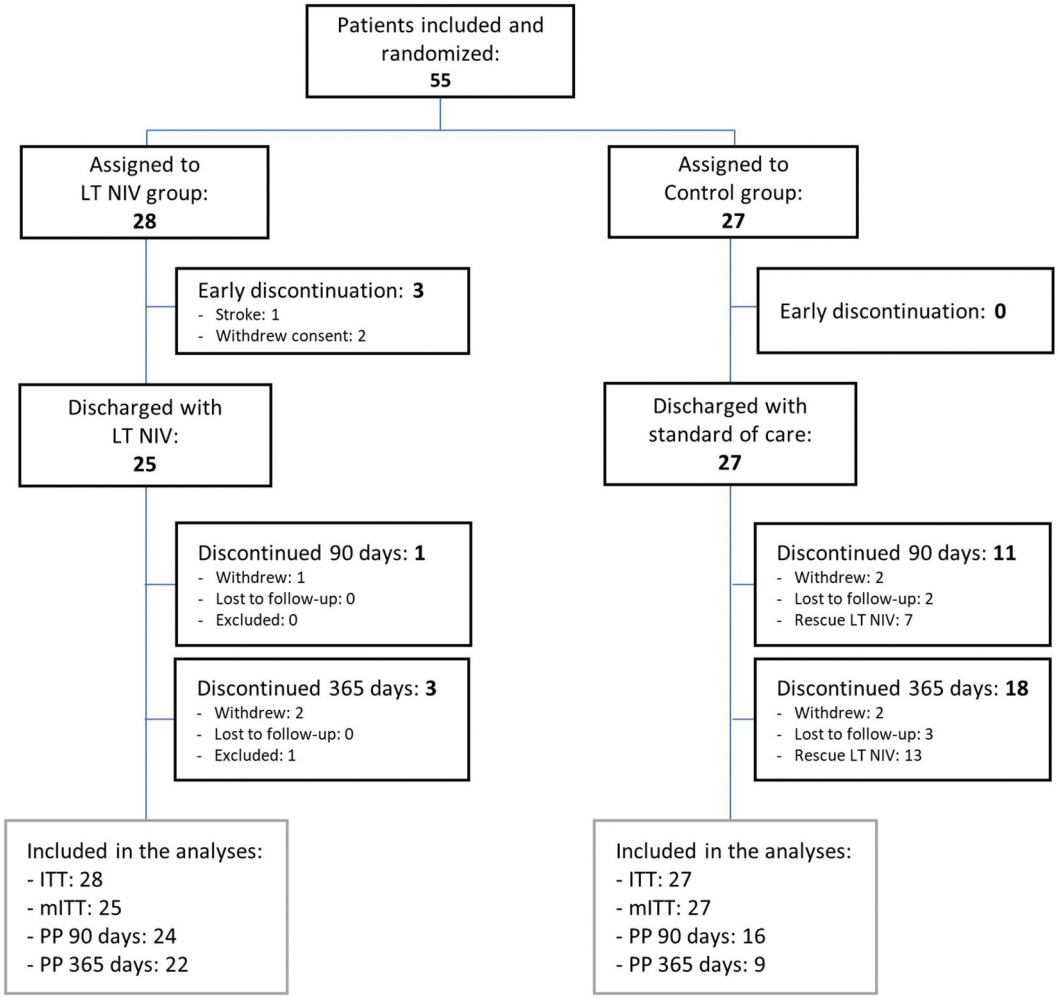

Figure 1. Consort flow diagram. ITT: Intention-To-Treat analysis, mITT: modified Intention-To-Treat analysis, PP: per protocol analysis.

Table 1. Baseline characteristics and index admission data for patients included in the intention-to-treat (ITT) analysis, presented as median (IQR) unless otherwise stated.

		ITT	
Baseline characteristics	n	LT-NIV ($n = 28$)	Control ($n = 27$)
Age, years,	55	70 (66–75)	73 (64–77)
Female Sex, n (%)	55	16 (57%)	13 (48%)
Body mass index (BMI), kg/m^2	52	27.7 (21.7–32.8)	21.8 (19.1–26.6)
Long-term oxygen treatment (LTOT), n (%)	55	14 (50%)	16 (59%)
Pack years	54	46 (35–50)	50 (30–55)
Smoking history, n (%)	55	13 (46%)	11 (41%)
– Current		15 (54%)	15 (56%)
– Previous		0 (0%)	1 (4%)
– Never			
Forced expiratory volume, first second of expiration (FEV_1), liter	54	0.6 (0.5–0.8)	0.6 (0.5–0.8)
FEV_1, % predicted	54	24 (21–30)	28 [18-]33)
Forced vital capacity (FVC), liter	54	1.4 (1.1–1.9)	1.7 (1.4–2.0)
FVC, % predicted	53	44 (41–53)	51 (43–67)
FEV_1/FVC ratio	54	0.4 (0.4–0.5)	0.4 (0.3–0.4)
COPD related medication, n (%)	55	27 (96%)	24 (89%)
- Long-acting muscarinic antagonist (LAMA)		27 (96%)	27 (100%)
- Long-acting beta2 agonist (LABA)		19 (68%)	23 (85%)
- Inhalation corticosteroids (ICS)		2 (7%)	2 (7%)
- Oral corticosteroids (OCS)		4 (14%)	1 (4%)
– Theophylline		3 (11%)	2 (7%)
– Roflumilast		3 (11%)	1 (4%)
– Azithromycin			
No. Moderate AECODP last year	55	2 (1–4)	2 (0–4)
No. admissions respiratory cause last year	55	1 (0–4)	1 (0–3)
No. admissions with AHRF last year	55	0 (0–1)	0 (0–1)
≥ 2 AHRF last year, n (%)		13 (46%)	10 (37%)
Comorbidities n (%)	55	8 (29%)	6 (22%)
– Heart failure		12 (43%)	7 (26%)
– Osteoporosis		5 (18%)	5 (19%)
– Depression			
Medical Research Council dyspnoea score (MRC)	53	4 (3,4)	4 (3,4)
Severe Respiratory Insufficiency questionnaire (SRI)	50	12 (3-28)	20 (11-27)
COPD Assessment Test (CAT)	53	22 (15-25)	20 [15-]26)
Epworth sleepiness scale (ESS)	52	9 (5–11)	6 (3–10)
Index admission data			
Length of hospital stay, days	52	7 (5–11)	6 (4–10)
Blood gas at admission, before initiation of acute NIV	55	10.0 (8.6–11.3)	9.0 (7.9–10.5)
- Partial arterial carbon dioxide pressure ($PaCO_2$), kPa	55	10.2 (8.2–12.6)	9.9 (8.0–11.5)
- Partial arterial oxygen pressure (PaO_2), kPa	55	7.29 (7.23–7.32)	7.28 (7.25–7.32)
– pH	53	92 (89–95)	92 (90–95)
- Oxygen saturation (SaO_2) (%)	53	27.5 (24.3–33.3)	28.5 (25.6–31.8)
- Standard bicarbonate ($StHCO_3$)	52	6.0 (2.6–8.8)	5.8 (3.2–10.0)
- Base Excess (BE)			
Blood gas at discharge	50	6.9 (6.3–7.6)	6.9 (6.1–7.5)
- $PaCO_2$ (kPa)	49	7.9 (7.4–9.1)	8.9 (7.2–10.6)
- PaO_2 (kPa)	50	7.43 (7.41–7.45)	7.42 (7.39–7.45)
– pH	49	92 (90–94)	93 (90–96)
- SaO_2	49	31.5 (30.1–34.2)	30.8 (28.7–32.9)
- $StHBO_3$	48	8.7 (6.6–12.1)	8.3 (5.4–11.4)
– BE			
$PaCO_2$ ≤6.0 kPa at discharge, n (%)	50	4 (16%)	8 (30%)
NIV maximum pressures, cmH_2O	47	21 (18-24)	18 (16-22)
- Inspiratory positive airway pressure (IPAP)	47	5 (5,6)	5 (5,6)
- Expiratory positive airway pressure (EPAP)			

NIV settings

Most patients, 71%, shifted from initial ST mode to AVAPS during follow-up. At the final 12-month visit, median IPAP was 24 cmH_2O (IQR 20–28), median EPAP 5 cmH_2O (IQR 5–5), and median back up rate 12 BPM (IQR 12–14).

Primary outcome

The time to readmission with AHRF or death within 12 months in the ITT population is presented in Kaplan-Meier Estimates (Figure 2), Log rank test: $p = 0.092$.

The crude cox proportional hazards regression model showed no significant effect of LT-NIV on the

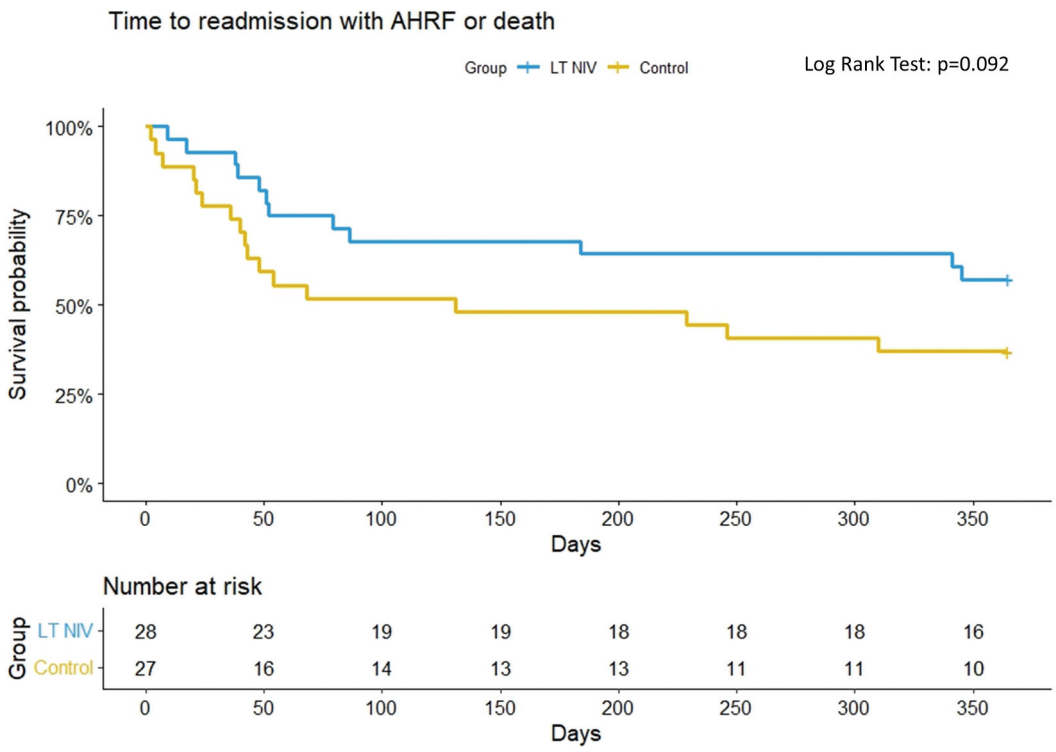

Figure 2. Kaplan-Meier curves of the primary outcome, time to event: readmission with acute hypercapnic respiratory failure (AHRF) or death, intention-to-treat analysis.

Table 2. Primary outcomes and exploratory outcomes for the intention-to-treat (ITT) analysis and modified intention-to-treat (mITT) analysis, HR: hazard ratio, OR: odds ratio.

Primary outcome analyses	ITT (n 55)	p	mITT (n 52)	P
Time to event; readmission with AHRF or death, Log rank test		0.092		0.196
Time to event; admission with AHRF or death, HR (95% Confidence Interval (CI))	0.53 (0.25–1.12)	0.097	0.62 (0.29–1.29)	0.200
Time to event; admission with AHRF or death, adjusted for age, HR (95%CI)	0.54 (0.26–1.13)	0.244	0.62 (0.29–1.30)	0.203
Exploratory outcome analyses				
Time to event; admission with AHRF or death, adjusted for history of AHRF, HR (95%CI)	0.51 (0.24–1.07)	0.004	0.57 (0.27–1.20)	0.139
Time to event; admission with AHRF or death, adjusted for age and history of AHRF, HR (95%CI)	0.51 (0.24–1.08)	0.010	0.57 (0.27–1.21)	0.142
Cumulative incidence for readmission with AHRF, adjusting for history of AHRF, OR (95%CI)	0.30 (0.11–0.87)	0.024	0.35 (0.12–0.99)	0.047

probability of event, readmission with AHRF or death, hazard ratio (HR) 0.53 (95%CI: 0.25–1.12), $p = 0.097$, nor in the additive model, adjusting for age (Table 2).

Explorative outcomes

In the first exploratory ITT analysis of the TTE, readmission with AHRF or death, the additive cox model adjusting history of AHRF showed a significant effect of LT-NIV, HR 0.51 (95%CI: 0.24–1.07), $p = 0.004$, with similar results when also adjusting for age (Table 2). In the second exploratory analysis of readmission with AHRF, with mortality as a competing risk, adjusting for history of AHRF, the odds ratio within 365 days was 0.30 (95%CI: 0.11–0.87), $p = 0.024$.

Secondary outcomes

Data on exacerbations, admissions and mortality are presented in Table 3. Number of AECOPD were significantly lower in the LT-NIV group in the ITT analysis, median 1 (IQR 0–1) compared to 2 (IQR 1–4), $p = 0.021$, as well as both short- and long-term follow-up in the PP analysis. Number of readmissions with AHRF were significantly lower in the LT-NIV group in the ITT analysis, median 0 (IQR 0–1) compared to 1 (IQR 0–1) $p = 0.016$, as well as short-term follow-up in the PP 90 days analysis. No difference was found in all-cause mortality and survival probability in the Kaplan-Meier survival estimator ITT analysis (Figure 3), Log rank test $p = 0.608$. The Cox model was not performed due to non-proportional hazards.

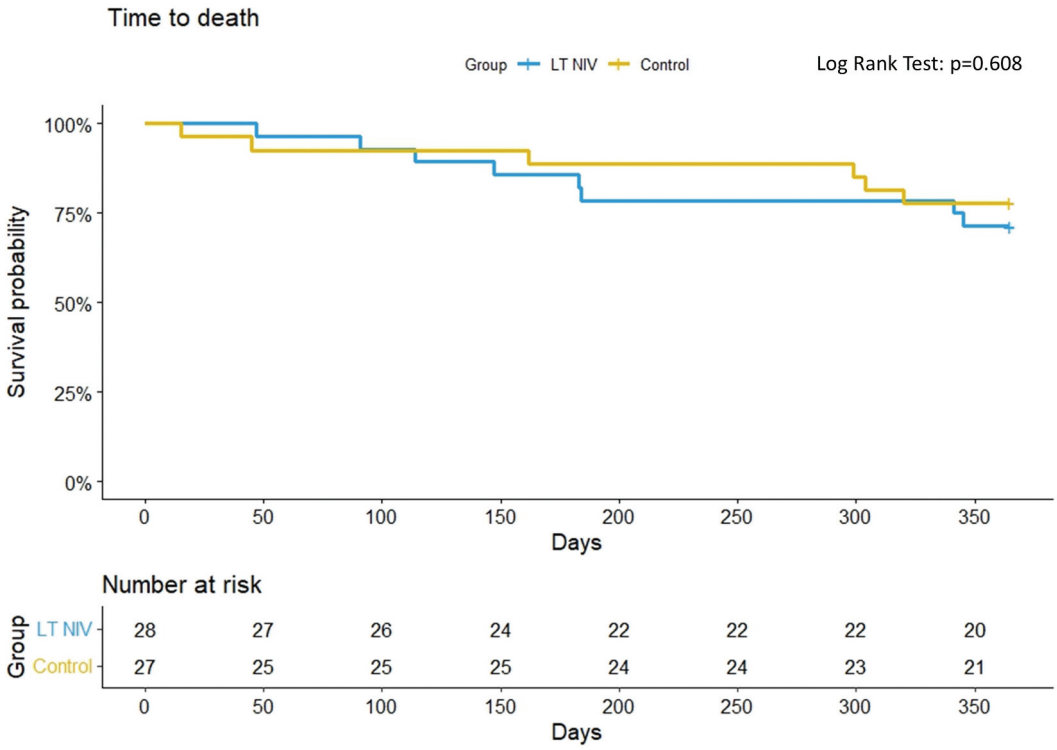

Figure 3. Kaplan-Meier survival curves.

Table 3. Secondary outcomes: number of acute exacerbations (AECOPD) treated with oral corticosteroids or oral antibiotics, admissions due to respiratory cause and admissions due to acute hypercapnic respiratory failure (AHRF). ITT: intention-to-treat analysis, mITT: modified intention-to-treat analysis, PP: per protocol analysis. Data are presented as median (IQR) or n (%). Analysis: Wilcoxon (exact) test for the continuous variables, Pearson's *chi-squared* test for categorical variables.

	ITT: 365 days follow-up		mITT: 365 days follow-up		PP: 90 days follow-up		PP: 365 days follow-up	
	LT-NIV (n 28)	Control (n 27)	LT-NIV (n 25)	Control (n 27)	LT-NIV (n 24)	Control (n 16)	LT-NIV (n 22)	Control (n 9)
No. AECOPD	1 (0–1)	2 (1–4) p = 0.021	1 (0–1)	2 (1–4) p = 0.025	1 (0–2)	4 [2–5] p = 0.001	1 (0–2)	4 [2–5] p = 0.002
No. admissions due to respiratory causes	1 (0–1)	1 (0–3) p = 0.108	1 (0–1)	1 (0–3) p = 0.173	1 (0–2)	3 [1–4] p = 0.034	1 (0–1)	1 (0–5) p = 0.156
No. admissions with AHRF	0 (0–1)	1 (0–1) p = 0.016	0 (0–1)	1 (1-0) p = 0.041	0 (0–1)	1 (0–2) p = 0.041	0 (0–1)	0 (0–1) p = 0.531
90 days mortality	2 (7%)	1 (4%) p = 0.574	1 (4%)	2 (7%) p = 0.609	1 (4%)	1 (6%) p = 0.767		
1-year mortality	9 (32%)	5 (18%) p = 0.246	8 (32%)	5 (18%) p = 0.331			7 (32%)	2 (22%) p = 0.286

Table 4 includes results on FEV_1 (% of predicted), BMI, MRC, CAT, SRI and ESS at 90 days, 365 days and change from baseline (absolute values) for the PP populations. There was a significantly lower BMI in the control group at 365 days follow-up, however with no significant change from baseline. No significant difference was seen in other secondary outcomes.

Among the eight intermittent users in the LT-NIV group, five (63%) died within 12 months follow-up. A sensitivity analysis of the secondary outcomes excluding intermittent uses from the LT-NIV group was performed (Table 6 supplement). Results were unchanged for all outcomes.

Measurements of $PaCO_2$ and PaO_2 during 1-year follow-up are presented in Table 5. At 30 days, follow-up median $PaCO_2$ was 6.0 kPa (IQR 5.5–7.34) and 7.1 kPa (IQR 6.3–8.0), $p = 0.248$ and PaO_2 9.0 kPa (IQR 7.8–9.3) and 7.3 kPa (IQR 6.3–8.0) $p = 0.069$, in the LT-NIV group and control group respectively.

Table 4. Secondary outcomes, including change from baseline in absolute values. Forced expiratory volume within first second of expiration (FEV_1 %), Body mass index (BMI), Medical Research Council dyspnoea score (MRC), COPD Assessment test (CAT), severe respiratory Insufficiency questionnaire (SRI), Epworth sleepiness scale (ESS). PP: patients included in the per protocol analysis. Presented as median (IQR) analysis: Wilcoxon test.

	PP: 90 days follow-up				PP: 365 days follow-up			
	Baseline (discharge)	At 90 days	Change within 90 days	n	Baseline (discharge)	At 1 year	Change within 1 year	n
FEV_1 %	24 (20-32)	24 (19-45)	−1.0 (−7.0–2.0)	18	24 (21–34)	35 (27–55)	−3.0 (−12.5 – −0.6)	11
- LT-NIV	29 (20-34)	26 (19-29)	1.4 (−1.9–4.1)	13	29 (18-35)	23 (15-35)	−0.4 (−2.6–2.0)	7
- Control	0.816	0.574	0.237		0.796	0.112	0.202	
p								
BMI	27.8 (21.2–33.6)	27.5 (24.4–32.1)	−0.4 (−1.8–0.6)	18	27.8 (20.1–34.4)	30.9 (27.4–33.7)	0.1 (−2.4–3.0)	10
- LT-NIV	22.9 (20.0–	24.1 (19.8–	−0.1 (−1.1–0.9)	13	21.8 (18.8–	26.7 (21.5–	−1.3 (−2.4–1.7)	7
- Control	27.2)	27.0)	0.275		26.6)	28.6)	0.601	
p	0.113	0.051			p 0.128	0.043		
MRC	4 (3–5)	3 (3-4)	1(0–1)	19	4 (3–5)	3 (3–5)	0 (0–1)	13
- LT-NIV	4 (3-4)	3 (3-4)	1(0–1)	13	4 (3-4)	3 (3,4)	0 (−1–1)	7
- Control	0.523	0.391	0.647		0.148	0.881	0.901	
p								
CAT	22 (16-25)	19 (10-27)	2(−1–7)	19	22 (16-25)	15 (12-22)	2 (−3–8)	11
- LT-NIV	20 (16-26)	18 (15–20)	4 (−2–8)	13	23 (20-27)	20 (16-28)	4 (−8–8)	7
- Control	0.874	0.872	0.711		0.561	0.205	0.893	
p								
SRI	12 (2-25)	12 (−1–28)	0.5 (−6–10)	19	12 (2-27)	15 (−15–21)	11 (3 – 32)	11
- LT-NIV	18 (11-23)	10 (0–26)	13 (−1–24)	12	20 (14-32)	16 (6– 24)	1 (−3–21)	7
- Control	0.284	0.904	0.369		0.179	0.424	0.456	
p								
ESS	8 (4–11)	4 (2–9)	2 (−3–6)	19	8 (5–11)	6 (1–9)	0 (−1–6)	11
- LT-NIV	7 (3–9)	3 (2–6)	1 (−1–3)	13	5 (4–9)	2 (2–8)	2 (0–4)	7
- Control	0.351	0.730	0.696		0.221	0.561	0.828	
p								

Discussion

In this randomized controlled clinical trial, where patients with COPD were allocated to LT-NIV or standard of care immediately after an admission with AHRF, we were not able to reach significant effect on the primary outcome; time to readmission with AHRF or death. However, in secondary outcomes, we found a significant reduction in time to readmissions with AHRF or death, as well as significantly lower likelihood of readmission with AHRF with LT-NIV in patients with a history of frequent AHRF. Additionally, AECOPD and readmissions with AHRF were lower in the LT-NIV group. The intervention aimed to normalize $PaCO_2$ with high-pressure NIV.

The present study was planned and initiated before the results from the three most recent RCTs were presented [2–4]. Patients enrolled in this study were unstable COPD patients with frequent exacerbations and admissions at baseline and during follow-up, resulting in the high number of patients in the control group receiving LT-NIV as rescue treatment. This is in contrast with the study by Köhnlein et al. which showed increased survival with high-pressure LT-NIV and included selected stable patients with few exacerbations and admissions during follow-up, quite atypical for patients with severe COPD [2]. Two RCTs included patients after admission with AHRF but inclusion criteria differed. Struik et al. included patients immediately after an admission with AHRF, with $PaCO_2$ >6.0 kPa after resolution of acute acidosis and found no effect on time to readmission with respiratory causes or death, nor on $PaCO_2$ [4]. Like the present study, patients were less stable with frequent hospital admission before inclusion. The most recent study by Murphy et al. was also performed post-exacerbation but patients were included in a stabilized phase 2–4 weeks after admission with AHRF, with $PaCO_2$ >7.1 kPa [3]. Results showed a positive effect of LT-NIV on time to hospital admission or death, a reduction of AECOPD and improved HRQoL. The intervention was aimed at reducing $PaCO_2$ using high-pressure NIV, like the present study. The notable difference between the studies by Murphy et al. and Struik et al. is the presence of hypercapnia at discharge or 2–4 weeks later, and cut-off level for hypercapnia. The present study did not require patients to be hypercapnic and no reassessment post-exacerbation was performed before inclusion. There was a trend towards lower $PaCO_2$ in LT-NIV group at 30-days

Table 5. Arterial carbon dioxide pressure ($PaCO_2$) and arterial oxygen pressure (PaO_2) measured during 1-year follow-up. Including change from baseline in absolute values. PP: patients included in the per protocol analysis. Presented as median (IQR) analysis: Wilcoxon test.

	PP: 90 days follow-up					PP: 365 days follow-up			
	Baseline (discharge)	At 30 days	At 90 days	Change within 90 days	n	Baseline (discharge)	At 1 year	Change within 1 year	n
$PaCO_2$	6.9 (6.3–7.6)	6.0 (5.5–7.34)	5.9 (5.3–6.8)	0.2 (−0.3–1.4)	17	6.9 (6.3–7.6)	6.1 (5.5–6.7)	1.2 (0.1–1.5)	13
- LT-NIV	7.1 (6.3–7.7)	7.1	6.3 (6.1–6.6)	0.9 (0.3–1.2)	13	6.9 (5.5–7.3)	6.1 (5.6–6.5)	0.9 (0.4–1.3)	7
- Control	0.652	(6.3–8.0)	0.508	0.400		0.501	0.939	0.643	
p		0.248							
PaO_2	7.7 (7.3–9.5)	9.0 (7.8–9.3)	9.0 (8.2–10.4)	−1.3 (−2.3 - −0.7)	17	7.7 (7.4–8.6)	8.7 (8.3–9.5)	−1.6 (−2.0 – −0.6)	13
- LT-NIV	8.5	7.3	8.6 (7.7–10.0)	−1.5 (−1.7–2.7)	13	8.0 (6.5–10.3)	9.4 (8.5–11.1)	−2.3 (−2.6- −1.9)	7
- Control	(6.8–10.9)	(6.3–8.0)	0.398	0.296		0.923	0.474	0.115	
p	0.652	0.069							

follow-up compared to controls although non-significant. No difference is seen later, which may be explained by the proportion of patients in the control group who were initiated on rescue LT-NIV and that completers remaining in the control group underwent spontaneous remission of hypercapnia in the post-exacerbation recovery phase. This is also seen in the study by Struik et al. including less selected patients of mixed phenotypes; patients with acute on chronic hypercapnic respiratory failure and patients without chronic respiratory failure.

Clinical guidelines on LT-NIV to patients with COPD recommend initiation of stabilized patients after re-evaluation 2–4 weeks after AECOPD, but cut off level for $PaCO_2$ vary [1,15].

The present study is unique in analysing patients' history of AHRF in the year prior to study inclusion. In the exploratory outcome analyses, history of frequent AHRF was a significant risk factor for future AHRF. This is the first RCT to confirm reduced risk of readmission with AHRF with LT-NIV in unstable COPD patients with frequent AHRF found in observational studies [10,11]. Frequent AHRF may be used for risk assessment of future admissions with AHRF, especially relevant in patients with short intervals between exacerbations, where follow-up after 2–4 weeks may be difficult. The present study is also the first RCT where furthermost patients used AVAPS, whereas previous RCTs only used ST mode.

Our finding does not support a regime with intermittent LT-NIV use as self-treatment of AECOPD. It was hypothesized to prevent admissions but unfortunately mortality was high among intermittent users. The strategy seems inferior to LT-NIV with compliance of minimum 6 h everyday use.

Limitations

The main limitation of the study is the lack of power due to the premature termination before reaching full sample size as well as missing records which could not be included in the analysis. Results should be concluded accordingly as there is risk of type II error, underestimating results with false negative conclusions, and type I error of overestimating results, why firm conclusions cannot be made.

With the study design, there is a risk of bias due to deviations from intended interventions, effecting both groups, i.e. Hawthorne effect. In the control group, a proportion of patients were initiated on the LT-NIV as rescue treatment which may have introduced bias. The patients who withdrew from the study differ from the patients remaining in the control group throughout the complete follow-up as they were assumably more severely ill, with frequent AHRF. However, results of the ITT and PP analysis were similar for both number of AECOPD as well as AHRF short term. Another potential bias is the intermittent LT-NIV users in the LT-NIV group. A sensitivity analysis was performed in attempt to determine this effect but showed no difference in outcomes when excluding intermittent users, as results were unaffected.

Unbalanced randomization caused baseline difference in BMI, with lower BMI the control group, which is a potential confounder. The role of BMI on patient outcome is not clear. However as underweight (BMI <20 kg/m^2) has been found to be associated with higher risk of mortality and severe AECOPD compared to normal weight [19] this does not necessarily weaken the study results.

All in all, the external validity and clinical implications of the present study are affected by the selected study population which were unstable patients with frequent exacerbations both on baseline and during

follow-up. The results support consideration of LT-NIV to the subgroup of unstable.

COPD patients with frequent AHRF to prevent future readmissions with AHRF and AECOPD.

It is uncertain whether further RCTs on LT-NIV will be performed with two previous trials presenting positive effect of high-pressure LT-NIV, results which are supported by the present study. Nevertheless, future studies on the optimal timing for initiation of LT-NIV and identifying patient groups eligible for treatment as well as studies investigating the role of AVAPS and simple outpatient LT-NIV initiation protocols would be of great value.

Conclusions

We did not find a significant effect of high-pressure LT-NIV on the time to readmission with AHRF or death in patients with COPD. Due to the insufficient power of the trial, our data should not be interpreted against the use of LT-NIV in COPD patients with frequent AHRF. Conversely, several secondary outcomes like risk of AHRF in patient with a history of frequent AHRF, number of episodes of AHRF and AECOPD were all in favour of high-pressure LT-NIV. Our data support the use of LT-NIV in unstable COPD patients with frequent AHRF to prevent readmissions with AHRF and AECOPD.

Disclosure statement

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Contributions

CH and JTW had full access to all data, are responsible for the overall content as guarantor and accept full responsibility for the work and conduct of the study and controlled the decision to publish. KLA, PT, JTW designed the study and obtained funding. Patient recruitment and data acquisition was made by KLA, JTW, TPS, EFH, HFA. CH performed statistical analysis. CH and JTW prepared and drafted manuscript. CH completed submission. All authors contributed to critical revision and final approval of manuscript.

Data availability statement

Data collected for this study, including individual participant data and a data dictionary defining each field in the set, will be made available to others in form of deidentified participant data. Informed consent forms will not be available according to Danish legislation. Data will become available from 1 January 2027, upon request from investigators. Requests, including study protocol with clear hypotheses should be sent to the principal investigator, and the project group will review it. If the hypothesis does comply with the informed consent supplied by the participants, and the hypothesis is judged to be valid, a data transfer agreement will be prepared, after which the data will be transferred. If the hypothesis is not covered by the informed consent, the project group will assist in preparing an application for dispensation to our ethics committee.

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