The Long-term Efficacy of Domiciliary Noninvasive Positive-Pressure Ventilation in Chronic Obstructive Pulmonary Disease: A Meta-Analysis of Randomized Controlled Trials

So Young Park, M.D., Ph.D.[1] , **Kwang Ha Yoo, M.D., Ph.D.**[2] , **Yong Bum Park, M.D., Ph.D.**[3] , **Chin Kook Rhee, M.D., Ph.D.**[4] , **Jinkyeong Park, M.D., Ph.D.**[5] , **Hye Yun Park, M.D., Ph.D.**[6] , **Yong Il Hwang, M.D., Ph.D.**[7] , **Dong Ah Park, Ph.D.**[8] and **Yun Su Sim, M.D.**[9]

*Author affiliations appear at the end of this article.

Background: We evaluated the long-term effects of domiciliary noninvasive positive-pressure ventilation (NIPPV) used to treat patients with chronic obstructive pulmonary disease (COPD).

Methods: Databases were searched to identify randomized controlled trials of COPD with NIPPV for longer than 1 year. Mortality rates were the primary outcome in this meta-analysis. The eight trials included in this study comprised data from 913 patients.

Results: The mortality rates for the NIPPV and control groups were 29% (118/414) and 36% (151/419), suggesting a statistically significant difference (risk ratio [RR], 0.79; 95% confidence interval [CI], 0.65–0.95). Mortality rates were reduced with NIPPV in four trials that included stable COPD patients. There was no difference in admission, acute exacerbation and quality of life between the NIPPV and control groups. There was no significant difference in withdrawal rates between the two groups (RR, 0.99; 95% CI, 0.72–1.36; p=0.94).

Conclusion: Maintaining long-term nocturnal NIPPV for more than 1 year, especially in patients with stable COPD, decreased the mortality rate, without increasing the withdrawal rate compared with long-term oxygen treatment.

Keywords: Noninvasive Positive-Pressure Ventilation; Chronic Obstructive Pulmonary Disease; Mortality

Address for correspondence: Yun Su Sim, M.D.
Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, Hallym University Kangnam Sacred Heart Hospital, 1 Singil-ro, Yeongdeungpo-gu, Seoul 07441, Republic of Korea
Phone: 82-2-829-5118, **Fax:** 82-2-846-4669
E-mail: sysliver@naver.com

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by irreversible limitation of air inflow induced by damage to the airway and lung parenchyma due to chronic inflammation[1,2]. Chronic hypoxia induced by long-term airflow limitation induces pulmonary vasoconstriction, polycythemia, right heart failure, and multi-organ dysfunction[1,2]. In particular, the muscle tone and respiratory muscle movements are reduced during nighttime rapid eye movement (REM) sleep[3]. Thus, ventilatory dysfunction is further exacerbated in patients with COPD in sleep state. In patients with COPD, hypoxic and hypercapnic states due to ventilatory disturbance at night are not fully resolved even during the daytime, resulting in poor prognosis[3].

Non-pharmacologic treatments for COPD include smoking cessation, oxygen therapy, rehabilitation, pneumococcal vaccination, and noninvasive positive-pressure ventilation (NIPPV)[1,2]. The use of NIPPV in patients with COPD prevents deterioration of patient's condition by assisting lung ventilation[4]. Although NIPPV treatment for acute respiratory failure resulting from COPD exacerbation improves mortality outcomes[5,6], the studies report a wide range of mortality in patients treated with domiciliary NIPPV[7-14]. A study using nasal NIPPV to treat patients with COPD found improvement in the ventilation index such as increased partial pressure of oxygen (PaO_2) and decreased partial pressure of carbon dioxide in the arterial blood ($PaCO_2$)[4]. In randomized trials of patients with COPD treated with NIPPV, the sleep quality or quality of life (QOL) improved, but not the survival rate or pulmonary function[12,14]. Other studies of patients with COPD treated with NIPPV showed improved survival outcomes[11,13,15]. A meta-analysis[16] of patients with COPD treated with NIPPV suggested that high baseline $PaCO_2$ levels are associated with good outcomes in terms of survival and hospital readmission.

Although meta-analyses of the effect of NIPPV on COPD associated with chronic respiratory failure have been conducted[16,17], few studies have analyzed the long-term efficacy of NIPPV in such patients. In the present study, we evaluated the effects of domiciliary NIPPV lasting more than a year on mortality rate, differences in QOL, admission rates, and treatment withdrawal of patients with COPD.

Materials and Methods

Databases were searched to identify randomized controlled trials (RCTs) involving long-term (more than 1 year) NIPPV treatment of COPD. The following search terms including medical keywords and headings were employed: "pulmonary disease, chronic obstructive", or "chronic obstructive lung disease", or "emphysema", and "respiratory therapy", or "non-invasive", or "bi-level". The detailed search strategy for retrieval method is included as a supplementary file (see Supplementary Table S1). Two researchers judged a number of articles on the feasibility of this study, and in case of conflict, the two
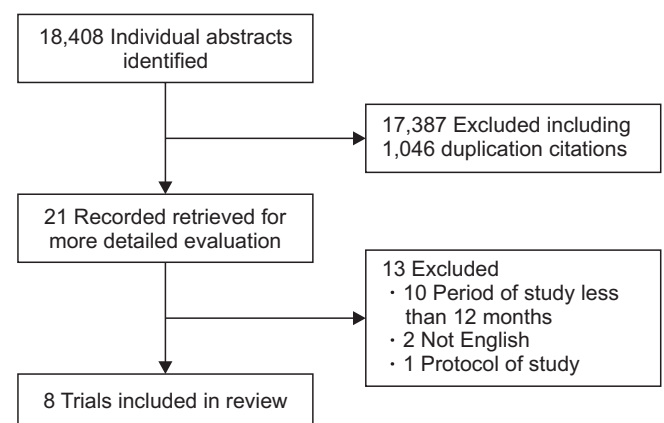

Figure 1. Study flow diagram.

Table 1. Baseline characteristics of randomized controlled trials included in the meta-analysis

Study	Patients	Male (%)	Study period (mo)	Enrollment criteria	Age (yr)	Baseline FEV$_1$ (% predicted)	Baseline PaCO$_2$ (kPa)
Casanova et al. (2000)[7]	52	98	12	Stable patients, no exacerbations in previous 3 months, PaCO$_2$ >6.93 kPa	64 vs. 68	29 vs. 31	6.8. vs. 7.1
Clini et al. (2002)[9]	90	80	24	Stable patients, pH >7.35, no exacerbations in previous 4 weeks, PaCO$_2$ >6.6 kPa	64 vs. 66	27 vs. 31	7.2 vs. 7.4
McEvoy et al. (2009)[12]	144	65	12	Stable patients, PaCO$_2$ >46 mmHg	69 vs. 61	25 vs. 23	7.0 vs. 7.3
Cheung et al. (2010)[8]	47	91	12	Post-hospital patients, PaCO$_2$ >6 kPa	70 vs. 71	28 vs. 31	10.2 vs. 10.7
Duiverman et al. (2011)[10]	72	59	24	Stable patients, no exacerbation in previous 4 weeks, PaCO$_2$ >6.0 kPa	63 vs. 61	NR	6.8 vs. 6.81
Kohnlein et al. (2014)[11]	195	62	12	Stable patients, no exacerbation in previous 4 weeks, PaCO$_2$ >7 kPa	62 vs. 64	26 vs. 28	7.8 vs. 7.7
Struik et al. (2014)[14]	201	41	12	Post-hospital patients, PaCO$_2$ > 6.0 kP	63 vs. 63	25.6 vs. 25.7	7.9 vs. 7.7
Murphy et al. (2017)[13]	116	47	12	Post-hospital patients, PaCO$_2$ >53 mmHg	66 vs. 67	24.0 vs. 22.9	7.9 vs. 7.9

Data are presented for noninvasive positive-pressure ventilation vs. usual care. All PaCO$_2$ measurements were converted into SI units (kPa).
FEV$_1$: forced expiratory volume in 1 second; PaCO$_2$: partial pressure of arterial carbon dioxide; NR: not reported.

Table 2. Treatments and outcomes of the randomized controlled trials included in the meta-analysis

Study	Treatment				Outcome					
	NIPPV target	Mean pressure (cm H$_2$O)	Actual duration of NIPPV	Treatment of control group	Mortality rate (%)	FEV$_1$	PaCO$_2$	Quality of life	Admissions	Withdrawal rate (%)
Casanova et al. (2000)[7]	Pressure	IPAP 12	6.2 hr/day (first 6 mo)	LTOT	22 vs. 22	ND	+0.05 vs. –0.11 (kPa)	NR	20 vs. 19 (no. of patients)	23 vs. 8
Clini et al. (2002)[9]	Pressure	IPAP 14	9 hr/day	LTOT	18 vs. 17	–0.3 (–13.1 to 2.4)	–0.26 kPa (NIPPV-usual)	SGRQ –5 vs. –4 (%)	6.996 (–4.30 to 18.29)	19 vs. 32
McEvoy et al. (2009)[12]	Pressure	IPAP 12.9	4.5 hr/day at night	LTOT	55 vs. 63	–1.2 vs. +2.4 (%)	–0.1 vs. –0.3 (kPa)	ND	NR	6 vs. 6
Cheung et al. (2010)[8]	Pressure	IPAP 14	7–9 hr/day at night	CPAP 5 cm H$_2$O	38.5 vs. 60.2	NR	–0.84 vs. –0.36 (kPa)	NR	56 vs. 71 (days) at first readmission	34 vs. 15
Duiverman et al. (2011)[10]	Blood gas	IPAP 23	6.9 hr/day	LTOT plus home rehabilitation	NR	0.12 (0.02–0.21)	–0.4 FkPa (NIPPV-usual)	CRQ –1.3 (–9.7 to 7.4)	NR	5 vs. 42
Kohnlein et al. (2014)[11]	Blood gas	IPAP 21.6	5.9 hr/day	LTOT	12 vs. 33	2.8 (0.2 to 5.4) (%)	–7.4 vs. –2.4 (%)	SGRQ 6.2 (0.7 to 11.8)	2.2 vs. 3.1 (no. of admissions)	2 vs. 0
Struik et al. (2014)[14]	Pressure	IPAP 21	6.3 hr/day	LTOT	30 vs. 29	–0.024 (–0.12 to 0.07)	–1.3 vs. –0.8 (kPa)	CRQ 0.01 (–0.4 to 0.4)	NR	25 vs. 24
Murphy et al. (2017)[13]	Pressure	IPAP 24	7.6 hr/day	LTOT	28 vs. 32	NR	–0.8 vs. –0.3 (kPa)	SGRQ 2.3 (–2.6 to 7.1)	0.66 (0.46–0.95)	9 vs. 22

Data are presented for NIPPV vs. usual care.

NIPPV: noninvasive positive-pressure ventilation; FEV$_1$: forced expiratory volume in 1 second; IPAP: inspiratory positive airway pressure; LTOT: long-term oxygen therapy; ND: no difference; NR: not reported; SGRQ: St. George's Respiratory Questionnaire; CPAP: continuous positive airway pressure; CRQ: Chronic Respiratory Questionnaire.

discussed and agreed. We included RCTs comparing domiciliary NIPPV with usual therapy, including long-term oxygen therapy, for the management of adult patients (18 years of age or above) with COPD.

We requested raw data for all included studies to analyze the mortality and outcomes of patient subgroups. Two authors replied, and one sent the materials in response to our request.

Two researchers independently analyzed data from the studies, including study population, year of publication, study design, NIPPV details (including duration of the study, enrollment criteria, baseline forced expiratory volume in 1 second [FEV_1], and $PaCO_2$ level), mean inspiratory positive airway pressure (IPAP) level, actual duration of NIPPV, treatment of the control group, and clinical outcomes (including mortality, QOL, admission rate, and withdrawal rate). Disagreements regarding the interpretation of data were resolved by consensus between the two investigators. The primary outcome was the all-cause mortality rate in patients with COPD. Patients were subdivided into two groups based on status at time of enrollment: (1) stable and (2) admitted to a hospital at the time of enrollment and subsequently discharged.

The methodological quality and risk of bias were assessed using a modified version of the Cochrane risk-of-bias instrument. If the two researchers disagreed about the quality and risk of bias of enrolled studies, the differences were resolved through discussion and an agreement was reached. Because NIPPV equipment was always visible to patients and medical staff, the study cannot be completely blinded to study participants. Therefore, all included studies had a high degree of performance bias. However, all studies were judged to be at low risk of bias in that the outcome measurements were not influenced by a lack of blinding of the study personnel.

We studied outcome data at the trial level and performed statistical calculations using Review Manager software (RevMan version 5.3, Nordic Cochrane Centre, Cochrane Collaboration, 2011). Continuous outcomes were reported as mean differences (a measure of absolute change), and binary outcomes were reported as risk ratios (RRs)[18]. All statistical results were two-sided. We considered p<0.05 to be statistically significant for all analyses with 95% confidential intervals (CIs)[18]. We reported the summary results for all individual trials. Further, we evaluated the between-study heterogeneity of each outcome using the I^2 statistic. We regarded statistical heterogeneity as low if I^2=25%–49%, moderate if I^2=50%–74%, and high if $I^2 \geq 75\%$[18].

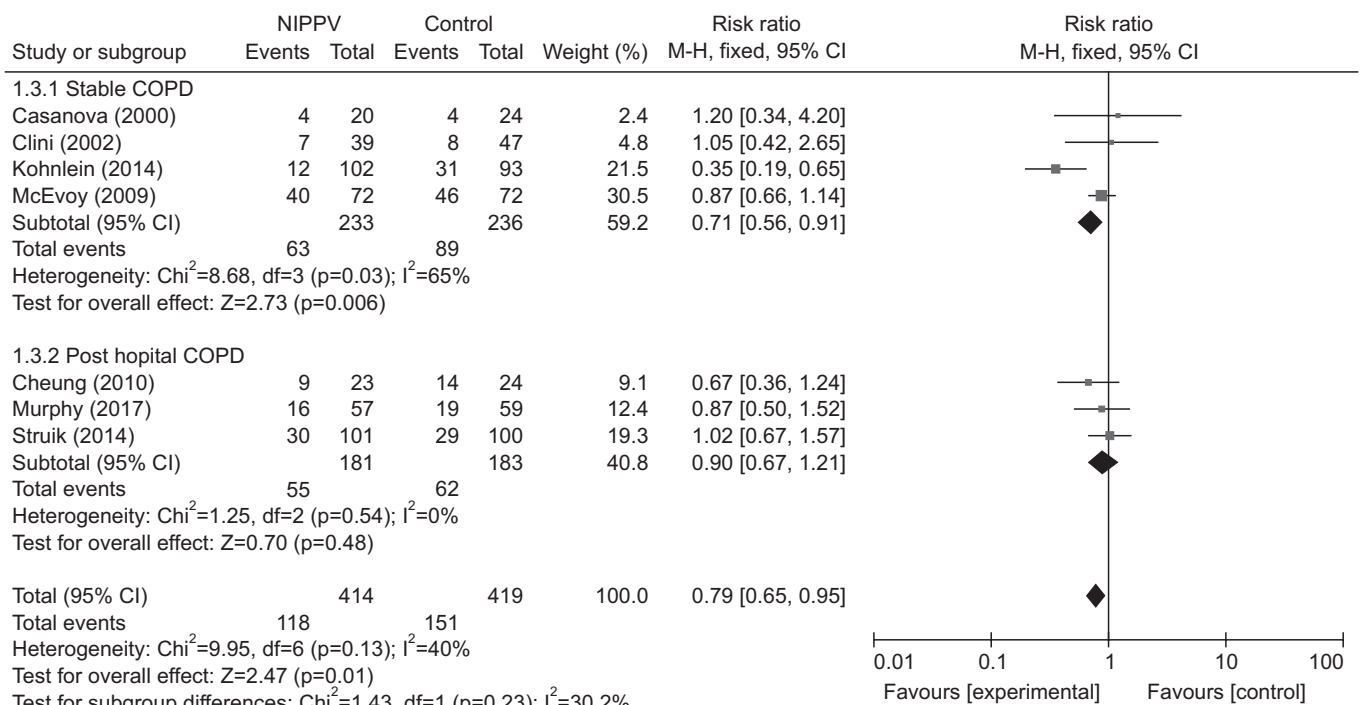| Study or subgroup	NIPPV Events	Total	Control Events	Total	Weight (%)	Risk ratio M-H, fixed, 95% CI
1.3.1 Stable COPD						
Casanova (2000)	4	20	4	24	2.4	1.20 [0.34, 4.20]
Clini (2002)	7	39	8	47	4.8	1.05 [0.42, 2.65]
Kohnlein (2014)	12	102	31	93	21.5	0.35 [0.19, 0.65]
McEvoy (2009)	40	72	46	72	30.5	0.87 [0.66, 1.14]
Subtotal (95% CI)		233		236	59.2	0.71 [0.56, 0.91]
Total events	63		89			
Heterogeneity: Chi²=8.68, df=3 (p=0.03); I²=65%						
Test for overall effect: Z=2.73 (p=0.006)						
1.3.2 Post hopital COPD						
Cheung (2010)	9	23	14	24	9.1	0.67 [0.36, 1.24]
Murphy (2017)	16	57	19	59	12.4	0.87 [0.50, 1.52]
Struik (2014)	30	101	29	100	19.3	1.02 [0.67, 1.57]
Subtotal (95% CI)		181		183	40.8	0.90 [0.67, 1.21]
Total events	55		62			
Heterogeneity: Chi²=1.25, df=2 (p=0.54); I²=0%						
Test for overall effect: Z=0.70 (p=0.48)						
Total (95% CI)		414		419	100.0	0.79 [0.65, 0.95]
Total events	118		151			
Heterogeneity: Chi²=9.95, df=6 (p=0.13); I²=40%						
Test for overall effect: Z=2.47 (p=0.01)						
Test for subgroup differences: Chi²=1.43, df=1 (p=0.23); I²=30.2%						

Figure 2. Forest plot describing the effect of noninvasive positive-pressure ventilation (NIPPV) on all-cause mortality, and the mortality rate according to the status of patients with chronic obstructive pulmonary disease (COPD)[7-9,11-14]. The vertical line depicts the equivalence in mortality rates between the two groups (NIPPV vs. control), and horizontal lines correspond to the 95% confidence intervals (CIs). The size of each square represents the proportion of information provided by each study.

Results

We identified 18,408 citations based on a search of electronic databases. Thirteen citations were retrieved for more detailed evaluation, and eight of those studies met the criteria for inclusion in our review (Figure 1). Two researchers reached a perfectly consistent decision through discussion with each other regarding inclusion of all studies. The eight trials[7-14] (Table 1) included in this study comprised data from 913 patients (median, 113 patients per trial; range, 47–201 patients). The follow-up periods in the included studies were 12–24 months.

Although there was no mortality outcome in the study of Duiverman et al.[10], we included it in our meta-analysis because it included withdrawal rates and QOL parameters.

The baseline characteristics of the included studies are presented in Table 1. Five studies involved stable COPD patients,

and three included COPD patients who were discharged after being hospitalized. Most of the patients were over 60 years of age and had severe airflow obstruction with a mean predicted FEV_1 <50%. The treatments, outcomes, and withdrawal rates documented in the studies are presented in Table 2. Data pertaining to mortality, FEV_1, QOL, admission, and withdrawal were pooled. The NIPPV target was pressure in six studies and blood gas in two studies. Four studies after 2011 set IPAP as high as 20 or higher. The actual application time of NIPPV in each study ranged from 4.5 hours to 9 hours. FEV_1 compared the two groups as a ratio or percent difference, and the degree of $PaCO_2$ decrease was compared in kPa or the difference between the two groups was described at the end of the study. The methodological quality of included trials is presented in Supplementary Figure S1.

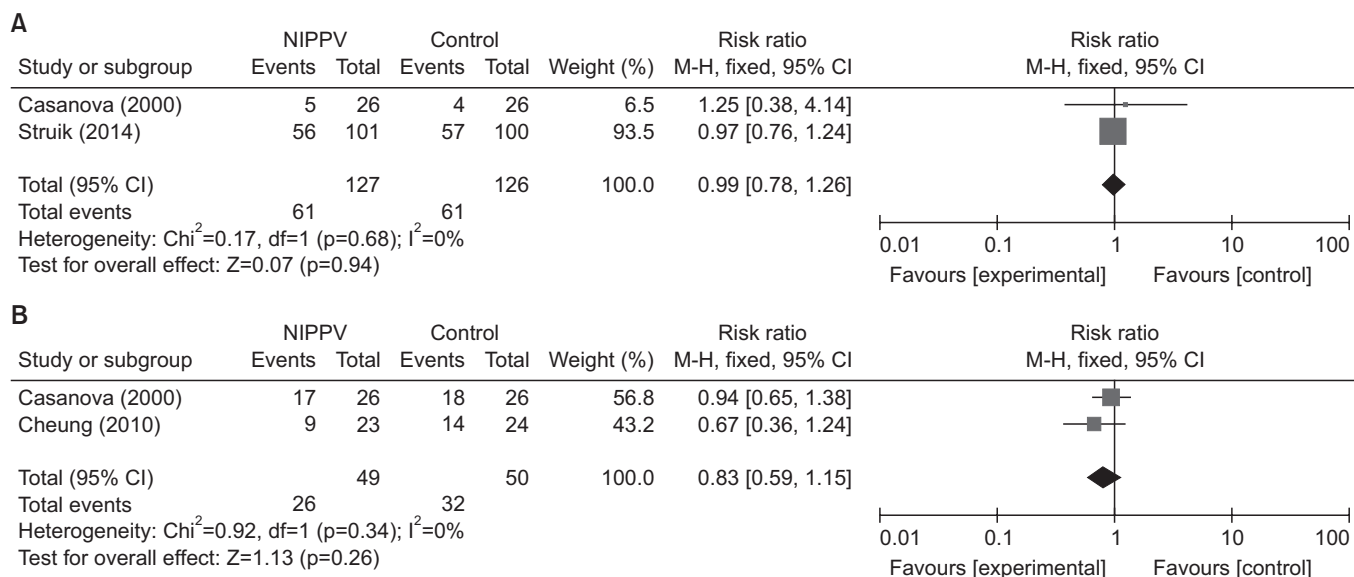Figure 2 presents mortality rates for the included stud-

A

Study or subgroup	NIPPV Events	Total	Control Events	Total	Weight (%)	Risk ratio M-H, fixed, 95% CI
Casanova (2000)	5	26	4	26	6.5	1.25 [0.38, 4.14]
Struik (2014)	56	101	57	100	93.5	0.97 [0.76, 1.24]
Total (95% CI)		127		126	100.0	0.99 [0.78, 1.26]
Total events	61		61			

Heterogeneity: Chi^2=0.17, df=1 (p=0.68); I^2=0%
Test for overall effect: Z=0.07 (p=0.94)

B

Study or subgroup	NIPPV Events	Total	Control Events	Total	Weight (%)	Risk ratio M-H, fixed, 95% CI
Casanova (2000)	17	26	18	26	56.8	0.94 [0.65, 1.38]
Cheung (2010)	9	23	14	24	43.2	0.67 [0.36, 1.24]
Total (95% CI)		49		50	100.0	0.83 [0.59, 1.15]
Total events	26		32			

Heterogeneity: Chi^2=0.92, df=1 (p=0.34); I^2=0%
Test for overall effect: Z=1.13 (p=0.26)

Figure 3. Forest plot depicting the effect of noninvasive positive-pressure ventilation (NIPPV) on admission (A) and acute exacerbation (B)[7,8,14]. The vertical line depicts the equivalence in mortality rates between the two groups (NIPPV vs. control), and the horizontal lines correspond to the 95% confidence intervals (CIs). The size of each square represents the proportion of information provided by each study.
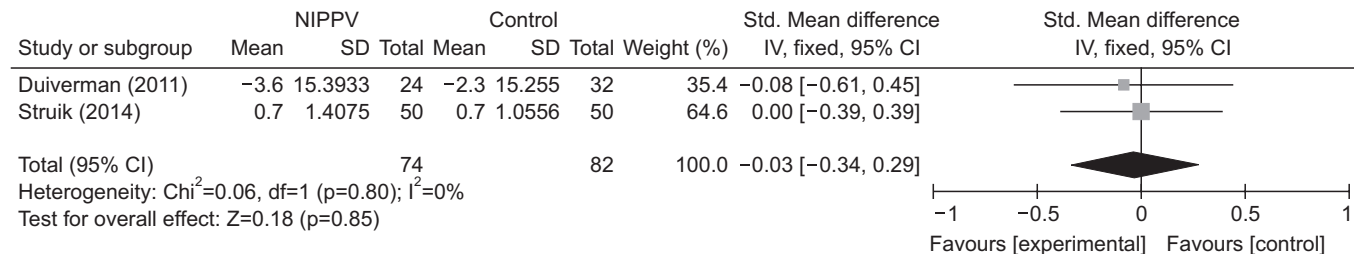
Study or subgroup	NIPPV Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Std. Mean difference IV, fixed, 95% CI
Duiverman (2011)	−3.6	15.3933	24	−2.3	15.255	32	35.4	−0.08 [−0.61, 0.45]
Struik (2014)	0.7	1.4075	50	0.7	1.0556	50	64.6	0.00 [−0.39, 0.39]
Total (95% CI)			74			82	100.0	−0.03 [−0.34, 0.29]

Heterogeneity: Chi^2=0.06, df=1 (p=0.80); I^2=0%
Test for overall effect: Z=0.18 (p=0.85)

Figure 4. Forest plot depicting the effect of noninvasive positive-pressure ventilation (NIPPV) on the Chronic Respiratory Questionnaire[10,14]. The vertical line depicts the equivalence in mortality rates between the two groups (NIPPV vs. control), and the horizontal lines correspond to the 95% confidence intervals (CIs). The size of each square represents the proportion of information provided by each study. SD: standard deviation.

ies[7-9,11-14], with the exception of Duiverman et al.[10]. The mortality rates for the NIPPV and control groups were 29% (118/414) and 36% (151/419). This difference was statistically significant (RR, 0.79; 95% CI, 0.65–0.95; p=0.01). There was statistical heterogeneity among the trials that provided mortality data (p=0.13, I²=40%). The RRs for mortality in the individual RCTs are presented in Figure 2.

The results of subgroup analyses are summarized in Figure 2. The mortality rates in the four trials that included patients with stable COPD[7,9,11,12] were reduced after exposure to NIPPV (RR, 0.71; 95% CI, 0.56–0.91; p=0.006). All-cause mortality rates in the three trials involving COPD patient post-hospital did not differ between the NIPPV and control groups (RR, 0.90; 95% CI, 0.67–1.21; p=0.48).

The results of admission and acute exacerbation in studies[7,8,14] are summarized in Figure 3. There was no difference in admission exacerbation (RR, 0.99; 95% CI, 0.78–1.26; p=0.94) and acute exacerbation (RR, 0.83; 95% CI, 0.59–1.15; p=0.26) between the NIPPV and control groups (Figure 3).

QOL was analyzed in studies[10,14] that reported Chronic Respiratory Questionnaire (CRQ) scores. There was no difference in QOL between the NIPPV and control groups (standardized mean difference, –0.037; 95% CI, –0.34 to 0.29; p=0.85) (Figure 4).

All included RCTs reported data concerning withdrawal or dropout in the NIPPV and control groups (Table 2, Figure 5). There was no significant difference in the dropout rate between the two groups (RR, 0.99; 95% CI, 0.72–1.36; p=0.94).

Discussion

The main finding of our meta-analysis was that the mortality of patients with COPD was reduced after treatment with domiciliary NIPPV for more than a year. Furthermore, the rate of withdrawal was not high in the NIPPV group, indicating that patients adapted relatively well to NIPPV.

The hypoxic and hypercapnic conditions of COPD with chronic ventilatory dysfunction lead to pulmonary vasoconstriction, polycythemia, and multiple organ dysfunction[1,2]. Therefore, the long-term use or effects of home oxygen improves survival of COPD patients[19]. However, oxygen therapy alone failed to facilitate the ventilation of patients with COPD, and occasionally, the administration of oxygen aggravated the ventilation and perfusion ratio (VQ) mismatch and increased carbon dioxide levels in the patients[19]. Because NIPPV improves ventilation in patients, it improves both hypoxic and hypercapnic status and prevents VQ mismatch in the lungs of patients treated with oxygen alone. Especially, the REM sleep state induces muscle paralysis and reduces the respiratory muscle tone in healthy people[3]. Patients with COPD exhibit a serious progression of this ventilatory dysfunction[3]. The exacerbation of hypoxia and hypercapnia during nighttime is not fully restored during daytime[3]. The deterioration in progress is accelerated in patients with COPD[3]. The improved ventilation in patients with COPD following long-term use of NIPPV may increase survival and QOL and reduce comorbidities or acute exacerbation. A small-population study reported that domiciliary NIPPV improved the ventilatory index, quality of sleep, and QOL in patients with COPD[4]. However, several randomized studies have reported conflicting results, particularly in terms of the mortality rate, ventilatory index, and QOL score[7-14]. Recently, Murphy et al.[13] suggested that home NIPPV prolonged the time to readmission or death within a 12-month period among patients with persistent hypercapnia following acute exacerbation of COPD.

A systematic review by Dretzke et al.[16] included both RCTs and retrospective studies of domiciliary NIPPV in COPD,

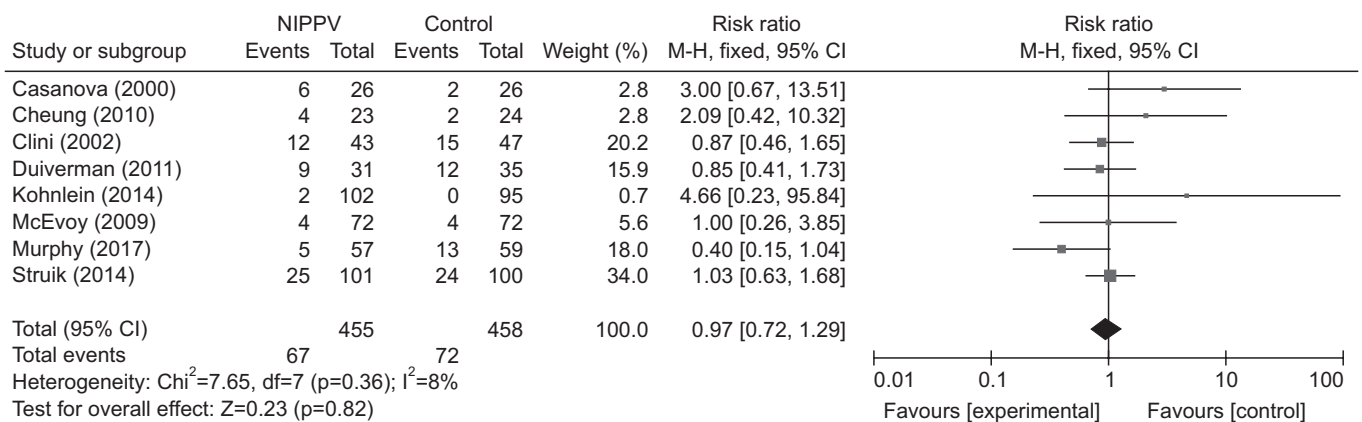| Study or subgroup | NIPPV | | Control | | | Risk ratio | Risk ratio |
	Events	Total	Events	Total	Weight (%)	M-H, fixed, 95% CI	M-H, fixed, 95% CI
Casanova (2000)	6	26	2	26	2.8	3.00 [0.67, 13.51]	
Cheung (2010)	4	23	2	24	2.8	2.09 [0.42, 10.32]	
Clini (2002)	12	43	15	47	20.2	0.87 [0.46, 1.65]	
Duiverman (2011)	9	31	12	35	15.9	0.85 [0.41, 1.73]	
Kohnlein (2014)	2	102	0	95	0.7	4.66 [0.23, 95.84]	
McEvoy (2009)	4	72	4	72	5.6	1.00 [0.26, 3.85]	
Murphy (2017)	5	57	13	59	18.0	0.40 [0.15, 1.04]	
Struik (2014)	25	101	24	100	34.0	1.03 [0.63, 1.68]	
Total (95% CI)		455		458	100.0	0.97 [0.72, 1.29]	
Total events	67		72				
Heterogeneity: Chi²=7.65, df=7 (p=0.36); I²=8%							
Test for overall effect: Z=0.23 (p=0.82)							

Figure 5. Forest plot depicting the effect of noninvasive positive-pressure ventilation (NIPPV) on withdrawal rates according to mean level of inspiratory positive airway pressure (IPAP) (≥20 cm H₂O)[7-14]. The vertical line depicts the equivalence in mortality rates between the two groups (NIPPV vs. control), and the horizontal lines correspond to the 95% confidence intervals (CIs). The size of each square represents the proportion of information provided by each study.

regardless of NIPPV duration. The review suggested that domiciliary NIPPV in COPD did not reduce mortality but did reduce mortality in stable COPD. Our analysis of all included studies involving patients with stable or post-hospital COPD showed decreasing mortality rates in patients receiving NIPPV longer than 12 months. Contrary to the results of Dretzke et al.[16], the improved survival rate of patients in the NIV-treated group in our study can be attributed to the omission of observation studies and inclusion of the latest study showing good survival rates. The subgroup analysis of COPD status showed that the mortality rates were not decreased among post-hospital COPD patients using NIPPV based on the analysis of a small number of studies. A recent study[13] included only COPD patients with persistent hypercapnia in post-hospital status, with improved mortality following home NIPPV. In the previous studies of home NIPPV involving patients of post-hospital status, the efficacy of NIPPV was not obvious because subjects with chronic ventilation dysfunction were combined with those manifesting good lung function after acute exacerbation. Although patients in the post-hospital group showed elevated $PaCO_2$ due to temporary exacerbation, the effect of NIPPV ventilation is not clear because the baseline $PaCO_2$ in stable post-hospital patients after recovery may not be high. In the other meta-analysis[16], the group with high $PaCO_2$ in the post-hospital group showed improved survival rate. The Kohnlein's study[13] reported a positive effect on mortality when patients with a high baseline $PaCO_2$ were enrolled in the post-hospital group

In the four studies investigating high IPAP after 2011, the reduction of $PaCO_2$ was greater in the NIPPV group, and the previous study showed mixed results of $PaCO_2$ suggesting that high IPAP can lead to effective ventilation and reduction of $PaCO_2$.

Analyses of additional outcomes associated with the long-term use of NIPPV, including QOL, lung function, and acute exacerbation, were difficult because of variation in the tools used for evaluation in the studies. Improvements in lung function in the included studies were assessed using the absolute FEV_1 value, the predicted value[12], or the mean difference[10,14]. It was also very difficult to assess the readmission rate or acute exacerbation rate in COPD patients. Various studies presented readmission data according to the number of re-admissions per patient[7], the total number of readmissions during the study period[11], the time to initial readmission[8], and the mean difference[13]. Further studies are required to analyze the efficacy of long-term NIPPV in COPD based on standard assessment tools for acute exacerbation, readmission, lung function, and QOL. Our study showed that QOL, as assessed by the CRQ, did not differ between the NIPPV and control groups. Additional studies investigating QOL improvement in COPD patients treated with NIPPV are needed as the benefits of intervention vary depending on the equipment used. The cost of NIPPV also needs further analysis.

A recent meta-analysis reviewed the effect of long-term NIPPV on stable hypercapnic COPD[20]; however, it included only stable patients with COPD manifesting hypercapnia, and lasted more than 3 months[20]. NIPPV may be useful in patients with persistent hypercapnia after acute exacerbation[13]. A meta-analysis of studies reporting survival in COPD following exposure to NIPPV longer than one year has yet to be reported.

NIPPV appears to be more difficult to adjust to than oxygen therapy for patients[21]. However, we did not find a difference in withdrawal rates between the NIPPV and control groups after more than a year, suggesting that patients with COPD adapted well to NIPPV over a long time, especially after adjustment.

The present analysis has several limitations. First, the included trials were somewhat diverse, given the differences in inclusion criteria, COPD severity, NIPPV duration, ventilation strategies, and associated treatments. We requested raw data for the included studies to analyze subgroups of patients and assess the settings employed by each study. Unfortunately, our request received either no response or a refusal. Second, it is likely that we did not include all of the relevant evidence because we limited our analysis to articles written in English. Third, the small number of available trials may have led to an underestimation of the heterogeneity and reduced the precision of our pooled-effect estimates.

Our systematic review demonstrated that maintaining long-term nocturnal NIPPV for more than 1 year in COPD patients, especially stable COPD, decreased the mortality rate, without increasing the withdrawal rate compared with long-term oxygen treatment. Further research in the form of large RCTs of post-hospital COPD patients with persistent hypercapnia is warranted.

*Author Affiliations

[1]Department of Internal Medicine, Ewha Womans University College of Medicine, Seoul, [2]Department of Internal Medicine, Konkuk University School of Medicine, Seoul, [3]Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, Hallym University Kandong Sacred Heart Hospital, Seoul, [4]Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, Catholic University of Korea, Seoul, [5]Division of Pulmonary, Department of Internal Medicine, Dongguk University College of Medicine, Seoul, [6]Division of Pulmonary and Critical Care Medicine, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, [7]Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, Hallym University Sacred Heart Hospital, Anyang, [8]Division of Healthcare Technology Assessment Research, Office of Health Technology Assessment Research, National Evidence-based Healthcare Collaborating Agency,

Seoul, [9]Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, Hallym University Kangnam Sacred Heart Hospital, Seoul, Republic of Korea

Authors' Contributions

Conflicts of Interest

Funding

Supplementary Material

Supplementary material can be found in the journal homepage (http://www.e-trd.org).

Supplementary Table S1. Medical subject headings and keywords in databases.

Supplementary Figure S1. Risk of bias using a modified version of the Cochrane risk-of-bias instrument.

References

1. Yoon HK, Park YB, Rhee CK, Lee JH, Oh YM; Committee of the Korean COPD Guideline 2014. Summary of the Chronic Obstructive Pulmonary Disease Clinical Practice Guideline Revised in 2014 by the Korean Academy of Tuberculosis and Respiratory Disease. Tuberc Respir Dis 2017;80:230-40.
2. Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2013;187:347-65.
3. Marrone O, Salvaggio A, Insalaco G. Respiratory disorders during sleep in chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2006;1:363-72.
4. Elliott MW, Simonds AK, Carroll MP, Wedzicha JA, Branthwaite MA. Domiciliary nocturnal nasal intermittent positive pressure ventilation in hypercapnic respiratory failure due to chronic obstructive lung disease: effects on sleep and quality of life. Thorax 1992;47:342-8.
5. Brochard L, Mancebo J, Wysocki M, Lofaso F, Conti G, Rauss A, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. N Engl J Med 1995;333:817-22.
6. Osadnik CR, Tee VS, Carson-Chahhoud KV, Picot J, Wedzicha JA, Smith BJ. Non-invasive ventilation for the management of acute hypercapnic respiratory failure due to exacerbation of chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2017;7:CD004104.
7. Casanova C, Celli BR, Tost L, Soriano E, Abreu J, Velasco V, et al. Long-term controlled trial of nocturnal nasal positive pressure ventilation in patients with severe COPD. Chest 2000;118:1582-90.
8. Cheung AP, Chan VL, Liong JT, Lam JY, Leung WS, Lin A, et al. A pilot trial of non-invasive home ventilation after acidotic respiratory failure in chronic obstructive pulmonary disease. Int J Tuberc Lung Dis 2010;14:642-9.
9. Clini E, Sturani C, Rossi A, Viaggi S, Corrado A, Donner CF, et al. The Italian multicentre study on noninvasive ventilation in chronic obstructive pulmonary disease patients. Eur Respir J 2002;20:529-38.
10. Duiverman ML, Wempe JB, Bladder G, Vonk JM, Zijlstra JG, Kerstjens HA, et al. Two-year home-based nocturnal noninvasive ventilation added to rehabilitation in chronic obstructive pulmonary disease patients: a randomized controlled trial. Respir Res 2011;12:112.
11. Kohnlein T, Windisch W, Kohler D, Drabik A, Geiseler J, Hartl S, et al. Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. Lancet Respir Med 2014;2:698-705.
12. McEvoy RD, Pierce RJ, Hillman D, Esterman A, Ellis EE, Catcheside PG, et al. Nocturnal non-invasive nasal ventilation in stable hypercapnic COPD: a randomised controlled trial. Thorax 2009;64:561-6.
13. Murphy PB, Rehal S, Arbane G, Bourke S, Calverley PM, Crook AM, et al. Effect of home noninvasive ventilation with oxygen therapy vs oxygen therapy alone on hospital readmission or death after an acute COPD exacerbation: a randomized clinical trial. JAMA 2017;317:2177-86.
14. Struik FM, Sprooten RT, Kerstjens HA, Bladder G, Zijnen M, Asin J, et al. Nocturnal non-invasive ventilation in COPD patients with prolonged hypercapnia after ventilatory support for acute respiratory failure: a randomised, controlled, parallel-group study. Thorax 2014;69:826-34.
15. Dreher M, Storre JH, Schmoor C, Windisch W. High-intensity versus low-intensity non-invasive ventilation in patients with stable hypercapnic COPD: a randomised crossover trial. Thorax 2010;65:303-8.
16. Dretzke J, Moore D, Dave C, Mukherjee R, Price MJ, Bayliss S, et al. The effect of domiciliary noninvasive ventilation on

clinical outcomes in stable and recently hospitalized patients with COPD: a systematic review and meta-analysis. Int J Chron Obstruct Pulmon Dis 2016;11:2269-86.

17. Struik FM, Lacasse Y, Goldstein RS, Kerstjens HA, Wijkstra PJ. Nocturnal noninvasive positive pressure ventilation in stable COPD: a systematic review and individual patient data meta-analysis. Respir Med 2014;108:329-37.

18. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.

19. Gorecka D, Gorzelak K, Sliwinski P, Tobiasz M, Zielinski J. Ef-

fect of long-term oxygen therapy on survival in patients with chronic obstructive pulmonary disease with moderate hypoxaemia. Thorax 1997;52:674-9.

20. Liao H, Pei W, Li H, Luo Y, Wang K, Li R, et al. Efficacy of long-term noninvasive positive pressure ventilation in stable hypercapnic COPD patients with respiratory failure: a meta-analysis of randomized controlled trials. Int J Chron Obstruct Pulmon Dis 2017;12:2977-85.

21. Ramsay M, Hart N. Current opinions on non-invasive ventilation as a treatment for chronic obstructive pulmonary disease. Curr Opin Pulm Med 2013;19:626-30.