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Association of Home Noninvasive Positive Pressure Ventilation With Clinical Outcomes in Chronic Obstructive Pulmonary Disease
A Systematic Review and Meta-analysis

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IMPORTANCE The association of home noninvasive positive pressure ventilation (NIPPV) with outcomes in chronic obstructive pulmonary disease (COPD) and hypercapnia is uncertain.

OBJECTIVE To evaluate the association of home NIPPV via bilevel positive airway pressure (BPAP) devices and noninvasive home mechanical ventilator (HMV) devices with clinical outcomes and adverse events in patients with COPD and hypercapnia.

DATA SOURCES Search of MEDLINE, EMBASE, SCOPUS, Cochrane Central Registrar of Controlled Trials, Cochrane Database of Systematic Reviews, National Guideline Clearinghouse, and Scopus for English-language articles published from January 1, 1995, to November 6, 2019.

STUDY SELECTION Randomized clinical trials (RCTs) and comparative observational studies that enrolled adults with COPD with hypercapnia who used home NIPPV for more than 1 month were included.

DATA EXTRACTION AND SYNTHESIS Data extraction was completed by independent pairs of reviewers. Risk of bias was evaluated using the Cochrane Collaboration risk of bias tool for RCTs and select items from the Newcastle-Ottawa Scale for nonrandomized studies.

MAIN OUTCOMES AND MEASURES Primary outcomes were mortality, all-cause hospital admissions, need for intubation, and quality of life at the longest follow-up.

RESULTS A total of 21 RCTs and 12 observational studies evaluating 51 085 patients (mean [SD] age, 65.7 [2.1] years; 43% women) were included, among whom there were 434 deaths and 27 patients who underwent intubation. BPAP compared with no device was significantly associated with lower risk of mortality (22.31% vs 28.57%; risk difference [RD], −5.53% [95% CI, −10.29% to −0.76%]; odds ratio [OR], 0.66 [95% CI, 0.51-0.87]; $P = .003$; 13 studies; 1423 patients; strength of evidence [SOE], moderate), fewer patients with all-cause hospital admissions (39.74% vs 75.00%; RD, −35.26% [95% CI, −49.39% to −21.12%]; OR, 0.22 [95% CI, 0.11-0.43]; $P < .001$; 1 study; 166 patients; SOE, low), and lower need for intubation (5.34% vs 14.71%; RD, −8.02% [95% CI, −14.77% to −1.28%]; OR, 0.34 [95% CI, 0.14-0.83]; $P = .02$; 3 studies; 267 patients; SOE, moderate). There was no significant difference in the total number of all-cause hospital admissions (rate ratio, 0.91 [95% CI, 0.71-1.17]; $P = .47$; 5 studies; 326 patients; SOE, low) or quality of life (standardized mean difference, 0.16 [95% CI, −0.06 to 0.39]; $P = .15$; 9 studies; 833 patients; SOE, insufficient). Noninvasive HMV use compared with no device was significantly associated with fewer all-cause hospital admissions (rate ratio, 0.50 [95% CI, 0.35-0.71]; $P < .001$; 1 study; 93 patients; SOE, low), but not mortality (21.84% vs 34.09%; RD, −11.99% [95% CI, −24.77% to 0.79%]; OR, 0.56 [95% CI, 0.29-1.08]; $P = .49$; 2 studies; 175 patients; SOE, insufficient). There was no statistically significant difference in the total number of adverse events in patients using NIPPV compared with no device (0.18 vs 0.17 per patient; $P = .84$; 6 studies; 414 patients).

CONCLUSIONS AND RELEVANCE In this meta-analysis of patients with COPD and hypercapnia, home BPAP, compared with no device, was associated with lower risk of mortality, all-cause hospital admission, and intubation, but no significant difference in quality of life. Noninvasive HMV, compared with no device, was significantly associated with lower risk of hospital admission, but there was no significant difference in mortality risk. However, the evidence was low to moderate in quality, the evidence on quality of life was insufficient, and the analyses for some outcomes were based on small numbers of studies.

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Supplemental content

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With a global prevalence estimated to be 11.7% in 2010, chronic obstructive pulmonary disease (COPD) is a respiratory illness characterized by airflow limitation and chronic respiratory symptoms.[1,2] COPD is associated with increased risk of mortality, morbidity, and health care utilization.[1] Patients with COPD are at risk for acute and chronic respiratory failure, often characterized by hypercapnia or hypoxia. Noninvasive positive pressure ventilation (NIPPV), or positive pressure ventilation delivered through a noninvasive interface, such as a facemask, can be used to improve oxygen and carbon dioxide gas exchange. In patients with acute respiratory failure due to an acute exacerbation of COPD, in-hospital use of NIPPV has been associated with decreased mortality, decreased need for intubation, shorter hospital length of stay, and fewer complications.[3]

Although in-hospital use of NIPPV for acute hypercapnic respiratory failure during exacerbation of COPD is well established, the data supporting home use for chronic hypercapnic respiratory failure in individuals with COPD are less clear.[4] Currently, there is significant variability in the use and prescribing patterns of NIPPV.[5] While a number of clinical guidelines address home use of NIPPV, there is marked variability in the conclusions, recommendations, and evidence basis for these guidelines. Some randomized clinical trials (RCTs) have shown benefits, while other RCTs have shown no benefit.[6,7] Some studies were not powered to detect important outcomes, such as mortality.[6] Previous systematic reviews have shown inconclusive results; focused on intermediary outcomes, such as improvement in gas exchange; or did not include recent RCTs.[8-10] The objective of this systematic review was to evaluate the association of the use of home NIPPV with clinical outcomes and adverse events in patients with COPD and hypercapnia. Devices evaluated were noninvasive home mechanical ventilator (HMV) and bilevel positive airway pressure (BPAP) devices.

Key Points

Question In patients with chronic obstructive pulmonary disease (COPD) and hypercapnia, is the use of home noninvasive positive pressure ventilation (NIPPV) associated with better outcomes?

Findings In this meta-analysis that included 51 085 patients with COPD and hypercapnia, home use of bilevel positive airway pressure, compared with no device, was significantly associated with lower risk of mortality (odds ratio [OR], 0.66), fewer patients with hospital admissions (OR, 0.22), and lower need for intubation (OR, 0.34), but no significant difference in quality of life. Noninvasive home mechanical ventilator, compared with no device, was significantly associated with lower risk of hospital admission (rate ratio, 0.50), but there was no significant difference in mortality risk. However, the evidence was low to moderate in quality.

Meaning Among patients with COPD and hypercapnia, home NIPPV, compared with no device use, was significantly associated with better clinical outcomes and no significant difference in quality of life. However, the evidence was low to moderate in quality, the evidence on quality of life was insufficient, and the analyses for some outcomes were based on small numbers of studies.

Methods

This article follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements,[11] and is part of a larger systematic review that evaluated NIPPV effectiveness in additional patient populations. The complete review is found in a scientific report published by the Agency for Healthcare Research and Quality. The study protocol (Supplement 1) was developed with input from patient representatives and clinical and research experts. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO #CRD42018085676) and is available online (https://www.ahrq.gov/sites/default/files/wysiwyg/research/findings/ta/topicrefinement/home-mechanical-ventilators-refinement.pdf).

Data Sources and Searches

We searched National Guideline Clearinghouse, EMBASE, Epub Ahead of Print, In-Process and Other Non-Indexed Citations, MEDLINE Daily, MEDLINE, Cochrane Central Registrar of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus for studies published from January 1, 1995, to November 6, 2019. We also searched the Food and Drug Administration Establishment Registration and Device Listing, ClinicalTrials.gov, Health Canada, Medicines and Healthcare Products Regulatory Agency, the Agency for Healthcare Research and Quality Horizon Scanning System, conference proceedings, patient advocate group websites, and medical society websites. Relevant clinical guidelines, systematic reviews, meta-analyses, and references of relevant publications were used to identify additional literature. A medical reference librarian, with the help of the study investigators, designed and executed the search strategy (eTable 1 in Supplement 2). An independent librarian peer reviewed the search strategy.

Study Selection

Eligible studies (1) evaluated adults aged at least 18 years with chronic hypercapnic respiratory failure due to COPD who received NIPPV supplied by a HMV device or BPAP device through a noninvasive interface for at least 1 month at home or in assisted living; (2) compared NIPPV with usual care or another mode or type of noninvasive ventilation; (3) reported outcomes of interest; and (4) were English-language articles published after 1994. We included RCTs and nonrandomized comparative studies (prospective and retrospective) and excluded single-group observational studies in which outcomes were measured both before an intervention and after completion of the intervention.

Pairs of independent reviewers screened the titles and abstracts of all citations using prespecified inclusion and exclusion criteria. Studies included by either reviewer were retrieved for full-text screening. Pairs of independent reviewers

then screened the full-text version of eligible references. Discrepancies between the reviewers were resolved through discussion. If consensus could not be reached, a third reviewer resolved the disagreement.

Device Nomenclature

NIPPV is the delivery of mechanical ventilation through a noninvasive interface (such as a tight-fitting mask) using a BPAP or HMV machine. A BPAP machine typically delivers pressure-targeted ventilation, although newer devices may have additional ventilator modes and monitoring capabilities. BPAP machines may also be referred to as *respiratory assist devices*. In comparison, an HMV machine is capable of delivering pressure-targeted, volume-targeted, and/or volume-preset ventilation. HMVs are usually the machine of choice for patients with tracheostomy (invasive interface), but may also be used in patients via a noninvasive interface (tight-fitting mask). Compared with BPAP machines, HMVs typically have additional ventilatory modes; monitoring; ventilator control; and safety, alarm, and backup power features. HMVs are classified by the US Food and Drug Administration as *life support devices*.[12] In this review, we included NIPPV delivered by either BPAP or HMV machines using noninvasive interfaces. The criteria that was used to define HMV and BPAP can be found in eTable 2 in Supplement 2.

Data Extraction and Quality Assessment

We developed a pilot-tested standardized data extraction form for this study. Reviewers worked independently to extract study details. An additional reviewer reviewed data extraction and resolved conflicts. We evaluated the risk of bias of the included studies using the Cochrane Collaboration risk of bias tool for RCTs[13] and select items (representativeness of the patients, ascertainment of exposure and outcomes, adequacy of follow-up, and possible conflicts of interest) from the Newcastle-Ottawa Scale for nonrandomized studies. We presented overall risk of bias for each study with focus on sequence generation, allocation concealment, and other sources of bias for RCTs and representativeness and ascertainment of exposure and outcomes for observational studies.

Outcome Measures

The primary outcomes were mortality, all-cause hospital admission, intubation, and quality of life. Secondary outcomes were hospital admissions for respiratory causes, emergency department visits, intensive care unit (ICU) admissions, COPD exacerbations, activities of daily living, dyspnea, sleep quality, exercise tolerance, and adverse events. Scales used for outcome measurement as well as their scoring methods and minimal clinically important differences are included in eTable 3 in Supplement 2. All outcomes were prespecified except for hospital admission for respiratory causes, which was added during data extraction. Adverse events were grouped into serious and nonserious adverse events (eTable 4 in Supplement 2). The outcomes reported in this article were estimates at the longest follow-up.

Data Synthesis and Analysis

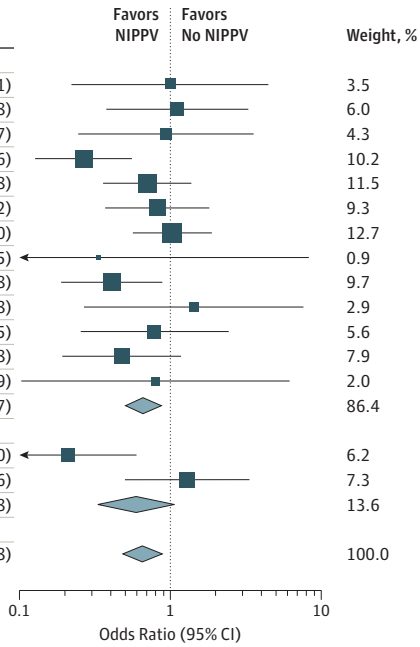
All analyses were based on the number of patients assigned to the intervention at randomization for RCTs (ie, the intention-to-treat principle) and the number of patients initially assigned to the intervention for observational studies. We calculated the odds ratio (OR), risk difference (RD), and corresponding 95% CIs for binary outcomes. For continuous outcomes, we extracted or calculated the difference between postintervention and baseline values for each group for all observational studies and for RCTs (whenever possible). When the difference between postintervention and baseline values was not presented in RCTs, we extracted postintervention data instead because baseline values between groups were typically balanced. When studies used different measures for the same outcome (eg, St George's Respiratory Questionnaire and Severe Respiratory Insufficiency Questionnaire for quality of life), we calculated the standardized mean difference (SMD). We standardized the direction of the measures and used higher scores to represent better outcomes. When studies used the same outcome measure, we used the original scale (eg, 6-minute walk distance test). For count data (ie, a patient may have more than 1 event, such as the number of hospital admissions and adverse events), we calculated the rate ratio (RR; ratio of the incidence rate of events within a given time between the intervention and the control). We also calculated the incidence rate of adverse events by device type regardless of comparisons. The DerSimonian and Laird random effect method was used, except when the number of studies included in the comparison was less than 3, in which cases we used the fixed-effect model based on the Mantel and Haenszel method because of concern about instability of study variance.[14] We evaluated heterogeneity between studies using the I^2 indicator. We conducted prespecified subgroup analyses based on the timing of the initiation of NIPPV treatment (initiation during stable COPD [no recent COPD exacerbation] vs initiation after recent exacerbation [≤1 month prior]). We conducted post hoc analyses to assess if study design (RCT and observational) and partial pressure of carbon dioxide ($PaCO_2$) thresholds to initiate NIPPV were associated with effect sizes for the 4 primary outcomes (mortality, need for intubation, quality of life, and all-cause hospital admissions). We defined the $PaCO_2$ threshold categories as 45 to 49 mm Hg, 50 to 51 mm Hg, and at least 52 mm Hg. We did not conduct interaction tests to evaluate statistical difference between subgroups. We were unable to use statistical methods (eg, funnel plots, Egger regression test) to assess publication bias because the number of studies included in the analysis was small (<20).[15] Two-tailed P values less than .05 were considered statistically significant. All statistical analyses were conducted using Stata/SE version 15.1 (StataCorp LLC). Because there was no adjustment for multiple comparisons and the potential for type I error, the findings from these analyses should be interpreted as exploratory.

Grading the Strength of Evidence

We graded the strength of evidence (SOE) for 4 outcomes (mortality, need for intubation, quality of life, and all-cause hospital admissions). We assigned an SOE rating of "high," "moderate,"

Figure 1. Mortality in Patients With Chronic Obstructive Pulmonary Disease Who Used Home Noninvasive Positive Pressure Ventilation (NIPPV) Compared With Patients Who Did Not

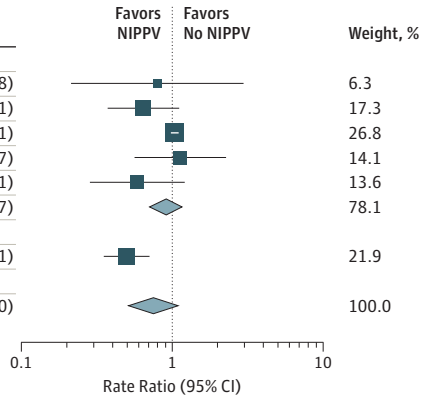
Study	Study Design	NIPPV Events/Patients	No NIPPV Events/Patients	Odds Ratio (95% CI)	Weight, %
BPAP vs no device					
Casanova et al,[19] 2010	RCT	4/26	4/26	1.00 (0.22-4.51)	3.5
Clini et al,[23] 2002	RCT	8/43	8/47	1.11 (0.38-3.28)	6.0
Duiverman et al,[26] 2011	RCT	5/37	5/35	0.94 (0.25-3.57)	4.3
Köhnlein et al,[36] 2014	RCT	12/102	31/93	0.27 (0.13-0.56)	10.2
McEvoy et al,[38] 2009	RCT	40/72	46/72	0.71 (0.36-1.38)	11.5
Murphy et al,[6] 2017	RCT	16/57	19/59	0.82 (0.37-1.82)	9.3
Struik et al,[7] 2014	RCT	30/101	29/100	1.03 (0.56-1.90)	12.7
Zhou et al,[46] 2017	RCT	0/57	1/58	0.33 (0.01-8.35)	0.9
Budweiser et al,[18] 2007	Observational	24/99	18/41	0.41 (0.19-0.88)	9.7
Clini et al,[22] 1996	Observational	4/17	3/17	1.44 (0.27-7.68)	2.9
Clini et al,[21] 1998	Observational	13/28	11/21	0.79 (0.25-2.45)	5.6
Galli et al,[32] 2014	Observational	8/78	17/88	0.48 (0.19-1.18)	7.9
Tsolaki et al,[44] 2008	Observational	2/27	2/22	0.80 (0.10-6.19)	2.0
Subtotal (I^2 = 5.9%; P = .39)				0.66 (0.50-0.87)	86.4
HMV vs no device					
Heinemann et al,[35] 2011	Observational	6/39	20/43	0.21 (0.07-0.60)	6.2
Paone et al,[42] 2014	Observational	13/48	10/45	1.30 (0.50-3.36)	7.3
Subtotal (I^2 = 84.3%; P = .01)				0.56 (0.29-1.08)	13.6
NIPPV (BPAP and HMV) vs no device					
Overall (I^2 = 27.3%; P = .16)				0.65 (0.48-0.88)	100.0



The size of data markers represents the weight each study has in the pooled result. BPAP indicates bilevel positive airway pressure; HMV, home mechanical ventilator; RCT, randomized clinical trial.

Figure 2. All-Cause Hospital Admissions in Patients With Chronic Obstructive Pulmonary Disease Who Used Home Noninvasive Positive Pressure Ventilation (NIPPV) Compared With Patients Who Did Not

Study	Study Design	No. of Patients NIPPV	No. of Patients No NIPPV	Rate Ratio (95% CI)	Weight, %
BPAP vs no device					
Casanova et al,[19] 2010	RCT	26	26	0.80 (0.21-2.98)	6.3
Clini et al,[23] 2002	RCT	23	24	0.64 (0.37-1.11)	17.3
McEvoy et al,[38] 2009	RCT	72	72	1.04 (0.98-1.11)	26.8
Clini et al,[22] 1996	Observational	17	17	1.13 (0.57-2.27)	14.1
Tsolaki et al,[44] 2008	Observational	27	22	0.59 (0.29-1.21)	13.6
Subtotal (I^2 = 27.2%; P = .240)				0.91 (0.71-1.17)	78.1
HMV vs no device					
Paone et al,[42] 2014	Observational	48	45	0.50 (0.35-0.71)	21.9
NIPPV (BPAP and HMV) vs no device					
Overall (I^2 = 76.6%; P = .001)				0.75 (0.52-1.10)	100.0



The size of data markers represents the weight each study has in the pooled result. BPAP indicates bilevel positive airway pressure; HMV, home mechanical ventilator; RCT, randomized clinical trial.

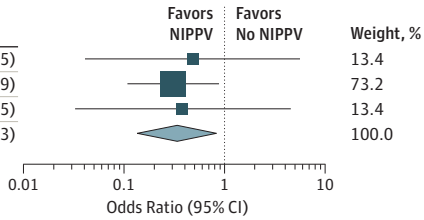
"low," or "insufficient evidence to estimate an effect" (definitions and grading criteria appear in eTable 5 in Supplement 2).[16]

Results

The literature search identified 6222 citations. An additional 83 citations were identified through reference searching and gray literature search (eFigure in Supplement 2). We included 33 studies (34 articles) evaluating 51 085 patients (mean [SD] age, 65.7 [2.1] years; 43% women).[6,7,17-48] We included 21 RCTs[6,17,19,20,23-28,30,33,34,36-39,41,43,46,48] and 12 observational studies.[18,21,22,29,31,32,35,40,42,44,45,47] These studies were conducted in the United States (n = 4), Canada (n = 1), Europe (n = 23), Asia (n = 3), Africa (n = 1), and Australia (n = 1). All included studies enrolled patients in the home setting, and no studies enrolled patients in assisted living settings. The BPAP modes used were BPAP spontaneous/timed, spontaneous, volume-assured pressure support ventilation, and pressure-controlled ventilation, or the mode was not

Figure 3. Intubations in Patients With Chronic Obstructive Pulmonary Disease Who Used Home Noninvasive Positive Pressure Ventilation (NIPPV) Compared With Patients Who Did Not

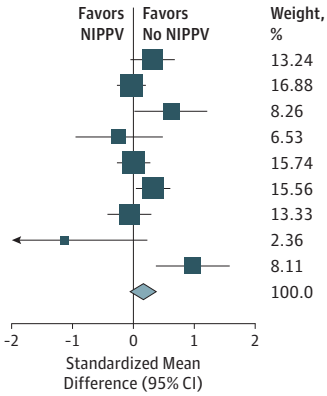
BPAP vs No Device	Study Design	NIPPV Events/Patients	No NIPPV Events/Patients	Odds Ratio (95% CI)
Casanova et al,[19] 2010	RCT	1/26	2/26	0.48 (0.04-5.65)
Galli et al,[32] 2014	Observational	5/78	16/88	0.31 (0.11-0.89)
Tsolaki et al,[44] 2008	Observational	1/27	2/22	0.38 (0.03-4.55)
Subtotal (I^2 = 0.0%; P = .94)				0.34 (0.14-0.83)



The size of data markers represents the weight each study has in the pooled result. BPAP indicates bilevel positive airway pressure; RCT, randomized clinical trial.

Figure 4. Quality of Life in Patients With Chronic Obstructive Pulmonary Disease (COPD) Who Used Home Noninvasive Positive Pressure Ventilation (NIPPV) Compared With Patients Who Did Not

BPAP vs No Device	Study Design	No. of Patients: NIPPV	No. of Patients: No NIPPV	Quality of Life Scale	Standardized Mean Difference (95% CI)
Zhou et al,[46] 2017	RCT	57	58	COPD assessment test	0.31 (-0.06 to 0.68)
Duiverman et al,[26] 2011	RCT	37	35	Chronic Respiratory Disease Questionnaire	-0.04 (-0.27 to 0.20)
Garrod et al,[33] 2000	RCT	23	22	Chronic Respiratory Disease Questionnaire	0.62 (0.02 to 1.21)
Márquez-Martín et al,[37] 2014	RCT	15	15	Chronic Respiratory Disease Questionnaire	-0.24 (-0.96 to 0.48)
Struik et al,[7] 2014	RCT	101	100	Chronic Respiratory Disease Questionnaire	0.00 (-0.28 to 0.28)
Köhnlein et al,[36] 2014	RCT	102	93	St George's Respiratory Questionnaire	0.32 (0.04 to 0.61)
Murphy et al,[6] 2017	RCT	57	59	St George's Respiratory Questionnaire	-0.07 (-0.43 to 0.29)
Oscroft et al,[41] 2010	RCT	5	5	St George's Respiratory Questionnaire	-1.14 (-2.50 to 0.22)
Tsolaki et al,[44] 2008	Observational	27	22	SF-36 physical component summary	0.97 (0.36 to 1.58)
Overall (I^2 = 61.7%; P = .007)					0.16 (-0.06 to 0.38)



The size of data markers represents the weight each study has in the pooled result. BPAP indicates bilevel positive airway pressure; RCT, randomized clinical trial; SF-36, 36-Item Short Form Health Survey.

specified. The noninvasive HMV modes used were volume- or pressure-controlled ventilation, pressure-support ventilation, or the mode was not specified. Baseline characteristics and NIPPV initiation criteria of included studies are found in eTables 6 and 7 in Supplement 2.

Overall risk of bias in RCTs was rated as moderate to high for issues related to blinding and possible risk of conflicts of interest. In observational studies, the risk of bias was also high due to the lack of clarity about patient selection methods, prognostic balance, and unknown conflicts of interest (eTables 8 and 9 in Supplement 2). Publication bias could not be statistically assessed.

BPAP Compared With No Device

Fifteen RCTs[6,7,17,19,23,24,26,27,33,34,36-38,41,43,46] and 6 observational[18,21,22,31,32,44] studies evaluated BPAP compared with no device. BPAP, compared with no device, was significantly associated with lower risk of mortality (22.31% vs 28.57%; RD, −5.53% [95% CI, −10.29% to −0.76%]; OR, 0.66 [95% CI, 0.51-0.87]; P = .003; 13 studies; 1423 patients; SOE, moderate) and need for intubation (5.34% vs 14.71%; RD, −8.02% [95% CI, −14.77% to −1.28%]; OR, 0.34 [95% CI, 0.14-0.83]; P = .02; 3 studies; 267 patients; SOE, moderate). There was no statistically significant difference in quality of life (SMD, 0.16 [95% CI, −0.06 to 0.39]; P = .15; 9 studies; 833 patients; SOE, insufficient). BPAP was significantly associated with fewer patients with all-cause hospital admissions (39.74% vs 75.00%; RD, −35.26% [95% CI, −49.39% to −21.12%]; OR, 0.22 [95% CI, 0.11-0.43]; P < .001; 1 study; 166 patients; SOE, low), but not the number of all-cause hospital admissions (RR, 0.91 [95% CI, 0.71-1.17]; P = .47; 5 studies; 326 patients; SOE, low). Meta-analysis results are depicted in **Figure 1**, **Figure 2**, **Figure 3**, and **Figure 4**.

Secondary clinical outcomes are presented in **Table 1**. Compared with no device, BPAP was significantly associated with fewer emergency department visits (1 study; 195 patients),[36] fewer patients with ICU admissions (1 study; 166 patients),[32] less dyspnea (6 studies; 468 patients),[7,17,23,26,33,37] and longer distance on the shuttle walk test (1 study; 45 patients).[33] There were no statistically significant differences in the number of hospital admissions for respiratory causes (1 study; 201 patients),[7] number of ICU admissions (2 studies; 81 patients),[22,23] number of COPD exacerbations (4 studies; 352 patients),[7,17,26,27,44] number of patients with COPD exacerbations (1 study; 52 patients),[19] activities of daily living (3 studies; 318 patients),[7,26,33] sleep quality (2 studies; 120 patients),[17,23] or 6-minute walk distance test (7 studies; 271 patients).[17,23,24,26,27,34,37,43]

Table 1. Secondary Clinical Outcomes in Patients With Chronic Obstructive Pulmonary Disorder (COPD) Who Used Home Bilevel Positive Airway Pressure Compared With No Device

Outcome	Study	Findings (95% CI)	*P* Value[a]	I^2, %[b]
No. of patients with hospital admission for respiratory causes	1 RCT (201 patients)	56.4% vs 57.0%	.94	NA
		Risk difference, −1% (−14% to 13%)		
		Odds ratio, 0.98 (0.56-1.71)		
No. of emergency department visits	1 RCT (195 patients)	Rate ratio, 0.72 (0.60 to 0.85)	<.001	NA
No. of ICU admissions	1 RCT and 1 observational study (81 patients)	Rate ratio, 0.43 (0.18 to 1.05)	.06	0.0
No. of patients with ICU admission	1 Observational study (166 patients)	7.7% vs 31.8%	.001	NA
		Risk difference, −24% (−36% to −13%)		
		Odds ratio, 0.18 (0.07 to 0.46)		
No. of COPD exacerbations	3 RCTs and 1 observational study (352 patients)	Rate ratio, 0.85 (0.67 to 1.07)	.17	32.7
No. of patients with COPD exacerbation	1 RCT (52 patients)	61.5% vs 65.4%	.17	NA
		Risk difference, −4% (−30% to 22%)		
		Odd ratio, 0.84 (0.26 to 2.68)		
Activities of daily living[c]	3 RCTs (318 patients)	Standardized mean difference, 0.09 (−0.13 to 0.31)	.41	52.2
Dyspnea[d]	6 RCTs (468 patients)	Standardized mean difference, 0.24 (0.03 to 0.45)	.02	44.3
Sleep quality[e]	2 RCTs (120 patients)	Standardized mean difference, 0.12 (−0.06 to 0.30)	.19	0.0
6-min Walk distance test	7 RCTs (271 patients)	23.83 m (−12.44 to 60.10)	.20	55.9
Shuttle walk test	1 RCT (45 patients)	72 m (12.9 to 131)	.01	NA

Abbreviations: ICU, intensive care unit; NA, not applicable; RCT, randomized clinical trial.

[a] Where risk difference and odds ratios were both analyzed, the *P* value was reported for the odds ratio.

[b] I^2 is the percentage of total variation across studies that is due to heterogeneity (between-study variability) rather than due to chance; range, 0% to 100%; higher values indicate higher heterogeneity between studies and higher inconsistency of results.

[c] Based on the Groningen Activity and Restriction Scale and London Chest Activity of Daily Living Scale; higher scores indicate a better outcome.

[d] Based on the Chronic Respiratory Disease Questionnaire, Medical Research Council dyspnoea scale, and Transitional Dyspnea Index; higher scores indicate a better outcome.

[e] Based on the Pittsburgh Sleep Quality Index and a semiqualitative multipoint scale with a range of 1 (best) to 4 (worst); higher scores indicate a better outcome.

HMV Compared With No Device

Two observational studies compared noninvasive HMV with no device.[35,42] HMV was significantly associated with fewer all-cause hospital admissions (RR, 0.50 [95% CI, 0.35-0.71]; *P* < .001; 1 study; 93 patients; SOE, low), but no statistically significant difference in mortality (21.84% vs 34.09%; RD, −11.99% [95% CI, −24.77% to 0.79%]; OR, 0.56 [95% CI, 0.29-1.08]; *P* = .49; 2 studies; 175 patients; SOE, insufficient) (Figure 1 and Figure 2).

NIPPV Compared With No Device

In a separate, prespecified analysis, 15 RCTs[6,7,17,19,23,24,26,27,33,34,36-38,41,43,46] and 8 observational studies[18,21,22,31,32,35,42,44] evaluated NIPPV (BPAP or HMV) compared with no device. NIPPV, compared with no device, was significantly associated with lower risk of mortality (22.26% vs 29.20%; RD, −6.29% [95% CI, −11.50% to −1.08%]; OR, 0.65 [95% CI, 0.48-0.88]; *P* < .01; 15 studies; 1598 patients; SOE, moderate), fewer patients with all-cause hospital admissions (39.74% vs 75.00%; RD, −35.26% [95% CI, −49.39% to −21.12%]; OR, 0.22 [95% CI, 0.11-0.43]; *P* < .001; 1 study; 166 patients; SOE, low), and lower need for intubation (5.34% vs 14.71%; RD, −8.02% [95% CI, −14.77% to −1.28%]; OR, 0.34 [95% CI, 0.14-0.83]; *P* = .02; 3 studies; 267 patients; SOE, moderate), but no statistically significant difference in quality of life (SMD, 0.16 [95% CI, −0.06 to 0.39]; 9 studies; 833 patients; SOE, insufficient) or number of all-cause hospital admissions (RR, 0.75 [95% CI, 0.52-1.10]; 6 studies; 419 patients; SOE, low) (Figure 1, Figure 2, Figure 3, and Figure 4).

Other Device Comparisons

Clinical outcomes for other device comparisons (NIPPV compared with other NIPPV devices or device settings) are presented in eTable 10 in Supplement 2. No studies examined mortality with HMV vs BPAP or HMV vs continuous positive airway pressure (CPAP). One observational study of 48 856 patients found that HMV, compared individually with BPAP and CPAP, was significantly associated with fewer all-cause hospital admissions (SOE, low).[45] This study also showed that HMV, compared with CPAP, was significantly associated with fewer patients with hospital admission for respiratory causes. However, the only data included from this large study were for treatment comparisons between HMV, BPAP, and CPAP. Data or other results from the control group (patients who did not receive positive airway pressure) were not able to be included, and therefore, the findings from this study were not included in any of the forest plots or other analyses. One RCT of 49 patients found that BPAP, compared with CPAP, showed no significant difference in the number of patients with COPD exacerbations (30.43% vs 53.85%; RD, −23% [95% CI, −50% to 3%]; OR, 0.38 [95% CI, 0.12-1.22]; *P* = .10; 1 study; 49 patients).[20] One RCT that included 26 patients found that patients who received BPAP for more than 6 months had a 43% increase in their 6-minute walk distance test, while the group who received treatment for less than 6 months had an 11% reduction (*P* = .04).[30] An observational study of 54 patients that compared patients with COPD who were adherent (≥4 hours per day on ≥70% of days) vs nonadherent to BPAP spontaneous mode treatment showed statistically significantly fewer

all-cause hospital admissions (0.4 vs 1.0 per patient; P = .006) and no statistically significant difference in ICU admissions (0.6 vs 1.2 per patient; P = .37) in adherent patients.[47] An RCT of 14 patients showed no statistically significant differences in outcomes with high-intensity HMV/BPAP mix (pressure-controlled ventilation) vs low-intensity HMV/BPAP mix (pressure-support ventilation) (quality of life [COPD assessment test]: weighted mean difference [WMD], 2.30 [95% CI, −2.23 to 6.83]; P = .32).[28]

No statistically significant differences in outcomes were found in an RCT of 40 patients that compared BPAP volume-assured pressure-support ventilation vs BPAP spontaneous/timed mode (mortality: 5.00% vs 10.00%; RD, −5% [95% CI, −21% to 11%]; OR, 0.47 [95% CI, 0.04-5.69]; P = .56; quality of life [St George's Respiratory Questionnaire]: WMD, −4.70 [95% CI, −15.97 to 6.57]; P = .41; shuttle walk test: WMD, −4.00 m [95% CI, −54.24 to 46.24]; P = .88; sleep quality [Epworth Sleepiness Scale]: WMD, −2.70 [95% CI, −6.07 to 0.67]; P = .12).[39] No statistically significant differences in outcomes or number of COPD exacerbations were found in an RCT that included 67 patients and evaluated patients who received BPAP spontaneous/timed mode in the home vs BPAP spontaneous/timed mode in the hospital (mortality: 6.06% vs 2.94%; RD, 3% [95% CI, −7% to 13%]; OR, 2.13 [95% CI, 0.18-24.67]; P = .55); quality of life [Severe Respiratory Insufficiency Questionnaire summary score]: WMD, −1.20 [95% CI, −9.92 to 7.52]; P = .79; dyspnea [Medical Research Council scale]: WMD, 0.10 [95% CI, −0.50 to 0.70]; P = .74; 6-minute walk distance: WMD, −19.00 [95% CI, −64.60 to 29.60]; P = .41; number of all-cause hospital admissions: WMD, −0.10 [95% CI, −0.60 to 0.40]; P = .40).[48] No statistically significant differences in outcomes were found in an RCT of 17 patients that evaluated HMV (pressure-controlled ventilation) vs HMV (pressure-support ventilation) (quality of life [Severe Respiratory Insufficiency Questionnaire summary score]: WMD, −0.14 [95% CI, −4.90 to 4.60]; P = .95; 6-minute walk distance: WMD, 14 [95% CI, −42 to 70]; P = .58).[25]

Stable COPD vs Recent Exacerbation

Nineteen studies[17,19,21,23,25-29,31,33,34,36-38,41,43,44,46,48] evaluated NIPPV initiated in patients with stable COPD (no recent exacerbation) and 14 studies[6,7,18,20,22,24,30,32,35,39,40,42,45,47] evaluated NIPPV initiated in patients with recent exacerbation of COPD. NIPPV initiated in patients with stable COPD, compared with no device, was significantly associated with lower risk of mortality (21.42% vs 28.88%; RD, −5% [95% CI, −12% to 2%]; OR, 0.62 [95% CI, 0.42-0.92]; P = .02; I^2 = 5.3%) and no significant difference in all-cause hospital admissions (RR, 0.84 [95% CI, 0.59-1.18]; P = .31; I^2 = 44.7%), intubations (3.77% vs 8.33%; RD, −5% [95% CI, −14% to 5%]; OR, 0.43 [95% CI, 0.08-2.46]; P = .34; I^2 = 0.0%), or quality of life (SMD, 0.24 [95% CI, −0.06 to 0.54]; I^2 = 66.9%).

NIPPV initiated in patients with recent COPD exacerbation, compared with no device, was not significantly associated with lower risk of mortality (23.01% vs 29.52%; RD, −8% [95% CI, −17% to 1%]; OR, 0.66 [95% CI, 0.41-1.06]; P = .09; I^2 = 48.6%) or quality of life (SMD, −0.03 [95% CI, −0.25 to 0.20]; P = 0.82; I^2 = 0.0%), but was associated with fewer all-cause hospital admissions (RR, 0.59 [95% CI, 0.43-0.81]; P = .001; I^2 = 76.5%) and lower need for intubation (6.41% vs 18.18%; RD, −12% [95% CI, −22% to −2%]; OR, 0.31 [95% CI, 0.11-0.89]; P = .03; I^2 = not applicable).

An observational study that compared patients with acute COPD exacerbation who received BPAP spontaneous/timed mode vs patients with stable COPD who received BPAP spontaneous/timed mode found that survival time was longer in patients with stable COPD (52.6 vs 28.6 months; P = .03).[40] A second observational study compared patients with a recent exacerbation of COPD who received NIPPV vs patients with stable COPD who received NIPPV and found no significant difference in mortality after 3-year follow-up.[29]

Subgroup Analyses by $Paco_2$ Initiation Threshold

No studies directly compared the association of $Paco_2$ initiation threshold with clinical outcomes. In a post hoc subgroup analysis, there were no significant differences in mortality or all-cause hospital admissions based on $Paco_2$ threshold initiation criteria. However, NIPPV treatment in patients with higher $Paco_2$ levels may be associated with improved quality of life compared with patients with lower levels ($Paco_2$ ≥52 mm Hg: SMD, 0.18 [95% CI, −0.05 to 0.40] [2 studies; 311 patients]; $Paco_2$ of 50 to 51 mm Hg: SMD, 0.97 [95% CI, 0.36-1.58] [1 study; 49 patients]; $Paco_2$ of 45 to 49 mm Hg: SMD, −0.06 [95% CI, −0.28 to 0.17] [2 studies; 102 patients]).

Sensitivity Analyses

Post hoc subgroup analyses of study design on primary outcomes when NIPPV was compared with no device are shown in **Table 2**. When evaluating observational studies only, NIPPV compared with no device was significantly associated with lower risk of mortality (20.83% vs 29.24%; RD, −9% [95% CI, −18% to 1%]; OR, 0.58 [95% CI, 0.35-0.96]; 7 studies; 613 patients),[18,21,22,32,35,42,44] lower need for intubation (5.71% vs 16.36%; RD, −10% [95% CI, −19% to −2%]; OR, 0.32 [95% CI, 0.12-0.83]; 2 studies; 215 patients),[32,44] and higher quality of life (SMD, 0.97 [95% CI, 0.36-1.58]; 1 study; 49 patients).[44] When evaluating RCTs only, NIPPV, compared with no device, was not associated with a significant difference in mortality (23.23% vs 29.18%; RD, −5% [95% CI, −11% to 2%]; OR, 0.72 [95% CI, 0.49-1.05]; 8 studies; 985 patients),[6,7,19,23,26,27,36,38,46] need for intubation (3.85% vs 7.69%; RD, −4% [95% CI, −17% to 9%]; OR, 0.48 [95% CI, 0.04-5.64]; 1 study; 52 patients),[19] or quality of life (SMD, 0.10 [95% CI, −0.09 to 0.29]; 8 studies; 784 patients).[6,7,26,27,33,36,37,41,46] The difference in the number of all-cause hospital admissions was not statistically significant regardless of study design (RCTs only: RR, 0.92 [95% CI, 0.67-1.26]; 3 studies; 243 patients[19,23,38]; observational studies only: RR, 0.65 [95% CI, 0.40-1.06]; 3 studies; 176 patients[22,42,44]).

Adverse Events

Only 11 of the 33 included studies reported the rates of adverse events. In 6 studies with direct comparisons between

Table 2. Post Hoc Subgroup Analyses of Primary Outcomes by Study Design of Noninvasive Positive Pressure Ventilation on Patients With Chronic Obstructive Pulmonary Disorder Compared With No Device

Outcome	Study Design	Findings (95% CI)	I^2, %[a]
Mortality	8 RCTs (985 patients)	23.23% vs 29.18%	26.9
		Risk difference, −5% (−11% to 2%)	
		Odd ratio, 0.72 (0.49 to 1.05)	
	7 Observational studies (613 patients)	20.83% vs 29.24%	31.9
		Risk difference, −9% (−18% to 1%)	
		Odd ratio, 0.58 (0.35 to 0.96)	
Need for intubation	1 RCT (52 patients)	3.85% vs 7.69%	NA
		Risk difference, −4% (−17% to 9%)	
		Odd ratio, 0.48 (0.04 to 5.64)	
	2 Observational studies (215 patients)	5.71% vs 16.36%	0.0
		Risk difference, −10% (−19% to −2%)	
		Odd ratio, 0.32 (0.12 to 0.83)	
No. of all-cause hospital admissions	3 RCTs (243 patients)	Rate ratio, 0.92 (0.67 to 1.26)	35.3
	3 Observational studies (176 patients)	Rate ratio, 0.65 (0.40 to 1.06)	53.0
Quality of life[b]	8 RCTs (784 patients)	Standardized mean difference, 0.10 (−0.09 to 0.29)	46.8
	1 Observational study (49 patients)	Standardized mean difference, 0.97 (0.36 to 1.58)	NA

Abbreviations: NA, not applicable; RCT, randomized clinical trial.

[a] I^2 is the percentage of total variation across studies that is due to heterogeneity (between-study variability) rather than due to chance; range, 0% to 100%; higher values indicate higher heterogeneity between studies and higher inconsistency of results.

[b] Higher scores indicate worse quality of life.

NIPPV and no device, no statistically significant difference was found between the groups (RR, 1.08 [95% CI, 0.52-2.21]; $P = .84$; $I^2 = 36.7\%$). In the NIPPV group, the pooled incidence rate was 0.21 per patient (95% CI, 0.12-0.37; $I^2 = 75.2\%$) for total number of adverse events, 0 per patient (95% CI, 0.00-0.01; $I^2 = 89.6\%$) for serious adverse events, and 0.24 per patient (95% CI, 0.12-0.47; $I^2 = 82.5\%$) for nonserious adverse events. The most commonly reported serious adverse event was acute respiratory failure. The most common nonserious adverse events included skin symptoms (eg, facial rash, nasal ulceration), eye symptoms (eg, dry eyes, conjunctivitis), nose/mouth symptoms (eg, nasal stuffiness, rhinorrhea, nosebleed, mucosal dryness, oral air leak), gastrointestinal symptoms (eg, gastric distension, aerophagia), and device/mask intolerance (eg, claustrophobia, discomfort, nonadherence). Mortality, all-cause hospital admission, and intubation were reported as primary outcomes and were not rereported as serious adverse events.

Discussion

In patients with COPD and hypercapnia, home BPAP, compared with no device, was significantly associated with a lower risk of mortality, all-cause hospital admission, and intubation, with no significant difference in quality of life. Use of HMV, compared with no device, was significantly associated with lower risk of all-cause hospital admission, but was not significantly associated with lower risk of mortality. The overall strength of evidence to support these associations was low to moderate, the evidence on quality of life was insufficient, and the analyses for some outcomes were based on small numbers of studies. The results for clinical outcomes for either device type were not statistically significant when evidence was limited to data from RCTs.

While the results of this systematic review suggest that NIPPV is associated with better outcomes for patients with COPD and hypercapnia, these results should be interpreted with caution given the limited quality of available evidence. Thus, despite this meta-analysis, fundamental questions remain regarding the association between NIPPV and better clinical outcomes, including whether higher-quality evidence would reach similar conclusions and whether any identified associations are causal. Given this, it continues to remain unclear which devices, device settings (including ventilator mode and intensity of pressure support), and device titration practices (including intensity of $Paco_2$ reduction) should be used for specific patient populations. While some studies have identified improved outcomes with higher-intensity NIPPV or devices with additional modes and features (eg, HMV vs BPAP devices),[39,45] other studies comparing device modes have identified no outcome differences.[25,28]

It also remains unclear which $Paco_2$ threshold should be used to initiate NIPPV and whether there are clinically significant benefits even with low thresholds. Current guidelines, recommendations, and practices are variable.[49-55] No trials that performed head-to-head threshold comparisons were identified in this review. While 12 of 31 included studies used a low $Paco_2$ threshold (>45 or >46 mm Hg), the 3 studies that individually demonstrated mortality benefits used higher $Paco_2$ thresholds (>50, >52.5, and >53 mm Hg).[18,35,36] A higher $Paco_2$ threshold (demonstrated for a longer period of time) has been postulated as one of the reasons why the HOT-HMV trial[6] showed clinical improvement with the addition of NIPPV, but the RESCUE trial[7] did not.[56]

The incidence rate of nonserious adverse events, such as facial rash and mucosal dryness, in patients who received NIPPV was close to 25%. Reported serious adverse events

were rare. Although there were no differences in the rates of adverse events in the NIPPV groups compared with the no device groups, there was lack of uniformity of reporting and classifying adverse events. Although assessing cost-effectiveness of NIPPV was outside the scope of this article, this remains an important concept because the cost of chronic respiratory failure in COPD is as high $50 billion annually in the United States.[57]

This systematic review has identified a number of knowledge gaps that require further research. Existing RCTs were limited by lack of treatment blinding (eg, not including a sham NIPPV group), unbalanced follow-up, high dropout rates, and the potential bias of industry funding. In addition, many RCTs were underpowered to measure important clinical outcomes, such as mortality. Future studies would benefit from inclusion of a blinded sham NIPPV group (in addition to an unblinded no device group). Well-conducted RCTs are required to determine the comparative effectiveness of devices (BPAP vs HMV), device settings, and device titration practices. The choice of device remains dependent on the clinical context, shared decision-making, patient and societal values, and resources.

Limitations

This study has several limitations. First, when analyzed separately, the pooled results from RCTs were imprecise and not statistically significant. It is important to recognize that the lower risk of mortality associated with NIPPV was demonstrated in a body of evidence that included a combination of randomized and nonrandomized studies. One of the randomized trials showed a statistically significant reduction in mortality,[36] whereas the remaining trials were imprecise (ie, had a low power due to a small number of events). Nevertheless, the estimates from randomized and nonrandomized studies were consistent (had overlapping CIs) and the overall analysis had no important heterogeneity (I^2 = 5.9%), suggesting that combining 2 study designs in the same analysis is reasonable. Second, there was limited evidence for comparative effectiveness of different devices and different modes. Third, there was limited evidence for patients with recent COPD exacerbation. Fourth, heterogeneity among included studies regarding outcome definitions, measurement tools (eg, variability in defining COPD exacerbation or different scales to measure quality of life), and different lengths of follow-up reduced the strength of evidence. Fifth, publication bias was unable to be statistically evaluated because of the number of studies included in a direct comparison. Sixth, the evaluation of adverse events was also limited because the majority (65%) of included studies did not evaluate adverse events or have a consistent approach to report them. Seventh, studies not published in English were excluded. Eighth, although a majority of studies excluded patients with suspected or confirmed obstructive sleep apnea, the effect of underlying obstructive sleep apnea in patients with COPD was unable to be assessed. Ninth, the findings from the post hoc subgroup analyses regarding $PaCO_2$ initiation threshold and study design are subject to high risk of bias. Statistical tests to evaluate differences between these subgroups were not conducted.

Conclusions

In this meta-analysis of patients with COPD and hypercapnia, home BPAP, compared with no device, was associated with lower risk of mortality, all-cause hospital admission, and intubation, but no significant difference in quality of life. Noninvasive HMV, compared with no device, was significantly associated with lower risk of hospital admission and there was no significant difference in mortality risk. However, the evidence was low to moderate in quality, the evidence on quality of life was insufficient, and the analyses for some outcomes were based on small numbers of studies.

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