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Meta-analysis: Noninvasive Ventilation in Acute Cardiogenic Pulmonary Edema

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Background: Noninvasive ventilation (NIV) is commonly used to treat patients with acute cardiogenic pulmonary edema (ACPE), but the findings of a recent large clinical trial suggest that NIV may be less effective for ACPE than previously thought.

Purpose: To provide an estimate of the effect of NIV on clinical outcomes in patients with ACPE that incorporates recent trial evidence and explore ways to interpret that evidence in the context of preceding evidence that favors NIV.

Data Sources: PubMed and EMBASE from 1966 to December 2009, Cochrane Central Register of Controlled Trials and conference proceedings through December 2009, and reference lists, without language restriction.

Study Selection: Randomized trials that compared continuous positive airway pressure and bilevel ventilation with standard therapy or each other.

Data Extraction: Two independent reviewers extracted data. Outcomes examined were mortality, intubation rate, and incidence of new myocardial infarction (MI).

Data Synthesis: Compared with standard therapy, continuous positive airway pressure reduced mortality (relative risk [RR], 0.64 [95% CI, 0.44 to 0.92]) and need for intubation (RR, 0.44 [CI, 0.32 to 0.60]) but not incidence of new MI (RR, 1.07 [CI, 0.84 to 1.37]). The effect was more prominent in trials in which myocardial ischemia or infarction caused ACPE in higher proportions of patients (RR, 0.92 [CI, 0.76 to 1.10] when 10% of patients had ischemia or MI vs. 0.43 [CI, 0.17 to 1.07] when 50% had ischemia or MI). Bilevel ventilation reduced the need for intubation (RR, 0.54 [CI, 0.33 to 0.86]) but did not reduce mortality or new MI. No differences were detected between continuous positive airway pressure and bilevel ventilation on any clinical outcomes for which they were directly compared.

Limitations: The quality of the evidence base was limited. Definitions, cause, and severity of ACPE differed among the trials, as did patient characteristics and clinical settings.

Conclusion: Although a recent large trial contradicts results from previous studies, the evidence in aggregate still supports the use of NIV for patients with ACPE. Continuous positive airway pressure reduces mortality more in patients with ACPE secondary to acute myocardial ischemia or infarction.

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Acute cardiogenic pulmonary edema (ACPE) is a common medical emergency (1) and a leading cause of hospitalization that accounts for 6.5 million hospital days each year (2). The in-hospital mortality rate from ACPE is 10% to 20%, particularly when it is associated with acute myocardial infarction (MI) (3). Although most patients respond to conventional medical therapy, some patients need temporary ventilator support. Noninvasive ventilation (NIV) has become an important tool for treating diverse forms of acute respiratory failure. It can be delivered by continuous positive airway pressure (CPAP), a noninvasive technique that maintains positive airway pressure during spontaneous ventilation throughout the whole respiratory cycle (4), or by bilevel ventilation, a mode of partial ventilatory assistance in which the ventilator can produce different inspiratory and expiratory pressures.

Although previous trials and meta-analyses (5–11) have reported reduced in-hospital mortality and intubation rates associated with NIV, the 3CPO (Three Interventions in Cardiogenic Pulmonary Oedema) trial (12), the largest study to evaluate NIV, showed no benefit from NIV for reducing intubation or short-term mortality rates. In the context of this negative trial, we systematically reviewed all trials of NIV in patients with ACPE, including more recent trials (12–19) not included in previous meta-analyses (5–11), to provide an overall estimate of the effect of NIV on clinically relevant outcomes and to explore various ways of interpreting the 3CPO trial findings in the context of the preceding evidence base favoring NIV.

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METHODS

Search Strategy

We performed this meta-analysis in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) conference statement (20). We searched PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials, without language restric-

Context

Noninvasive ventilation (NIV) is commonly used to treat patients with acute cardiogenic pulmonary edema (ACPE). The 3CPO (Three Interventions in Cardiogenic Pulmonary Oedema) trial in 2008 suggested that NIV might be less effective than previously believed.

Contribution

This meta-analysis suggests that NIV reduces mortality and need for mechanical ventilation in patients with ACPE, especially those with the acute coronary syndrome (ACS).

Caution

Most trials of NIV are small and of lower quality.

Implication

Noninvasive ventilation seems effective for treating ACPE, especially when ACS is the cause. One possible explanation for the divergent 3CPO trial findings is that relatively few patients in that trial had ACS.

—The Editors

tions, from 1966 through December 2009, and used Google Scholar to search the Internet (**Appendix Table 1**, available at www.annals.org). We searched abstracts from the American College of Cardiology (1966 to December 2009, poster presentations), European Society of Cardiology (1966 to December 2009, poster presentations), and American College of Chest Physicians conferences (1966 to December 2009, meeting abstracts). We also evaluated the references in the review articles and meta-analyses we found with our electronic search to identify relevant studies that we had not captured with our primary search.

Study Selection

To be eligible for inclusion, studies needed to be parallel randomized trials that compared all-cause in-hospital mortality, need for intubation, and incidence of new MI (diagnosed after admission) in patients older than 18 years who had ACPE and received noninvasive interventions (CPAP, bilevel ventilation, or standard therapy [oxygen by facemask, diuretics, nitrates, and other supportive care]). Two reviewers screened and assessed the eligibility of all studies on the basis of these criteria and settled differences of opinion by consensus or after consultation with a third investigator. Agreement between the reviewers was good ($\kappa = 0.846$; $P < 0.001$).

Data Extraction

Two reviewers independently extracted information about the trials, including authors; publication year; study location; number of patients; baseline patient characteristics, such as Pa_{O_2}–F_{IO_2} ratio, incidence of MI or ischemia at admission; between-group differences in respiratory rate, heart rate, and Pa_{O_2} at 30 minutes and 1 hour after treatment; NIV protocol; and main outcomes. They based their assessment of the methodological quality of each study on 11 items used in the PEDro (Physiotherapy Evidence Database) scale (21) (**Appendix Table 2**, available at www.annals.org) and settled differences of opinion by consensus or after consultation with a third investigator.

Statistical Analysis

To provide an overall estimate of the effect of NIV on clinically relevant outcomes, we estimated pooled relative risks (RRs) by using a random-effects model with the Mantel–Haenszel method and assessed heterogeneity by using the Cochran Q test ($P < 0.100$ indicates heterogeneity) and the I^2 statistic.

We used random-effects meta-regression (22) to assess whether patient baseline characteristics and mortality and intubation rates in control groups (markers of baseline risk and severity of illness in the trial cohort [23]) influenced the estimate of effect of interventions across trials. We excluded trials from each of these analyses when data on the baseline characteristics, mortality and intubation rate in control groups, or individual outcomes were not available.

To assess publication bias, we visually inspected funnel plots and used the Begg rank correlation method ($P < 0.05$ indicated significant bias).

To explore various ways of interpreting the 3CPO trial findings in the context of the preceding evidence base favoring NIV, we performed several additional sensitivity and meta-analyses. First, we omitted each trial in turn and recalculated the pooled effect size estimate to assess which trial influenced our estimate the most. We considered any trial that altered the RR estimate by 10% or more to be influential. Second, we assessed the contribution of the 3CPO trial to the overall estimate of effect across the entire range of possible weightings of the trial (0% to 100%). Third, we performed cumulative meta-analyses on the basis of trial quality (for example, whether trials had concealed allocation or blinding of patients or staff or reported low dropout rates) and date of publication to explore whether and how risk estimates changed with trial quality and time. Fourth, we performed subgroup analyses by trial quality; because so few trials had blinding or large dropout rates, we report results only for concealed allocation. Finally, we performed Bayesian hierarchical meta-analysis (**Appendix,** available at www.annals.org) to better account for between-trial heterogeneity.

We used R software, version 2.10.0 (R Foundation for Statistical Computing, Vienna, Austria), for all analyses and STATA/SE, version 10.0 (StataCorp, College Station, Texas), for meta-analysis.

Role of the Funding Source

We received no funding for this study. The authors had full access to all data and had final responsibility for the decision to submit for publication.

Table. **Study Characteristics, Quality Score, and Outcome Data**

Study, Year (Reference)	Country	Clinical Setting	Baseline Characteristics		
			Age, *y*	Acute MI or Ischemia, *n/N*	Pao_2–FIo_2 Ratio, *mm Hg*
CPAP vs. ST					
Räsänen et al, 1985 (24)	Finland	ICU	CPAP, 74; ST, 73	CPAP, 9/20; ST, 10/20	CPAP, 248; ST, 248†
Bersten et al, 1991 (25)	Australia	ED and ICU	CPAP, 76; ST, 75	CPAP, 7/19; ST, 10/20	CPAP, 138; ST, 136
Lin et al, 1995 (26)	Taiwan	ED	CPAP, 72; ST, 73	CPAP, 10/50; ST, 11/50	NA
Takeda et al, 1997 (27)	Japan	ICU	CPAP, 69; ST, 64	CPAP, 5/15; ST, 6/15	NA
Takeda et al, 1998 (28)	Japan	CCU	CPAP, 74; ST, 75	CPAP, 11/11; ST, 11/11	CPAP, 137; ST, 174
Delclaux et al, 2000 (29)	France	ICU	CPAP, 56; ST, 60	CPAP, 5/22; ST, 9/20	NA
Kelly et al, 2002 (30)	United Kingdom	ED	CPAP, 77; ST, 78	NA	CPAP, 361; ST, 482†
Hao et al, 2002 (31)	China	NA	CPAP, 68; ST, 67	CPAP, 5/25; ST, 4/26	CPAP, 205; ST, 204†
L'Her et al, 2004 (32)	France	ED	CPAP, 84; ST, 84	CPAP, 7/43; ST, 6/46	CPAP, 157; ST, 167
Plaisance et al, 2007 (17)	France	Prehospital	CPAP, 76.7; ST, 77.9	CPAP, 12/63; ST, 14/61	CPAP, 238; ST, 233
Bilevel ventilation vs. ST					
Masip et al, 2000 (33)	Spain	ICU	Bilevel, 75.3; ST, 78.5	Bilevel, 5/19; ST, 6/18	Bilevel, 140; ST, 146
Levitt, 2001 (34)	United States	ED	Bilevel, 67.4; ST, 68.5	NA	Bilevel, 433; ST, 529†
Nava et al, 2003 (35)	Italy	ED	Bilevel, 72.1; ST, 73.1	NA	Bilevel, 154; ST, 160
Ferrer et al, 2003 (36)	Spain	ICU	Bilevel, 61; ST, 62	NA	Bilevel, 102; ST, 103
Weitz et al, 2007 (13)	Germany	Prehospital	Bilevel, 54 to 86; ST, 72 to 92	NA	NA
Bilevel ventilation vs. CPAP					
Mehta et al, 1997 (37)	United States	ED	Bilevel, 76; CPAP, 77	Bilevel, 1/14; CPAP, 1/13	Bilevel, 122; CPAP, 107
Bollaert et al, 2002 (38)	France	ICU	Bilevel, 72; CPAP, 77	Bilevel, 3/17; CPAP, 3/19	NA
Martin-Bermudez et al, 2002 (39)	Spain	NA	NA	NA	NA
Liesching et al, 2003 (40)	Canada	NA	NA	NA	Bilevel, 135; CPAP, 162
Cross et al, 2003 (41)	Australia	ED	Bilevel, 75; CPAP, 73	NA	NA
Bellone et al, 2004 (4)	Italy	ED	Bilevel, 77.3; CPAP, 76.8	NA	Bilevel, 149; CPAP, 145
Bellone et al, 2005 (42)	Italy	ED	Bilevel, 76.8; CPAP, 76.8	Bilevel, 2/18; CPAP, 0/18	Bilevel, 159; CPAP, 183
Ferrari et al, 2006 (14)	Italy	ED	Bilevel, 77.4; CPAP, 76.8	NA	Bilevel, 132; CPAP, 160
Moritz et al, 2007 (15)	France	ED	Bilevel, 77.7; CPAP, 77.6	Bilevel, 22/50; CPAP, 22/59	NA
Ferrari et al, 2007 (16)	Italy	ED	Bilevel, 74.2; CPAP, 76.7	Bilevel, 0/25; CPAP, 0/27	Bilevel, 112; CPAP, 93
Ferrari et al, 2009 (18)	Italy	ED	Bilevel, 76.6; CPAP, 77.3	Bilevel, 16/40; CPAP, 12/40	Bilevel, 148; CPAP, 129.26
CPAP vs. bilevel ventilation vs. ST					
Park et al, 2001 (43)	Brazil	ED	69	CPAP, 3/9; bilevel, 3/7; ST, 3/10	CPAP, 224; bilevel, 252; ST, 219†
Crane et al, 2004 (44)	United Kingdom	ED	CPAP, 74.9; bilevel, 76.0; ST, 74.6	NA	CPAP, 491; bilevel, 446; ST, 480†
Park et al, 2004 (45)	Brazil	ED	CPAP, 61; bilevel, 66; ST, 65	CPAP, 10/27; bilevel, 11/27; ST, 14/26	CPAP, 172; bilevel, 145; ST, 152
Gray et al, 2009 (46)	United Kingdom	ED	CPAP, 78; bilevel, 77; ST, 79	CPAP, 22/346; bilevel, 22/356; ST, 22/367	CPAP, 482; bilevel, 479; ST, 468†
Ghanem, 2009 (19)	Egypt	ICU	NA	NA	NA

CCU = coronary care unit; CPAP = continuous positive airway pressure; ED = emergency department; ICU = intensive care unit; MI = myocardial infarction; NA = not available; ST = standard therapy.
* Between-group differences.
† Calculated according to the formula ($Pao_2 \div FIo_2$).
‡ Differences at 30 minutes after treatment.
§ At 45 minutes.

RESULTS

Study Characteristics

Our initial search identified 1650 potentially relevant publications, 52 of which we retrieved for detailed review (**Appendix Figure 1**, available at www.annals.org). Thirty-one randomized, controlled trials (4, 12–19, 24–45), involving 2887 patients, met our inclusion criteria (**Table**). Most of the patients were elderly (aged 51 to 92 years), and 49.6% were male.

Ten studies (17, 24–32) compared CPAP with standard therapy; 5 (13, 33–36) compared bilevel ventilation with standard therapy; 11 (4, 14–16, 18, 37–42) compared bilevel ventilation with CPAP; and 5 (12, 19, 43–45) were 3-group trials that evaluated standard therapy, CPAP, and bilevel ventilation. In these studies, CPAP pressures ranged from 25 to 20 cm H_2O and bilevel ventilation pressures ranged from 8 to 20 cm H_2O (inspiratory) and 3 to 10 cm H_2O (expiratory).

Table—Continued

Clinical Outcome				
Respiratory Rate Difference at 1 h, *breaths/min**	Heart Rate Difference at 1 h, *beats/min**	Pao_2 Difference at 1 h, *mm Hg**	Death, *n/N*	Need for Intubation, *n/N*
−2.0	11.0	13.0	CPAP, 3/20; ST, 6/20	CPAP, 6/20; ST, 12/20
−6.0‡	−12.0‡	NA	CPAP, 2/19; ST, 4/20	CPAP, 0/19; ST, 7/20
NA	NA	NA	CPAP, 4/50; ST, 6/50	CPAP, 8/50; ST, 18/50
NA	NA	NA	CPAP, 1/15; ST, 3/15	CPAP, 1/15; ST, 6/15
NA	NA	NA	CPAP, 1/11; ST, 7/11	CPAP, 2/11; ST, 8/11
NA	NA	NA	CPAP, 7/22; ST, 7/20	CPAP, 6/22; ST, 6/20
−4.0	−14.0	57.8	CPAP, 2/27; ST, 7/31	CPAP, 0/27; ST, 0/31
−3.0	−17.0	47.8	NA	CPAP, 1/25; ST, 9/26
−4.0	−14.0	NA	CPAP, 12/43; ST, 14/46	CPAP, 2/43; ST, 4/46
0§	0§	12§	CPAP, 2/63; ST, 8/61	CPAP, 6/63; ST, 16/61
−1.5	3.0	NA	Bilevel, 0/19; ST, 2/18	Bilevel, 1/19; ST, 6/18
−1.7	10.0	17.6	Bilevel, 3/21; ST, 3/17	Bilevel, 5/21; ST, 7/17
−3.0	−5.0	36.7	Bilevel, 6/65; ST, 9/65	Bilevel, 13/65; ST, 16/65
NA	NA	NA	Bilevel, 1/15; ST, 2/15	Bilevel, 1/15; ST, 2/15
NA	6.8	NA	Bilevel, 1/13; ST, 1/10	NA
−2.0	−3.0	2.0	Bilevel, 1/14; CPAP, 2/13	Bilevel, 1/14; CPAP, 1/13
0.9	7.0	−11.0‡	Bilevel, 4/17; CPAP, 4/19	Bilevel, 5/17; CPAP, 4/19
NA	NA	NA	Bilevel, 2/41; CPAP, 5/39	NA
NA	NA	NA	NA	Bilevel, 0/13; CPAP, 1/14
NA	NA	NA	Bilevel, 3/35; CPAP, 5/36	Bilevel, 1/35; CPAP, 4/36
−0.3	0.8	NA	Bilevel, 0/24; CPAP, 2/22	Bilevel, 2/24; CPAP, 1/22
−0.1	NA	NA	Bilevel, 0/18; CPAP, 1/18	Bilevel, 2/18; CPAP, 1/18
NA	NA	NA	Bilevel, 11/53; CPAP, 4/53	Bilevel, 3/53; CPAP, 0/53
NA	NA	NA	Bilevel, 4/50; CPAP, 8/59	Bilevel, 2/50; CPAP, 1/59
NA	NA	NA	Bilevel, 3/25; CPAP, 2/27	Bilevel, 1/25; CPAP, 0/27
0	1.1	NA	Bilevel, 7/40; CPAP, 2/40	Bilevel, 3/40; CPAP, 0/40
CPAP vs. ST, −5.0; bilevel vs. ST, −7.0; bilevel vs. CPAP, −2.0	CPAP vs. ST, −11.0; bilevel vs. ST, −16.0; bilevel vs. CPAP, −5.0	CPAP vs. ST, −18.0; bilevel vs. ST, 26.0; bilevel vs. CPAP, 44.0	CPAP, 1/9; bilevel, 0/7; ST, 0/10	CPAP, 3/9; bilevel, 0/7; ST, 4/10
CPAP vs. ST, −2.0; bilevel vs. ST, −2.0; bilevel vs. CPAP, 0	CPAP vs. ST, 3.0; bilevel vs. ST, 1.0; bilevel vs. CPAP, −2.0	CPAP vs. ST, −28.7; bilevel vs. ST, −12.3; bilevel vs. CPAP, 16.4	CPAP, 0/20; bilevel, 5/20; ST, 6/20	CPAP, 1/20; bilevel, 1/20; ST, 0/20
CPAP vs. ST, −6.0; bilevel vs. ST, −6.0; bilevel vs. CPAP, 0	CPAP vs. ST, 0.0; bilevel vs. ST, 0; bilevel vs. CPAP, 0	CPAP vs. ST, −7.0; bilevel vs. ST, −14.0; bilevel vs. CPAP, −7.0	CPAP, 1/27; bilevel, 2/27; ST, 6/26	CPAP, 2/27; bilevel, 2/27; ST, 11/26
CPAP vs. ST, −1.2; bilevel vs. ST, −1.0; bilevel vs. CPAP, 0.2	CPAP vs. ST, −5.0; bilevel vs. ST, −4.0; bilevel vs. CPAP, 1.0	CPAP vs. ST, −10.5; bilevel vs. ST, −3.0; bilevel vs. CPAP, 7.5	CPAP, 33/346; bilevel, 34/356; ST, 36/367	CPAP, 1/346; bilevel, 4/356; ST, 3/367
NA	NA	NA	NA	CPAP, 5/44; bilevel, 4/44; ST, 10/41

All trials were randomized, and most had clearly described eligibility criteria (**Appendix Table 2**, available at www.annals.org). Fifteen trials (48%) reported concealed allocation. Only 1 was double-blind (37). Twenty-six studies (84%) used intention-to-treat analyses, and 29 (94%) described similar baseline characteristics. Dropout rates ranged from 0% to 19.4% and were less than 15% for 27 studies (93%).

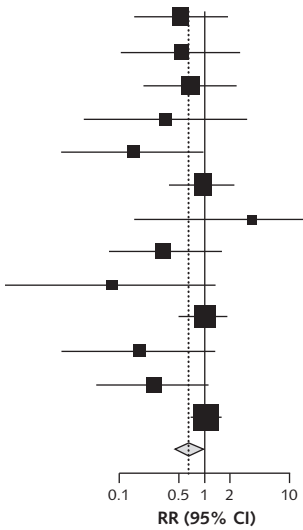
Clinical Outcomes

Of the 15 studies that compared CPAP with standard therapy, 14 reported mortality outcomes, all reported intubation outcomes, and 4 reported incidence of MI (1 trial had 0 events). Continuous positive airway pressure reduced in-hospital mortality (RR, 0.64 [95% CI, 0.44 to 0.92]) (**Figure 1**) and need for intubation (RR, 0.44 [CI, 0.32 to 0.60]) (**Figure 2**) but did not affect incidence of MI (RR, 1.07 [CI, 0.84 to 1.37]).

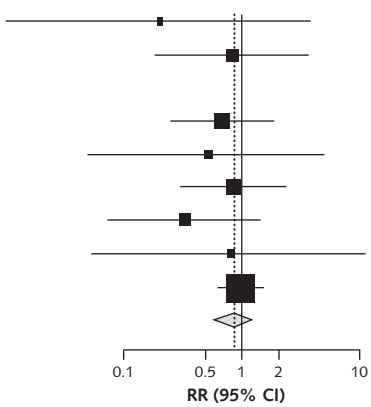
Of the 10 studies that compared bilevel ventilation with standard therapy, 9 reported mortality outcomes, 9 reported intubation outcomes, and 6 reported incidence of MI (2 trials had 0 events). Bilevel ventilation had no statistically significant effect on in-hospital mortality (RR, 0.82 [CI, 0.58 to 1.15]) (**Figure 1**) or incidence of MI (RR, 1.09 [CI, 0.87 to 1.37]) but reduced the need for intubation (RR, 0.54 [CI, 0.33 to 0.86]) (**Figure 2**).

Figure 1. **Forest plot for in-hospital mortality.**

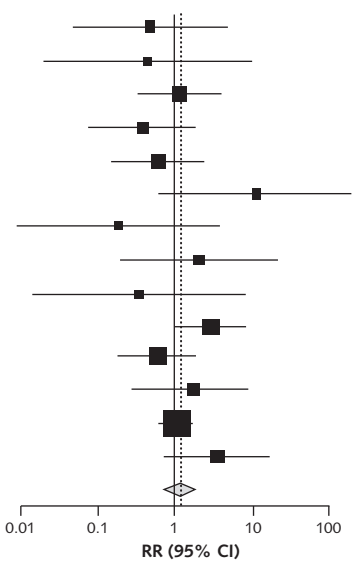
Study, Year (Reference)	CPAP		Standard Therapy		RR (95% CI)	W (random), %
	Events, *n*	Patients, *n*	Events, *n*	Patients, *n*		
Räsänen et al, 1985 (24)	3	20	6	20	0.50 (0.14–1.73)	7.2
Bersten et al, 1991 (25)	2	19	4	20	0.53 (0.11–2.55)	4.7
Lin et al, 1995 (26)	4	50	6	50	0.67 (0.20–2.22)	7.6
Takeda et al, 1997 (27)	1	15	3	15	0.33 (0.04–2.85)	2.7
Takeda et al, 1998 (28)	1	11	7	11	0.14 (0.02–0.98)	3.3
Delclaux et al, 2000 (29)	7	22	7	20	0.91 (0.39–2.14)	12.9
Park et al, 2001 (43)	1	9	0	10	3.32 (0.15–72.00)	1.3
Kelly et al, 2002 (30)	2	27	7	31	0.33 (0.07–1.45)	5.3
Crane et al, 2004 (44)	0	20	6	20	0.08 (0.00–1.28)	1.6
L'Her et al, 2004 (32)	12	43	14	46	0.92 (0.48–1.76)	18.5
Park et al, 2004 (45)	1	27	6	26	0.16 (0.02–1.24)	2.9
Plaisance et al, 2007 (17)	2	63	8	61	0.24 (0.05–1.09)	5.1
Gray et al, 2009 (12)	33	346	36	367	0.97 (0.62–1.52)	26.8
Random-effects model	69	672	110	697	0.64 (0.44–0.92)	100



Study, Year (Reference)	Bilevel Ventilation		Standard Therapy		RR (95% CI)	W (random), %
	Events, *n*	Patients, *n*	Events, *n*	Patients, *n*		
Masip et al, 2000 (33)	0	19	2	18	0.19 (0.01–3.69)	1.3
Levitt, 2001 (34)	3	21	3	17	0.81 (0.19–3.51)	5.5
Park et al, 2001 (43)	0	7	0	10		0
Nava et al, 2003 (35)	6	65	9	65	0.67 (0.25–1.77)	12.5
Ferrer et al, 2003 (36)	1	15	2	15	0.50 (0.05–4.94)	2.3
Crane et al, 2004 (44)	5	20	6	20	0.83 (0.30–2.29)	11.6
Park et al, 2004 (45)	2	27	6	26	0.32 (0.07–1.45)	5.2
Weitz et al, 2007 (13)	1	13	1	10	0.77 (0.05–10.85)	1.7
Gray et al, 2009 (12)	34	356	36	367	0.97 (0.62–1.52)	59.8
Random-effects model	52	543	65	548	0.82 (0.58–1.15)	100



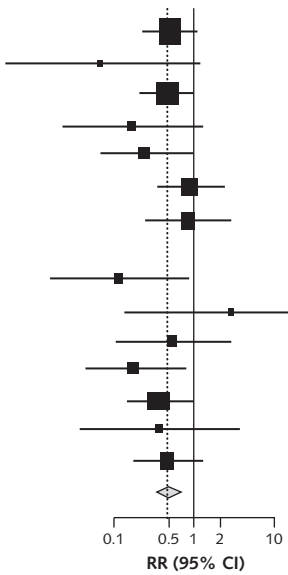
Study, Year (Reference)	Bilevel Ventilation		CPAP		RR (95% CI)	W (random), %
	Events, *n*	Patients, *n*	Events, *n*	Patients, *n*		
Mehta et al, 1997 (37)	1	14	2	13	0.46 (0.05–4.53)	2.8
Park et al, 2001 (43)	0	7	1	9	0.42 (0.02–8.95)	1.6
Bollaert et al, 2002 (38)	4	17	4	19	1.12 (0.33–3.79)	8.8
Martin-Bermudez et al, 2002 (39)	2	41	5	39	0.38 (0.08–1.85)	5.5
Cross et al, 2003 (41)	3	35	5	36	0.62 (0.16–2.39)	7.3
Crane et al, 2004 (44)	5	20	0	20	11.00 (0.65–186.32)	1.8
Bellone et al, 2004 (4)	0	24	2	22	0.18 (0.01–3.62)	1.7
Park et al, 2004 (45)	2	27	1	27	2.00 (0.19–20.77)	2.6
Bellone et al, 2005 (42)	0	18	1	18	0.33 (0.01–7.66)	1.5
Ferrari et al, 2006 (14)	11	53	4	53	2.75 (0.93–8.09)	10.8
Moritz et al, 2007 (15)	4	50	8	59	0.59 (0.19–1.84)	9.9
Ferrari et al, 2007 (16)	3	25	2	27	1.62 (0.29–8.91)	4.8
Gray et al, 2009 (12)	34	356	33	346	1.00 (0.63–1.58)	34.9
Ferrari et al, 2009 (18)	7	40	2	40	3.50 (0.77–15.83)	6
Random-effects model	76	727	70	728	1.06 (0.72–1.57)	100



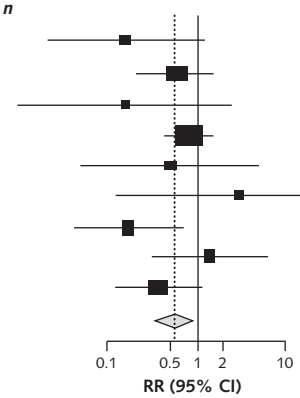
CPAP = continuous positive airway pressure; RR = relative risk.

Figure 2. **Forest plot for need for intubation.**

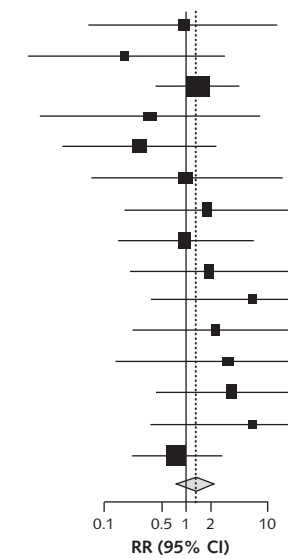
Study, Year (Reference)	CPAP		Standard Therapy		RR (95% CI)	W (random), %
	Events, *n*	Patients, *n*	Events, *n*	Patients, *n*		
Räsänen et al, 1985 (24)	6	20	12	20	0.50 (0.23–1.07)	17.1
Bersten et al, 1991 (25)	0	19	7	20	0.07 (0.00–1.15)	1.3
Lin et al, 1995 (26)	8	50	18	50	0.44 (0.21–0.93)	18.3
Takeda et al, 1997 (27)	1	15	6	15	0.17 (0.02–1.22)	2.5
Takeda et al, 1998 (28)	2	11	8	11	0.25 (0.07–0.92)	5.8
Delclaux et al, 2000 (29)	6	22	6	20	0.91 (0.35–2.36)	10.8
Park et al, 2001 (43)	3	9	4	10	0.83 (0.25–2.76)	6.9
Kelly et al, 2002 (30)	0	27	0	31		0
Hao et al, 2002 (31)	1	25	9	26	0.12 (0.02–0.85)	2.5
Crane et al, 2004 (44)	1	20	0	20	3.00 (0.13–69.42)	1
L'Her et al, 2004 (32)	2	43	4	46	0.53 (0.10–2.77)	3.6
Park et al, 2004 (45)	2	27	11	26	0.18 (0.04–0.72)	5
Plaisance et al, 2007 (17)	6	63	16	61	0.36 (0.15–0.87)	13.1
Gray et al, 2009 (12)	1	346	3	367	0.35 (0.04–3.38)	1.9
Ghanem et al, 2009 (19)	5	44	10	41	0.47 (0.17–1.25)	10.2
Random-effects model	44	741	114	764	0.44 (0.32–0.60)	100



Study, Year (Reference)	Bilevel Ventilation		Standard Therapy		RR (95% CI)	W (random), %
	Events, *n*	Patients, *n*	Events, *n*	Patients, *n*		
Masip et al, 2000 (33)	1	19	6	18	0.16 (0.02–1.19)	5.2
Levitt, 2001 (34)	5	21	7	17	0.58 (0.22–1.50)	18.9
Park et al, 2001 (43)	0	7	4	10	0.16 (0.01–2.48)	2.8
Nava et al, 2003 (35)	13	65	16	65	0.81 (0.43–1.55)	32.3
Ferrer et al, 2003 (36)	1	15	2	15	0.50 (0.05–4.94)	4.1
Crane et al, 2004 (44)	1	20	0	20	3.00 (0.13–69.42)	2.2
Park et al, 2004 (45)	2	27	11	26	0.18 (0.04–0.72)	10
Gray et al, 2009 (12)	4	356	3	367	1.37 (0.31–6.10)	9
Ghanem et al, 2009 (19)	4	44	10	41	0.37 (0.13–1.10)	15.6
Random-effects model	31	574	59	579	0.54 (0.33–0.86)	100

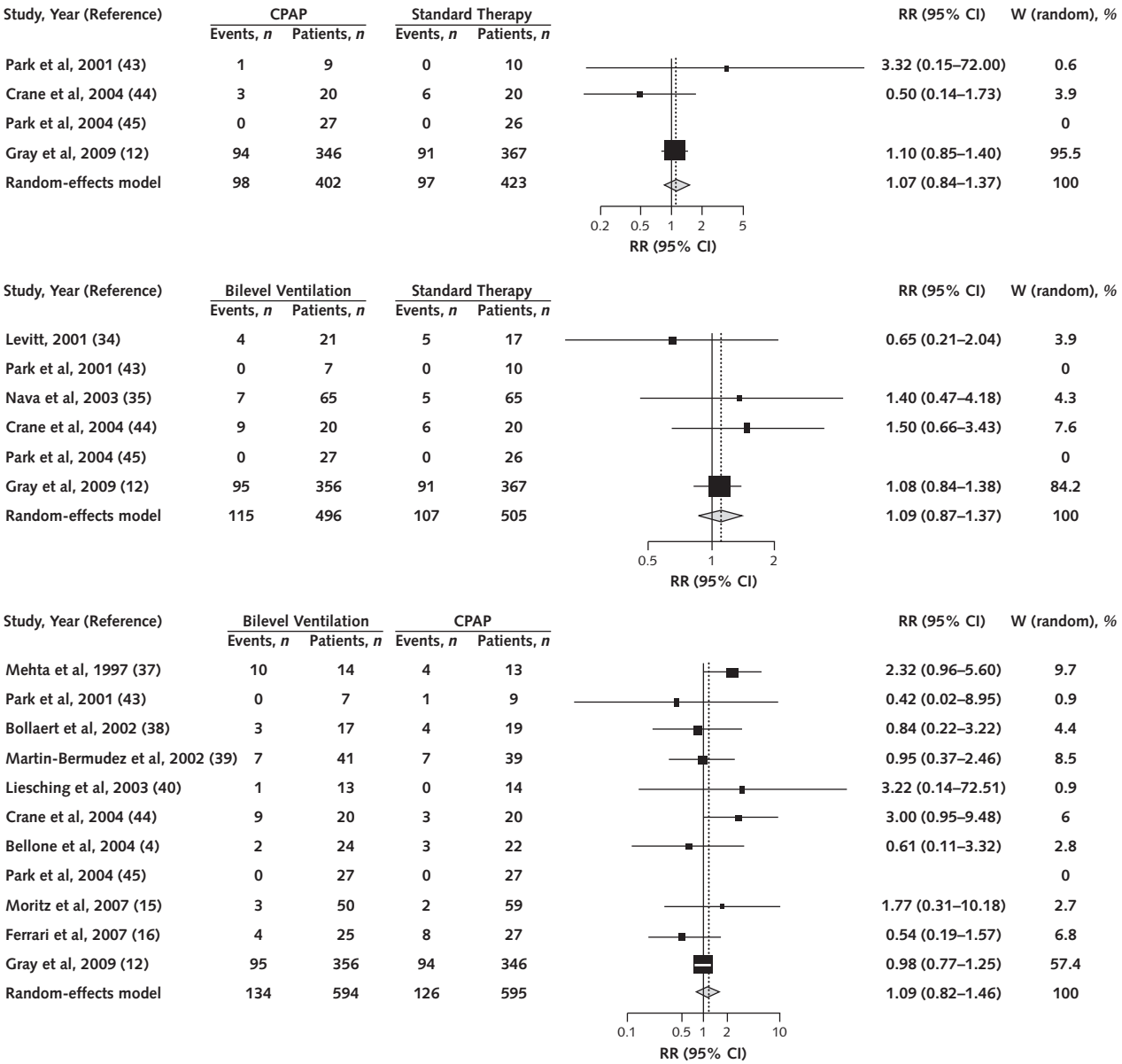


Study, Year (Reference)	Bilevel Ventilation		CPAP		RR (95% CI)	W (random), %
	Events, *n*	Patients, *n*	Events, *n*	Patients, *n*		
Mehta et al, 1997 (37)	1	14	1	13	0.93 (0.06–13.37)	4
Park et al, 2001 (43)	0	7	3	9	0.18 (0.01–2.99)	3.6
Bollaert et al, 2002 (38)	5	17	4	19	1.40 (0.45–4.37)	21.9
Liesching et al, 2003 (40)	0	13	1	14	0.36 (0.02–8.06)	2.9
Cross et al, 2003 (41)	1	35	4	36	0.26 (0.03–2.19)	6.2
Crane et al, 2004 (44)	1	20	1	20	1.00 (0.07–14.90)	3.9
Bellone et al, 2004 (4)	2	24	1	22	1.83 (0.18–18.84)	5.2
Park et al, 2004 (45)	2	27	2	27	1.00 (0.15–6.59)	8
Bellone et al, 2005 (42)	2	18	1	18	2.00 (0.20–20.15)	5.3
Ferrari et al, 2006 (14)	3	53	0	53	7.00 (0.37–132.26)	3.3
Moritz et al, 2007 (15)	2	50	1	59	2.36 (0.22–25.26)	5.1
Ferrari et al, 2007 (16)	1	25	0	27	3.24 (0.14–75.87)	2.9
Gray et al, 2009 (12)	4	356	1	346	3.89 (0.44–34.61)	6
Ferrari et al, 2009 (18)	3	40	0	40	7.00 (0.37–131.22)	3.3
Ghanem et al, 2009 (19)	4	44	5	44	0.80 (0.23–2.78)	18.3
Random-effects model	31	743	25	747	1.23 (0.72–2.10)	100



CPAP = continuous positive airway pressure; RR = relative risk.

Figure 3. **Forest plot for incidence of new myocardial infarction.**



CPAP = continuous positive airway pressure; RR = relative risk.

Of the 16 studies that compared bilevel ventilation with CPAP, 14 reported mortality outcomes, 15 reported intubation outcomes, and 11 reported incidence of MI. The forms of ventilation did not significantly differ in in-hospital mortality (RR, 1.06 [CI, 0.72 to 1.57]) (**Figure 1**), need for intubation (RR, 1.23 [CI, 0.72 to 2.10]) (**Figure 2**), or incidence of MI (RR, 1.09 [CI, 0.82 to 1.46]) (**Figure 3**).

Estimates of effect were identical when we used fixed-effects models. Our review of funnel plots did not exclude publication bias, but no bias was evident when we applied the Begg rank correlation method (Begg test P value > 0.15 for all trial interventions and outcomes) except for the comparison of the effects of CPAP and standard therapy on mortality ($P = 0.002$) (**Appendix Figure 2**, available at www.annals.org).

Baseline Characteristics

In general, NIV was not significantly associated with reductions in mortality or need for intubation for any of the trial comparisons and outcomes, on the basis of baseline PaO_2–FIO_2 ratio; between-group differences in respiratory rate, heart rate, or PaO_2; or rates of mortality and need for intubation in control groups. The lone exception was that compared with standard therapy, use of CPAP was associated with a statistically significant reduction in in-

hospital mortality among patients whose pulmonary edema was caused by acute MI or ischemia (**Appendix Tables 3** to **5**, available at www.annals.org). Trials with lower proportions of patients who had previous MI or ischemia showed less reduction in mortality rate than those with higher proportions of these patients (RR, 0.92 [CI, 0.76 to 1.10] when 10% of patients had ischemia or MI vs. 0.43 [CI, 0.17 to 1.07] when 50% had ischemia or MI; average reduction in risk ratio per 10% increase in the proportion of patients with acute MI or ischemia at admission, 17.4% [CI, 0.7% to 31.2%]). Although this result seemed to depend heavily on a single small trial that enrolled only patients with acute MI or ischemia at baseline (28), removing this trial from the analysis did not change the findings (**Figure 4**).

Sensitivity and Cumulative Meta-analyses

Influence Analyses

When we omitted each study in turn and recalculated pooled estimates of effect, we found that only the 3CPO trial (12, 46) consistently influenced our estimates of effect across comparisons and outcomes. This trial decreased the estimate of mortality effect (shifted the risk estimate toward the null) for comparisons of CPAP and bilevel ventilation with standard therapy. It also influenced the risk estimates of effect on MI for all trial comparisons, but the changes in estimates did not alter the statistical or clinical significance of these findings (**Appendix Figure 3**, available at www.annals.org).

Weighting the 3CPO Trial

We gave the 3CPO trial (12, 46) a weight of 26.8% in the standard meta-analysis that assessed mortality in comparisons of CPAP with standard therapy. **Figure 5**, *top left*, shows pooled estimates across all possible weightings of the trial, anticipating belief that the trial should be weighted higher (because it contributes about half the total number of events and patients to the pooled estimate of effect) or lower (because it had higher dropout rates and its findings contradict the entire previous evidence base). At a weight of 0%, the pooled estimate of effect is 0.56 (CI, 0.38 to 0.84), identical to the estimate based on the other 12 trials (**Appendix Figure 3**, *A*). At a weight of 100%, the estimate is that from the 3CPO trial, 0.97 (CI, 0.62 to 1.52). At a weight of approximately 50%, the pooled estimate of effect becomes statistically insignificant.

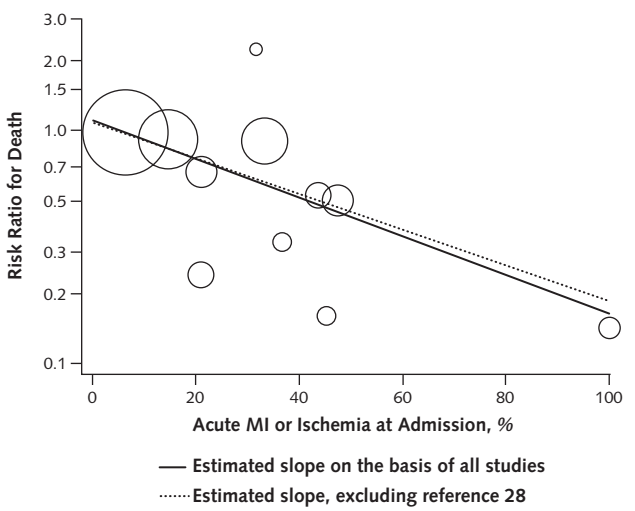
The weight assigned to the 3CPO trial (12, 46) did not affect findings of effect for any of the other trial comparisons and outcomes, except for the comparison of the effect of CPAP and standard therapy on need for intubation (initial trial weight, 1.9%; effect becomes statistically insignificant at weight of approximately 40%) (**Figure 5**, *middle left*) and the comparison of bilevel ventilation with standard therapy on need for intubation (initial trial weight, 9%; effect becomes statistically insignificant at weight of approximately 20%) (**Figure 5**, *center*).

Cumulative Analyses

Cumulative meta-analyses based on quality score suggest that category of study quality influenced estimates of effect (**Appendix Figures 4** to **6**, available at www.annals.org). Although estimates of effect remained qualitatively similar, inclusion of trials with lower quality scores decreased the estimate of effect on mortality in comparisons of CPAP with standard therapy and decreased the estimate of effect on MI for all trial comparisons. By contrast, inclusion of trials with lower quality scores increased the estimate of effect on mortality in comparisons of bilevel ventilation with standard therapy and increased the estimate of effect on need for intubation in comparisons of both CPAP and bilevel ventilation with standard therapy. In all comparisons and for all outcomes, including the 3CPO trial (12), the most recent trial of NIV and a trial with a lower quality score, shifted risk estimates toward lesser effect.

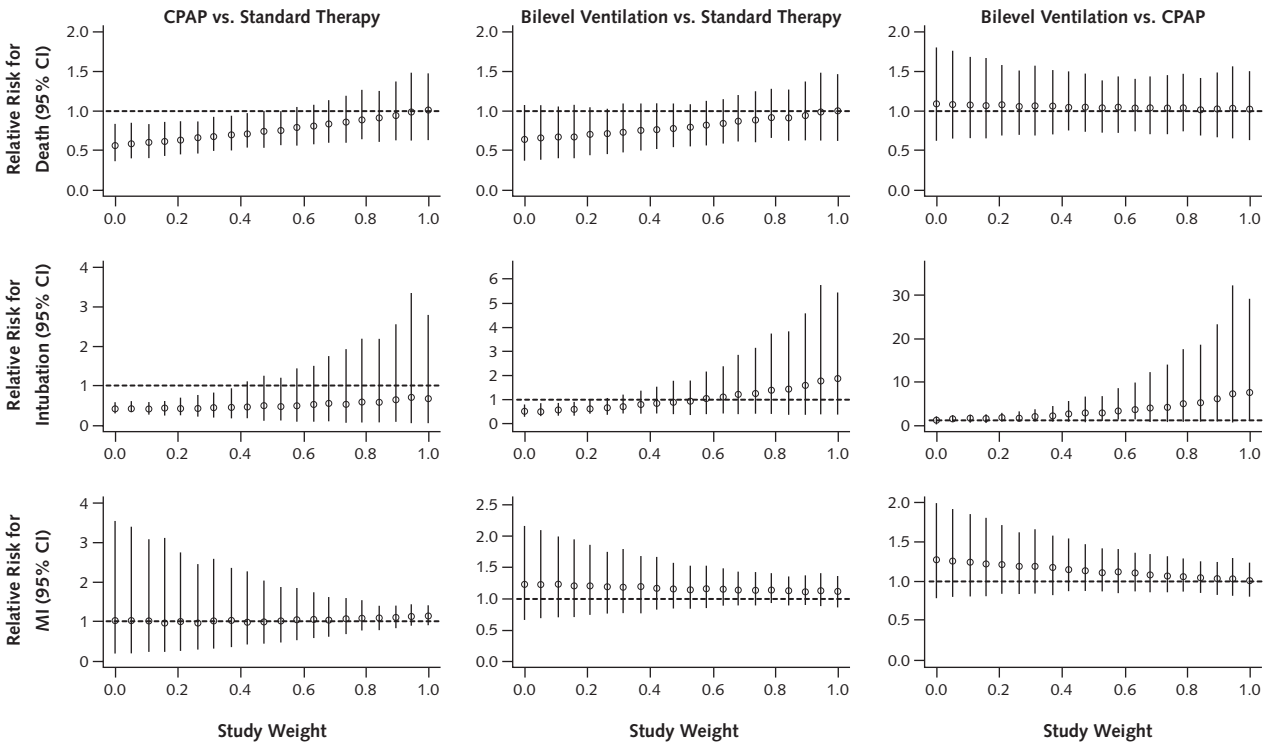
Cumulative meta-analyses by date of publication suggest that evidence was in place by 2002 to conclude that CPAP decreased the risk for death (**Appendix Figure 7**, *A*, available at www.annals.org), by 1995 to conclude that CPAP decreased the need for mechanical ventilation (**Appendix Figure 8**, *A*, available at www.annals.org), and by 2004 to conclude that bilevel ventilation decreased the need for mechanical ventilation, all compared with standard therapy (**Appendix Figure 8**, *B*). Publication of subsequent studies did not alter the estimate of benefit for these outcomes. **Appendix Figure 7**, *B* and *C*, and **Appendix Figure 9** (available at www.annals.org) show other cumulative results.

Figure 4. **Risk for in-hospital mortality as a function of acute MI or ischemia at admission, comparing continuous positive airway pressure with standard therapy.**



Regression equation: log risk ratio = 0.103 – 1.906 × (percentage of patients with acute MI or ischemia at admission). The crude risk estimates from the individual studies are plotted along with their regression line. MI = myocardial infarction.

Figure 5. **Weight of the 3CPO (Three Interventions in Cardiogenic Pulmonary Oedema) trial as a function of pooled RRs with their associated 95% CIs.**



Calculated according to the formula $\ln(\textit{Pooled RR}) = (1 - wt) \times \ln(RR_1) + wt \times \ln(RR_2)$, where wt = weight, RR_1 = meta-analysis of other trials by using the Mantel–Haenszel method, and RR_2 = meta-analysis of the 3CPO trial by using the inverse variance method. MI = myocardial infarction; RR = relative risk.

Subgroup Analyses

Compared with meta-analyses that included all trials (**Figures 1** to **3**), those restricted to trials with allocation concealment suggested greater effects on mortality (8 trials; RR, 0.45 [CI, 0.25 to 0.82]) and need for mechanical ventilation (8 trials; RR, 0.46 [CI, 0.29 to 0.71]) from CPAP versus standard therapy, and greater effects on need for mechanical ventilation (3 trials; RR, 0.27 [CI, 0.07 to 1.08]) from bilevel ventilation versus standard therapy (**Appendix Table 6**, available at www.annals.org).

Bayesian meta-analyses suggested similar directions of effect for all comparisons and outcomes, but with greater estimates of benefit (**Appendix Figures 10** to **12**, available at www.annals.org).

Discussion

In this meta-analysis of trials evaluating the benefit and safety of NIV for patients with ACPE, CPAP was associated with a statistically significant reduction in in-hospital mortality and need for intubation, but not incidence of new MI, compared with standard therapy (oxygen, diuretics, nitrates, and supportive care). The effect was especially prominent among patients in whom myocardial ischemia or infarction was a cause of pulmonary edema. Bilevel ventilation was associated with a statistically significant reduction in the need for intubation, but not in mortality or incidence of new MI, compared with standard therapy. Bilevel ventilation and CPAP did not significantly differ on any clinical outcome in which they were directly compared.

Despite these findings, questions about the efficacy of NIV remain because the 3CPO trial (12, 46), the largest and most recent trial to compare modes of ventilation with standard therapy and each other, detected no differences in mortality or need for intubation, in contrast to most preceding studies (although it did find more rapid improvements in patient-reported dyspnea, acidosis, and hypercapnia). We attempted to address this discrepancy by performing multiple analyses to evaluate how the estimates of effect of NIV changed when we included or excluded the 3CPO trial or varied the weight of the trial and by assessing the entire evidence base by quality and time of publication and using Bayesian meta-analysis. These analyses generally confirmed the findings of the primary analyses but indicated that at higher weights—which might be assigned to the 3CPO trial because it contributed half of all available trial evidence and used the most contemporary ventilation and standard therapies—the trial's negative findings dominate the overall estimate of effect, and NIV

becomes no different from standard therapy at reducing mortality or the need for intubation.

The mortality and intubation findings of the 3CPO trial (12, 46) may differ from nearly the entire preceding evidence base for several reasons. First, the trial excluded sick patients who required life-saving or emergency intervention, a population that might be more likely to benefit from NIV; the mortality and intubation rates were much lower in the 3CPO trial than in preceding trials (6, 7), which indicates that the study samples were different (5). Similarly, only about 20% of trial patients had myocardial ischemia or infarction as the cause of their pulmonary edema, a baseline characteristic that our analyses suggest is associated with greater estimates of effect. Second, the 3CPO trial had considerable crossover among treatment groups (12, 46); interventions were defined only for the first 2 hours, after which treatment was at the discretion of clinicians, and 80.6% of those randomly assigned to receive standard therapy ultimately received NIV (19.4% did not complete their assigned treatment), which may have obscured differences among the treatment groups (47). Third, standard monitoring and therapy for ACPE may have improved since the first trials of NIV. As the most recently published trial of NIV, the 3CPO trial may have incorporated those standards in ways that were unmeasured or unreported, which may also have obscured potential differences among treatment groups. Finally, our estimated effect of NIV is derived from calculations that assign different importance (weight) to the individual studies. The weight of the 3CPO trial in analyses that found favorable effects on mortality and ventilation was not greater than 50%, so the trial's negative findings did not dominate the overall estimates of effect in those analyses, but using a different weighting scheme from the default meta-analysis could lead to different interpretations (for example, allocating more importance to the 3CPO trial yields less support for the favorable effects). Besides the need to compensate for the output of the statistical methods and program, other reasons for assigning a lower weight to the 3CPO trial include notable differences in patient characteristics between the 3CPO trial and all other trials and existing beliefs about the efficacy of NIV based on those previous trials.

Our review has limitations. The quality of the evidence base was limited; no trial met all standard quality criteria, and we found only small differences in size when we analyzed the trials by quality and date of publication. Criteria for diagnosis of ACPE are not well established, and the definitions, causes, and severity of ACPE differed among the trials; the evidence base was heterogeneous with respect to other patient characteristics and clinical settings. Finally, we could not exclude the possibility of publication bias for some comparisons and outcomes.

In conclusion, findings from this meta-analysis support previous assessments that the use of CPAP reduces mortality and intubation rates in patients with ACPE, especially those with myocardial ischemia or MI at presentation, and bilevel ventilation reduces the need for intubation compared with standard therapy. Neither form of ventilation seems better than the other, and neither reduces the risk for acute MI. These conclusions differ from the findings of the most recent and largest single trial of NIV, possibly because of differences in patient population or trial conduct or improvements in contemporary standard therapy. Firm conclusions about the efficacy of NIV depend on the weight assigned to that most recent trial and to the findings of ongoing and future trials (such as 2 French trials that are currently recruiting participants [48, 49]).

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Collection and assembly of data: Q.H. Liu.

Appendix: Statistical Methods for Bayesian Hierarchical Meta-analysis

Patient variability and differences in trial design, inclusion and exclusion criteria, and target populations made it unrealistic to assume that the effects of noninvasive ventilation estimated from each of these trials would be identical, as implied by a fixed-effects meta-analysis model. We therefore used a Bayesian hierarchical (random-effects) meta-analytic model to analyze these 31 studies.

In our model, we allowed the probability of an event in each group of each trial to vary between the treatment and control groups within each study and between each study. We modeled the baseline log risk ratio of an event as a normal random variable drawn from a normal distribution, with the mean equal to the baseline log risk ratio in the population of possible studies and the variance representing the variability across studies. Similarly, we modeled the change in log risk ratio of an event attributable to treatment as a normal random variable drawn from a normal distribution, with the mean equal to the population effect of the treatment on the log risk ratio and the variance representing the variability in treatment effect across studies. We used low-information a priori distributions throughout so that the data from the trials dominated the final inferences. In particular, we used normal (mean = 0, variance = 100) a priori distributions for all means; we set one precision as γ (0.0001, 0.0001) a priori distributions and another as the inverse square of a uniform distribution over an interval of 4. We defined "precision" as the reciprocal of the variance. We report our results as posterior means with 95% equal-tailed credible intervals, the Bayesian analogue of CIs. We conducted separate sensitivity analyses with various uniform and inverse-γ a priori distributions for the variance to test the robustness of the posterior inference.

We used WinBUGS software (version 1.4, MRC Biostatistics Unit, Cambridge, United Kingdom) for all analyses.

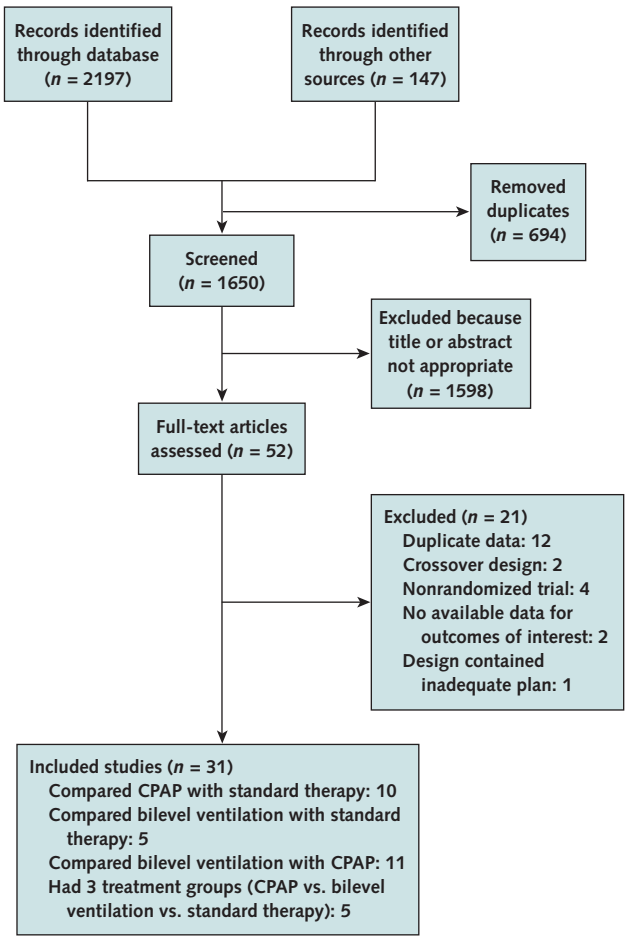
Results

An advantage of Bayesian analysis is that the risk ratio in mortality may be displayed as a probability density curve, in which the area under the curve between any 2 points shows the probability that the reduction in mortality is in that interval (**Appendix Figure 12**). From this perspective, the probability that continuous positive airway pressure significantly decreased risk for death compared with standard therapy is 95% with a risk ratio of 0.74 and 90% with a risk ratio of 0.68. Similarly, the probability that continuous positive airway pressure decreased the need for intubation is 95% with a risk ratio of 0.49 and 90% with a risk ratio of 0.46 (**Appendix Figure 12** and **Appendix Table 7**).

Sensitivity Analysis

In most cases, Bayesian hierarchical model inferences are most sensitive to the choice of a priori distribution for variances in the baseline and treatment effects. However, our results were not sensitive to different choices of low-information a priori distribution. For example, we compared the uniform distribution over a wide interval, the low-information inverse-γ distribution, and the low-information γ distribution, and our model remained robust with these different choices. Notably, we tried a wide range of low-information values for our γ distributions and different upper limits for our uniform distributions, and none affected our model's posterior inferences.

Appendix Figure 1. **Literature search and selection.**



CPAP = continuous positive airway pressure.

Appendix Table 1. Search Strategies

PubMed

#1 Search "pulmonary edema" [Mesh]
#2 Search "pulmonary edema" [tw]
#3 Search "pulmonary oedema" [tw]
#4 Search "lung oedema" [tw]
#5 Search "lung edema" [tw]
#6 Search "wet lung" [tw]
#7 Search (ACPE OR CPE OR CPO) AND (lung OR pulmonary)
#8 Search "cardiogenic edema" [tw]
#9 Search "cardiogenic oedema" [tw]
#10 Search "heart failure" [Mesh]
#11 Search "heart failure" [tw]
#12 Search "cardiac failure" [tw]
#13 Search "cardiac insufficiency" [tw]
#14 Search "heart insufficiency" [tw]
#15 Search "left ventricle dysfunction" [tw]
#16 Search "Respiratory Insufficiency" [Mesh]
#17 Search "Respiratory Insufficiency" [tw]
#18 Search "Respiratory failure" [tw]
#19 Search #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18
#20 Search "Respiration, Artificial" [Mesh]
#21 Search "nose breathing" [tw]
#22 Search "nose ventilation" [tw]
#23 Search "nasal ventilation" [tw]
#24 Search "artificial ventilation" [tw]
#25 Search "noninvasive ventilation" [tw]
#26 Search "non-invasive ventilation" [tw]
#27 Search noninvasive ventilat* [tw]
#28 Search non-invasive ventilat* [tw]
#29 Search NIV [tw]
#30 Search "noninvasive support ventilation" [tw]
#31 Search "non-invasive support ventilation" [tw]
#32 Search "positive pressure respiration" [tw]
#33 Search "noninvasive positive pressure ventilation" [tw]
#34 Search "continuous positive airway pressure" [tw]
#35 Search continuous positive airway* [tw]
#36 Search CPAP [tw]
#37 Search PEEP [tw]
#38 Search "intermittent positive pressure ventilation" [tw]
#39 Search "noninvasive ventilatory assistance apparatus" [tw]
#40 Search "bilevel positive airway pressure" [tw]
#41 Search "bi-level positive airway pressure" [tw]
#42 Search bilevel positive airway* [tw]
#43 Search "bilevel ventilation" [tw]
#44 Search "bi-level ventilation" [tw]
#45 Search "biphasic intermittent positive airway" [tw]
#46 Search Bipap [tw]
#47 Search nippv [tw]
#48 Search nppv [tw]
#49 Search niav [tw]
#50 Search ippb [tw]
#51 Search ippV [tw]
#52 Search "assisted ventilation" [tw]
#53 Search #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52
#54 Search (randomized controlled trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR random allocat* [tw] OR randomly allocat* [tw] OR double-blind method[mh] OR single-blind method [mh] OR double blind* [tw] OR single blind* [tw] OR triple blind* [tw] OR clinical trial [pt] OR clinical trials [mh]) NOT (animal [mh] NOT human [mh]))
#55 Search #53 AND #54 AND #19
#56 Search #53 AND #54 AND #19 Limits: All Adult: 19+ years

EMBASE

#1 'lung edema'/exp OR 'lung edema'
#2 'lung oedema'
#3 'pulmonary edema'/exp OR 'pulmonary edema'
#4 'pulmonary oedema'/exp OR 'pulmonary oedema'
#5 'wet lung'
#6 'acute pulmonary edema'/exp OR 'acute pulmonary edema'

Continued on following page

Appendix Table 1—**Continued**

#7 'cardiogenic pulmonary edema'
#8 'cardiogenic pulmonary oedema'
#9 'cardiogenic edema'
#10 'cardiogenic oedema'
#11 'heart failure'/exp OR 'heart failure'
#12 'ACPE' OR 'CPE' OR 'CPO'
#13 'cardiac failure'/exp OR 'cardiac failure'
#14 'cardiac insufficiency'/exp OR 'cardiac insufficiency'
#15 'heart insufficiency'/exp OR 'heart insufficiency'
#16 'heart left ventricle dysfunction'
#17 'respiratory failure'/exp OR 'respiratory failure'
#18 'respiratory insufficiency'/exp OR 'respiratory insufficiency'
#19 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18
#20 'nose breathing'/exp OR 'nose breathing'
#21 'nasal ventilation'/exp OR 'nasal ventilation'
#22 'artificial ventilation'/exp OR 'artificial ventilation'
#23 'noninvasive ventilation'
#24 'non+invasive ventilation'
#25 noninvasive AND ventilat*
#26 non+invasive AND ventilat*
#27 niv
#28 'lung ventilation'/exp OR 'lung ventilation'
#30 'positive end expiratory pressure'/exp OR 'positive end expiratory pressure'
#31 'positive pressure respiration'/exp OR 'positive pressure respiration'
#32 'noninvasive positive pressure ventilation'
#33 'noninvasive support ventilation' OR 'non+invasive support ventilation'
#34 'continuous positive airway pressure'/exp OR 'continuous positive airway pressure'
#35 continuous AND positive AND airway*
#36 'cpap'/exp OR cpap
#37 'intermittent positive pressure ventilation'/exp OR 'intermittent positive pressure ventilation'
#38 'peep'/exp OR peep
#39 'noninvasive ventilatory assistance apparatus' OR 'non+invasive ventilatory assistance apparatus'
#40 'bilevel positive airway pressure'
#41 'bi+level positive airway pressure'
#42 'bilevel ventilation' OR 'bi+level ventilation'
#43 'bi level' AND positive AND airway*
#44 bilevel AND positive AND airway*
#45 'biphasic intermittent positive airway'
#46 bipap
#47 nippv
#48 nppv OR niav OR 'ippb'/exp OR ippb OR 'ippv'/exp OR ippv
#49 'assisted ventilation'/exp OR 'assisted ventilation'
#50 #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49
#51 'randomized controlled trial'/exp OR 'randomized controlled trial'
#52 'randomized controlled trials'/exp OR 'randomized controlled trials'
#53 'randomization'/exp OR 'randomization'
#54 random AND allocat*
#55 randomly AND allocat*
#56 'double blind procedure'/exp OR 'double blind procedure'
#57 'double-blind method'/exp OR 'double-blind method'
#58 'single blind procedure'/exp OR 'single blind procedure'
#59 'single-blind method'/exp OR 'single-blind method'
#60 single AND blind*
#61 double AND blind*
#62 triple AND blind*
#63 'triple blind procedure'/exp OR 'triple blind procedure'
#64 'clinical trials'/exp OR 'clinical trials'
#65 'clinical trial'/exp OR 'clinical trial'
#66 #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67
#67 #19 AND #52 AND #68 AND ([adult]/lim OR [aged]/lim) AND [humans]/lim AND [embase]/lim
#68 #19 AND #52 AND #68

Cochrane Central Register of Controlled Trials

#1 MeSH descriptor Respiration, Artificial explode all trees
MeSH descriptor Heart Failure explode all trees
#2 (cardiogenic near edema):ti,ab,kw or (cardiogenic near oedema):ti,ab,kw or (pulmonary near edema):ti,ab,kw or (pulmonary near oedema):ti,ab,kw or (wet near lung):ti,ab,kw in Clinical Trials

Continued on following page

Appendix Table 1—Continued

#3 (cardiac next failure):ti,ab,kw or (heart next failure):ti,ab,kw or (cardiac next insufficiency):ti,ab,kw or (heart next insufficiency):ti,ab,kw or (left next ventricle next dysfunction):ti,ab,kw in Clinical Trials
#4 (respiratory next insufficiency):ti,ab,kw or (respiratory next failure):ti,ab,kw in Clinical Trials
#5 (#1 OR #2 OR #3 OR #4)
#6 MeSH descriptor Respiration, Artificial explode all trees
#7 (nasal next ventilation):ti,ab,kw or (nose next breathing):ti,ab,kw or (lung near ventilatio*):ti,ab,kw or (noninvasive next support next ventilation):ti,ab,kw or (noninvasive next positive next pressure next respiration):ti,ab,kw in Clinical Trials
#8 (continuous next positive next airway next pressure):ti,ab,kw or (intermittent next positive next pressure next ventilation):ti,ab,kw or (positive next end next expiratory next pressure):ti,ab,kw or (noninvasive next ventilatory next assistance next apparatus):ti,ab,kw or (bilevel next positive next airway next pressure):ti,ab,kw in Clinical Trials
#9 (bi-level next positive next airway next pressure):ti,ab,kw or (bilevel next ventilation):ti,ab,kw or (bi-level next ventilation):ti,ab,kw or (biphasic next intermittent next positive next airway):ti,ab,kw or (non-invasive next ventilation):ti,ab,kw in Clinical Trials
#10 (CPAP):ti,ab,kw or (PEEP):ti,ab,kw or (Bipap):ti,ab,kw or (nippv):ti,ab,kw or (nppv):ti,ab,kw in Clinical Trials
#11 niav:ti,ab,kw or (ippb):ti,ab,kw or (ippv):ti,ab,kw in Clinical Trials
#12 (#6 OR #7 OR #8 OR #9 OR #10 OR #11)
#13 (#5 AND #12) in Clinical Trials

Google Scholar

allintitle: nasal OR continuous OR positive OR airway OR pressure OR noninvasive OR ventilation OR bilevel OR CPAP "cardiogenic pulmonary edema" -"Non Cardiogenic"

Appendix Table 2. Study Quality Score

Trial	Eligibility Criteria Specified	Random Allocation	Concealed Allocation	Groups Similar at Baseline	Patient Blinding	Therapist Blinding	Assessor Blinding	Dropout Rate Less Than 15%	Intention-to-Treat Analysis	Between-Group Statistical Comparisons	Point Measures and Variability Data
CPAP vs. ST											
Räsänen et al, 1985 (24)	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes
Bersten et al, 1991 (25)	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes
Lin et al, 1995 (26)	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes
Takeda et al, 1997 (27)	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes
Takeda et al, 1998 (28)	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes
Delclaux et al, 2000 (29)	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes
Kelly et al, 2002 (30)	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes
Hao et al, 2002 (31)	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes
L'Her et al, 2004 (32)	Yes	Yes	Yes	No	No	No	No	Yes	Yes	Yes	Yes
Plaisance et al, 2007 (17)	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes
Bilevel ventilation vs. ST											
Masip et al, 2000 (33)	Yes	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Yes
Levitt, 2001 (34)	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes
Nava et al, 2003 (35)	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes
Ferrer et al, 2003 (36)	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes
Weitz et al, 2007 (13)	Yes	Yes	No	Yes	No	No	No	Yes	NA	Yes	Yes
Bilevel ventilation vs. CPAP											
Mehta et al, 1997 (37)	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Bollaert et al, 2002 (38)	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes
Martin-Bermudez et al, 2002 (39)	Yes	Yes	NA	Yes	No	No	No	NA	Yes	Yes	Yes
Liesching et al, 2003 (40)	NA	Yes	No	Yes	NA	NA	NA	NA	NA	Yes	Yes
Cross et al, 2003 (41)	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes
Bellone et al, 2004 (4)	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes
Bellone et al, 2005 (42)	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes
Ferrari et al, 2006 (14)	Yes	Yes	NA	Yes	No	No	No	NA	Yes	Yes	Yes
Moritz et al, 2007 (15)	Yes	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Yes
Ferrari et al, 2007 (16)	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes
Ferrari et al, 2009 (18)	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes
CPAP vs. bilevel ventilation vs. ST											
Park et al, 2001 (43)	Yes	Yes	No	Yes	No	No	No	Yes	Yes	No	Yes
Crane et al, 2004 (44)	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes
Park et al, 2004 (45)	Yes	Yes	Yes	No	No	No	No	Yes	No	Yes	Yes
Gray et al, 2009 (46)	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes
Ghanem et al, 2009 (19)	Yes	Yes	NA	Yes	No	No	No	Yes	Yes	Yes	Yes

CPAP = continuous positive airway pressure; NA = not available; ST = standard therapy.

Appendix Table 3. **Meta-regression Models Investigating Association of Between-Group Differences in Respiratory Rate, Heart Rate, and Pao_2 at 30 Minutes or 1 Hour After Treatment, With Log Risk Ratios of Clinical Outcomes**

Comparison	Slope Coefficient (95% CI)		
	Respiratory Rate Differences*	Heart Rate Differences*	Pao_2 Difference*
Mortality			
CPAP vs. standard therapy	0.019 (−0.320 to 0.358)	−0.032 (−0.106 to 0.043)	−0.007 (−0.045 to 0.030)
Bilevel ventilation vs. standard therapy	0.169 (0.176 to 0.514)	−0.024 (−0.132 to 0.084)	−0.003 (−0.035 to 0.030)
Bilevel ventilation vs. CPAP	0.337 (−0.574 to 1.248)	0.005 (−0.231 to 0.241)	−0.002 (−0.074 to 0.070)
Intubation rate			
CPAP vs. standard therapy	0.033 (−0.217 to 0.283)	−0.032 (−0.106 to 0.043)	−0.014 (−0.047 to 0.020)
Bilevel ventilation vs. standard therapy	0.265 (−0.157 to 0.687)	−0.006 (−0.140 to 0.127)	0.012 (−0.028 to 0.053)
Bilevel ventilation vs. CPAP	0.303 (−0.619 to 1.224)	0.058 (−0.161 to 0.276)	−0.023 (−0.094 to 0.048)

CPAP = continuous positive airway pressure.
* Between-group differences.

Appendix Table 4. **Meta-regression Models Investigating Association of Acute MI or Ischemia and Pao_2–Fio_2 Ratio at Baseline, With Log Risk Ratios of Clinical Outcomes**

Comparison	Slope Coefficient (95% CI)	
	Acute MI or Ischemia at Baseline	Pao_2–Fio_2 Ratio at Baseline
Mortality		
CPAP vs. standard therapy	−1.906 (−3.745 to −0.066)	0.001 (−0.004 to 0.006)
Bilevel ventilation vs. standard therapy	−2.650 (−10 550 to 5.249)	0.002 (−0.001 to 0.005)
Bilevel ventilation vs. CPAP	0.628 (−1.848 to 3.103)	−0.002 (−0.004 to 0.001)
Intubation rate		
CPAP vs. standard therapy	−0.517 (−2.351 to 1.317)	0.004 (−0.003 to 0.010)
Bilevel ventilation vs. standard therapy	−5.182 (−16 043 to 5.678)	0.003 (−0.003 to 0.008)
Bilevel ventilation vs. CPAP	−1.086 (−7.626 to 5.454)	0.001 (−0.006 to 0.007)

CPAP = continuous positive airway pressure; MI = myocardial infarction.

Appendix Table 5. **Meta-regression Models Investigating Association of Event Rate in the Control Group, With Log Risk Ratios of Clinical Outcomes**

Control Group Comparison	Slope Coefficient (95% CI)
Mortality	
CPAP vs. standard therapy	−1.163 (−4.469 to 2.142)
Bilevel ventilation vs. standard therapy	−1.107 (−6.651 to 4.436)
Bilevel ventilation vs. CPAP	0.459 (−5.094 to 6.011)
Intubation rate	
CPAP vs. standard therapy	−0.333 (−2.483 to 1.818)
Bilevel ventilation vs. standard therapy	−3.401 (−7.782 to 0.980)
Bilevel ventilation vs. CPAP	−0.128 (−5.054 to 4.797)

CPAP = continuous positive airway pressure.

Appendix Table 6. **Results of Subgroup Meta-analysis, by Allocation Concealment**

Comparison	Allocation Concealment	Studies, *n*	Relative Risk (95% CI)
Mortality			
CPAP vs. standard therapy	Yes	8	0.45 (0.25–0.82)
	No	5	0.88 (0.59–1.31)
Bilevel ventilation vs. standard therapy	Yes	3	0.57 (0.25–1.27)
	No	5	0.89 (0.61–1.30)
Bilevel ventilation vs. CPAP	Yes	8	1.24 (0.62–2.47)
	No	4	0.92 (0.60–1.39)
	NA	2	1.12 (0.16–7.71)
Intubation rate			
CPAP vs. standard therapy	Yes	8	0.46 (0.29–0.71)
	No	6	0.37 (0.19–0.70)
	NA	1	0.47 (0.17–1.25)
Bilevel ventilation vs. standard therapy	Yes	3	0.27 (0.07–1.08)
	No	5	0.73 (0.45–1.19)
	NA	1	0.37 (0.13–1.10)
Bilevel ventilation vs. CPAP	Yes	8	1.66 (0.81–3.40)
	No	5	0.69 (0.17–2.87)
	NA	2	1.59 (0.21–12.26)
New myocardial infarction			
CPAP vs. standard therapy	Yes	2	1.10 (0.86–1.41)
	No	2	0.50 (0.14–1.73)
Bilevel ventilation vs. standard therapy	Yes	2	1.50 (0.66–3.43)
	No	4	1.07 (0.84–1.35)
Bilevel ventilation vs. CPAP	Yes	6	1.08 (0.53–2.20)
	No	4	1.26 (0.70–2.24)
	NA	1	0.95 (0.37–2.46)

CPAP = continuous positive airway pressure; NA = not available.

Appendix Table 7. **Probability of Improvement in Mortality and the Need for Intubation With CPAP**

Probability	Risk Ratio	
	Mortality	Need for Intubation
97.5%	0.78	0.52
95%	0.74	0.49
90%	0.68	0.46
75%	0.59	0.40

CPAP = continuous positive airway pressure.

Correction

In their meta-analysis (1), Weng and colleagues incorrectly classified 3 trials as having no allocation concealment. The "Concealed Allocation" cells in Appendix Table 2 for Bersten et al (1991), Nava et al (2003), and Gray et al (2008) should be "yes" rather than "no." The **Table** shows relative risk estimates from subgroup analyses by allocation concealment using these correct classifications. The meta-analysis and Appendix Table 2 incorrectly gave the withdrawal rate for the 3CPO trial as 19.4% and more than 15%, respectively, although the primary outcome was assessed in 99% of trial participants. Cumulative meta-analysis results based on quality scores used the incorrect assessments (in the text and in Appendix Figures 4 and 6). Corrected cumulative analyses by trial quality were qualitatively unchanged.

In the corresponding author address, Dr. Zhao's affiliation is Beijing Chaoyang Hospital. In the online Appendix, the second line of the first paragraph should have read: "We therefore used a Bayesian hierarchical (random-effects) meta-analytic model to analyze these 31 studies."

This has been corrected in the online version.

Reference

1. Weng CL, Zhao YT, Liu QH, Fu CJ, Sun F, Ma YL, et al. Meta-analysis: noninvasive ventilation in acute cardiogenic pulmonary edema. Ann Intern Med. 2010;152:590-600. [PMID: 20439577].

Table. **Subgroup Meta-analysis by Allocation Concealment**

Outcome	Allocation Concealment	Studies, *n*	Relative Risk (95% CI)
Mortality			
CPAP vs. standard therapy	Yes	10	0.58 (0.37 to 0.90)
	No	3	0.68 (0.25 to 1.83)
Bilevel ventilation vs. standard therapy	Yes	5	0.83 (0.58 to 1.19)
	No	4	0.72 (0.23 to 2.19)
Bilevel ventilation vs. CPAP	Yes	9	1.09 (0.72 to 1.67)
	No	3	0.55 (0.19 to 1.63)
	NA	2	1.12 (0.16 to 7.71)
Intubation rate			
CPAP vs. standard therapy	Yes	10	0.43 (0.28 to 0.66)
	No	4	0.40 (0.19 to 0.84)
Bilevel ventilation vs. standard therapy	Yes	5	0.56 (0.23 to 1.41)
	No	3	0.50 (0.26 to 1.16)
	NA	1	0.37 (0.13 to 1.10)
Bilevel ventilation vs. CPAP	Yes	9	1.81 (0.92 to 3.57)
	No	4	0.34 (0.09 to 1.26)
	NA	2	1.59 (0.21 to 12.26)
New MI			
CPAP vs. standard therapy	Yes	3	3.30 (0.15 to 72.08)
	No	1	0.50 (0.14 to 1.73)
Bilevel ventilation vs. standard therapy	Yes	4	1.12 (0.89 to 1.41)
	No	2	0.65 (0.21 to 2.04)
Bilevel ventilation vs. CPAP	Yes	7	1.01 (0.72 to 1.43)
	No	3	1.21 (0.93 to 4.75)
	NA	1	0.95 (0.37 to 2.46)

CPAP = continuous positive airway pressure; MI = myocardial infarction; NA = not available.