Prehospital Noninvasive Ventilation for Acute Respiratory Failure: Systematic Review, Network Meta-analysis, and Individual Patient Data Meta-analysis

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Abstract

Objectives: This meta-analysis aimed to determine the effectiveness of prehospital continuous positive airway pressure (CPAP) or bilevel inspiratory positive airway pressure (BiPAP) in acute respiratory failure.

Methods: Fourteen electronic databases and research registers were searched from inception to August 2013. Randomized or quasi-randomized controlled trials that reported mortality or intubation rate for prehospital CPAP or BiPAP were selected and compared to a relevant comparator in patients with acute respiratory failure. An aggregate data network meta-analysis was used to jointly estimate intervention effects relative to standard care. A network meta-analysis using a mixture of individual patient-level data and aggregate data was carried out to assess potential treatment effect modifiers.

Results: Eight randomized and two quasi-randomized controlled trials (six CPAP, four BiPAP, sample sizes 23 to 207) were identified. The aggregate data network meta-analysis suggested that CPAP was the most effective treatment in terms of mortality (probability = 0.989) and intubation rate (probability = 0.639) and reduced both mortality (odds ratio [OR] = 0.41; 95% credible interval [CrI] = 0.20 to 0.77) and intubation rate (OR = 0.32; 95% CrI = 0.17 to 0.62), compared to standard care. The effect of BiPAP on mortality (OR = 1.94; 95% CrI = 0.65 to 6.14) and intubation rate (OR = 0.40; 95% CrI = 0.14 to 1.16) was uncertain. The network meta-analysis using individual patient-level data and aggregate data suggested that sex was a modifier of the effect of treatment on mortality.

Conclusions: Prehospital CPAP can reduce mortality and intubation rates compared to standard care, while the effectiveness of prehospital BiPAP is uncertain.

A
cute respiratory failure is a common but life-
threatening medical emergency, especially in
elderly patients with respiratory and cardiac
diseases. It is caused by a number of common cardiac
or respiratory conditions, including heart failure,
pneumonia, and exacerbation of chronic obstructive
pulmonary disease. The definitive treatment of acute
respiratory failure depends on the underlying cause, but
patients often require prehospital treatment. At this
point it is difficult to accurately determine the underly-
ing cause, so prehospital treatment of acute respiratory
failure often follows a common pathway, rather than
being specific to the underlying cause.

Noninvasive ventilation (NIV) can be used to treat
acute respiratory failure. It involves providing respira-
ry support through a tight-fitting mask that is
usually applied around the patient’s mouth and nose
and may take the form of continuous positive airway
pressure (CPAP) or bilevel inspiratory positive airway
pressure (BiPAP), including noninvasive pressure sup-
port ventilation. It is normally used in the hospital, but
it may be more effective if treatment is commenced
prior to arrival. Prehospital NIV is considered in some
guidelines,

but widespread use is limited by the need for
additional training and equipment and may be
informed by robust evidence of clinical effectiveness
and cost-effectiveness.

Prehospital NIV has been evaluated in a number of
studies, which have been summarized in systematic
reviews and meta-analysis. These suggest that
prehospital NIV, and specifically prehospital CPAP, can
improve outcomes. Existing systematic reviews have
been limited by failure to undertake meta-analyses,

inclusion of nonrandomized studies in the meta-analys-
es, failure to include studies only published in abstract
form, analysis of CPAP and BiPAP together, lack of a
network meta-analysis to compare CPAP and BiPAP,
and lack of individual patient data meta-regression
to explore potential causes of heterogeneity. We
aimed to address these limitations by undertaking a
systematic review, aggregate data network meta-
analys-

Study Selection
All titles were examined for inclusion by one reviewer
and any citations that clearly did not meet the
inclusion criteria (e.g., nonhuman, unrelated to acute
respiratory failure) were excluded. All abstracts and full
text articles were then examined independently by two
reviewers (EP, AP). Any disagreements in the selection
process were resolved through discussion.

Data Collection Process
Data abstraction was performed by one reviewer (EP)
onto a standardized data extraction form and indepen-
dently checked for accuracy by a second (AP). Discrep-
ancies were resolved by discussion between the two
reviewers, and if agreement could not be reached, a
third reviewer (SG) was consulted. Where multiple pub-
lications of the same study were identified, data were
extracted and reported as a single study.

Data Items
The following information was extracted for all studies
when reported: study characteristics (author, year of
publication, country, study design, setting, duration of
follow-up, funding), participant details (age, sex, diag-
nosis, comorbidities, baseline physiology), intervention
(system used, pressure(s) used, duration of treatment,
practitioners providing intervention), comparator (any
use of NIV, supplemental oxygen), details including
information on any specified cotreatments, and out-
comes (including definitions). The authors of all
included studies were contacted to clarify details, obtain
missing data, and request individual patient data for
meta-analysis.

Methods
We undertook a systematic review in accordance with
the general principles recommended in the Preferred
Reporting Items for Systematic Reviews and Meta-
Analyses (PRISMA) statement and the checklist for
the review of evidence synthesis for decision-making.
The review was registered on the PROSPERO interna-
tional prospective register of systematic reviews,
and the protocol is available at

Eligibility Criteria
We included randomized or quasi-randomized con-
trolled trials that compared prehospital CPAP or BiPAP
to a relevant comparator treatment in patients with
acute respiratory failure.

Information Sources
The following electronic databases and research regis-
ters were searched from inception to August 2013:
MEDLINE In-Process & Other Non-Indexed Citations
and MEDLINE, EMBASE, Cumulative Index to Nursing
and Allied Health Literature, Cochrane Database of
Systematic Reviews, Cochrane Central Register of Con-
trolled Trials, Health Technology Assessment Database,
Database of Abstracts of Review of Effects, BIOSIS
Previews, Science Citation Index Expanded, Conference
Proceedings Index-Science, UK Clinical Research Net-
work Portfolio Database, National Research Register
Archive, Current Controlled Trials, and ClinicalTri-
als.gov. Searches were supplemented by hand-search-
ing the reference lists and performing a citation search
of relevant articles, contacting key experts in the field,
and undertaking systematic keyword searches of the
internet using the Google search engine. No language
or date restrictions were used on any database. Details
of the search strategies are provided in Data Supple-
ment S1 (available as supporting information in the
online version of this paper).

Study Selection
All titles were examined for inclusion by one reviewer
and any citations that clearly did not meet the
inclusion criteria (e.g., nonhuman, unrelated to acute
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practitioners providing intervention), comparator (any
use of NIV, supplemental oxygen), details including
information on any specified cotreatments, and out-
comes (including definitions). The authors of all
included studies were contacted to clarify details, obtain
missing data, and request individual patient data for
meta-analysis.

Assessment of Risk of Bias in Individual Studies
The methodologic quality of each included study was
assessed by one reviewer (EP) and independently
checked by another (AP) to ensure consistency. In cases of disagreement a third reviewer (SG) was consulted. The study quality characteristics were assessed according to adapted criteria based on those proposed by Verhagen et al. for randomized clinical trials.

**Summary Measures**

Results of the network meta-analysis are presented as odds ratios (OR) and 95% credible intervals (CrIs) relative to the baseline intervention (i.e., standard care). The 95% CrIs represent the 95% probability that the true underlying effect lies in the interval specified. The between-study standard deviations (SDs) together with their 95% CrIs are also presented.

**Planned Methods of Analysis**

A random-effects network meta-analysis of aggregate data of the number of events (i.e., mortality and intubation) was conducted using Markov chain Monte Carlo simulation to jointly estimate the intervention effects relative to standard care. Separate one-stage random effects network meta-regressions using a mixture of individual patient data and aggregate data (where individual patient data were not available) were carried out to assess whether study characteristics (i.e., age, sex, provider, primary diagnosis, and severity of acute respiratory failure) were treatment effect modifiers. Any missing covariates in the individual patient data were assumed missing completely at random and were imputed using multiple imputation.

Sensitivity analyses were planned to explore the potential sources of heterogeneity, in particular whether CPAP or BiPAP was used and whether prehospital providers were paramedics or physicians. In the event, these issues were explored in the network meta-analysis and meta-regression. A post hoc sensitivity analysis was undertaken excluding quasi-randomized trials from the network meta-analysis of aggregate data.

We performed separate analyses of the aggregate data using different prior distribution for the between-study SDs (i.e., a vague Uniform(0,2)) prior distribution and two weakly informative prior distributions (i.e., Half-Normal(0,0.32) and Half-Normal(0,0.40)). A Uniform(0,2) prior distribution for a between-study SD implies that we believe a priori that extreme heterogeneity is plausible and as likely as mild heterogeneity. The conclusions and point estimates were consistent across the three analyses and, as we would expect, the CrIs for the ORs were slightly narrower when weakly informative prior distributions were used. A vague prior distribution for a between-study SD is not noninformative when there are relatively few studies, as we have in this case, so results of the aggregate and individual patient data meta-analyses are based on using Half-Normal(0,0.40) prior distributions for the between-study SDs.

Convergence of the Markov chains to their stationary distributions was assessed using the Gelman-Rubin statistic. The Markov chains in each aggregate data network meta-analysis converged quickly and we used a burn-in of 10,000 iterations. The Markov chains in the mixed individual patient data and aggregate data network meta-analyses took longer to converge and we used a burn-in of 50,000 iterations. Parameters were estimated based on 10,000 iterations of the Markov chains after thinning them by retaining every fifth iteration. Goodness of fit of the aggregate data models was assessed using total residual deviance. The total residual deviance is the mean of the deviance under the current model minus the deviance for the saturated model, so that each data point should contribute about one to the deviance. The effect of the covariates in the mixed individual patient data and aggregate data meta-regression was assessed using the deviance information criteria.

The aggregate data network meta-analysis was implemented using WinBUGS 1.4.3 and the individual patient data network meta-analysis was implemented using OpenBUGS (http://www.openbugs.net/). Code is available on request.

**RESULTS**

**Study Selection**

The literature searches identified 2,284 citations. Eight randomized and two quasi-randomized controlled trials satisfied the inclusion criteria (participant numbers ranging from 23 to 207). The authors of seven of these 10 studies provided data from 650 patients for individual patient data meta-analysis. The process is described in a PRISMA flow diagram (Figure 1).

**Characteristics of Included Studies**

Table 1 shows the study characteristics. The studies were undertaken in Australia, France, Germany, Spain, Canada, and the United States and were published between 2000 and 2012. Six studies were limited to patients with acute cardiogenic pulmonary edema and one to patients with exacerbation of chronic obstructive pulmonary disease. Six studies evaluated CPAP, and four evaluated BiPAP. One study compared early CPAP to delayed CPAP, while use of in-hospital NIV in the control arm was allowed in three of the other studies, prohibited in one, and not recorded in five. The results of the individual trials are presented in Figures 2 and 3 for mortality and intubation rates, respectively.

**Risk of Bias Within Studies**

Data Supplements S2 and S3 (available as supporting information in the online version of this paper) present the methodologic quality of the included studies. Six studies achieved positive assessments in at least six of the nine methodologic quality items. The potential sources of bias most frequently identified in studies concerned lack of blinding of outcome assessment and lack of adequate power to detect differences in the primary outcome. Two studies were quasi-randomized studies: randomization in Weitz et al. was based on date of birth; Craven et al. did not provide details on the method of randomization, although 10 emergency service units were divided into five matched pairs with one unit from each pair equipped with a BiPAP ventilation system and one without.
Data Analysis Issues
There were no deaths in the study by Schmidbauer et al.27 Although the study is included in the analysis for completeness, the sample data provide no information about the effect of treatment on mortality. The study-specific ORs that are presented in Figures 2 and 3 are sample estimates and the pooled estimates are from the random-effects models. There are no feedback loops in the evidence network so there is not a mixture of direct and indirect evidence about treatment effects. Consequently, there are no potential inconsistencies in the evidence about treatment effects.

Effects of Interventions
Aggregate Data Network Meta-analysis. Continuous positive airway pressure is the most effective treatment on mortality (probability = 0.989), with OR of 0.41 (95% CrI = 0.20 to 0.77) compared to standard care. There was considerable uncertainty associated with the effect of BiPAP relative to standard care (OR = 1.94; 95% CrI = 0.65 to 6.14). The between-study SD of ±0.29 (95% CrI = 0.02 to 0.85) is indicative of mild heterogeneity between studies but with considerable uncertainty. Sensitivity analysis excluding two quasi-randomized trials and one study comparing early prehospital CPAP to late prehospital CPAP produced similar results, with CPAP more effective than standard care (OR = 0.45; 95% CrI = 0.21 to 0.93), while the effect of BiPAP relative to standard care remained uncertain (OR = 1.95; 95% CrI = 0.43 to 9.46).

CPAP was estimated to be the most effective treatment on intubation rate (probability = 0.639), with an OR of 0.32 (95% CrI = 0.17 to 0.62) compared to standard care. There was uncertainty associated with the effect of BiPAP relative to standard care (OR = 0.40; 95% CrI = 0.14 to 1.16). The between-study SD of ±0.21 (95% CrI = 0.01 to 0.73) is indicative of mild heterogeneity between studies but with considerable uncertainty. Sensitivity analysis excluding one quasi-randomized trial29 (the other30 did not report intubation rate) and one study comparing early prehospital CPAP to late prehospital CPAP25 produced similar results, with CPAP more effective than standard care (OR = 0.34; 95% CrI = 0.15 to 0.77), while the effect of BiPAP relative to standard care remained uncertain (OR = 0.53; 95% CrI = 0.11 to 2.28).
<table>
<thead>
<tr>
<th>Author, Year, Country</th>
<th>Design (n)</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Primary Outcomes</th>
<th>Duration of Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austin and Wills 2012&lt;sup&gt;21&lt;/sup&gt;; Australia (abstract)</td>
<td>RCT (n = 50)</td>
<td>Adults with presumed ACPO experiencing severe respiratory distress with insufficient respiratory effort</td>
<td>CPAP (no details provided) (n = 24) Provider: NR</td>
<td>CMT including oxygen (n = 26) In-hospital NIV use: NR</td>
<td>Mortality (prehospital or in-hospital)</td>
<td>NR</td>
</tr>
<tr>
<td>Ducros et al. 2011&lt;sup&gt;22&lt;/sup&gt;; France</td>
<td>RCT (n = 207)</td>
<td>Adults with presumed ACPO (orthopnea, diffuse crackles [Killip score ≥ III], RR &gt; 25 breaths/min, SpO&lt;sub&gt;2&lt;/sub&gt; &lt; 90%)</td>
<td>CPAP; 7.5 to 10 cm H&lt;sub&gt;2&lt;/sub&gt;O, FiO&lt;sub&gt;2&lt;/sub&gt; 0.3 to 1.0 by face mask (n = 107) Provider: physician</td>
<td>CMT including oxygen at 15 L/min (n = 100) In-hospital NIV use: prohibited</td>
<td>Composite endpoint of death, need for intubation, persistence of all symptoms or circulatory failure</td>
<td>Until time of hospital discharge or death</td>
</tr>
<tr>
<td>Frontin et al. 2011&lt;sup&gt;23&lt;/sup&gt;; France</td>
<td>RCT (n = 122)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>Adults with presumed ACPO (orthopnea, diffuse crackles without signs of pulmonary aspiration or infection, RR &gt; 25 breaths/min, SpO&lt;sub&gt;2&lt;/sub&gt; &lt; 90%)</td>
<td>CPAP; 10 cm H&lt;sub&gt;2&lt;/sub&gt;O by face mask for 1 hour (n = 60) Provider: physician</td>
<td>CMT including oxygen at 15 L/min (n = 62) In-hospital NIV use: allowed</td>
<td>Treatment success&lt;sup&gt;†&lt;/sup&gt;</td>
<td>30 days</td>
</tr>
<tr>
<td>Plaisance et al. 2007&lt;sup&gt;25&lt;/sup&gt;; France</td>
<td>RCT (n = 124)</td>
<td>Adults with presumed ACPO (orthopnea, diffuse crackles without signs of pulmonary aspiration or infection, SpO&lt;sub&gt;2&lt;/sub&gt; ≤ 90%)</td>
<td>Early CPAP: the first 30 minutes at 7.5 cm H&lt;sub&gt;2&lt;/sub&gt;O, FiO&lt;sub&gt;2&lt;/sub&gt; 0.33 to 0.37 by face mask (n = 63) Provider: physician</td>
<td>Late CPAP included CMT with oxygen for the initial 15 minutes, followed by CPAP [7.5 cm H&lt;sub&gt;2&lt;/sub&gt;O] for another 15 minutes (n = 61) In-hospital NIV use: mandated</td>
<td>Effect of early CPAP on dyspnea score&lt;sup&gt;‡&lt;/sup&gt; and arterial blood gases</td>
<td>Until time of hospital discharge death</td>
</tr>
<tr>
<td>Schmidbauer et al. 2010&lt;sup&gt;27&lt;/sup&gt;; Germany</td>
<td>RCT (n = 36)</td>
<td>Adults presenting with acute exacerbated COPD (acute dyspnea, RR &gt; 25 breaths/ min, SpO&lt;sub&gt;2&lt;/sub&gt; &lt; 90%)</td>
<td>CPAP; 5 to 30 cm H&lt;sub&gt;2&lt;/sub&gt;O, FiO&lt;sub&gt;2&lt;/sub&gt; 0.5 to 1.0 by face mask (n = 18) Provider: physician</td>
<td>SOT delivered by face mask (flow rate NR) (n = 18) In-hospital NIV use: mandated</td>
<td>Intubation rate</td>
<td>Until time of hospital discharge or death</td>
</tr>
<tr>
<td>Thompson et al. 2008&lt;sup&gt;28&lt;/sup&gt;; Canada</td>
<td>RCT (n = 71)</td>
<td>Adults presenting with severe respiratory distress (failing respiratory effort, accessory muscle use, RR &gt; 25 breaths/ min, hypoxia)</td>
<td>CPAP; 10 cm H&lt;sub&gt;2&lt;/sub&gt;O by face mask (n = 36) Provider: physician</td>
<td>CMT with oxygen by face mask (n = 35) In-hospital NIV use: allowed (n = 4)</td>
<td>Intubation rate</td>
<td>Until time of hospital discharge death</td>
</tr>
<tr>
<td>Mas et al. 2002&lt;sup&gt;24&lt;/sup&gt;; Spain (abstract)</td>
<td>RCT (n = 56)</td>
<td>Adults presenting with ARF (RR &gt; 28 breaths/ min, SpO&lt;sub&gt;2&lt;/sub&gt; &lt; 92% or SpO&lt;sub&gt;2&lt;/sub&gt; &lt; 90% at any RR)</td>
<td>BiPAP; EPAP, 7 cm H&lt;sub&gt;2&lt;/sub&gt;O, IPAP, 19 cm H&lt;sub&gt;2&lt;/sub&gt;O (n = 28) Provider: paramedic and physician</td>
<td>Standard therapy, not specified (n = 28) In-hospital NIV use: NR</td>
<td>Intubation rate</td>
<td>Until time of hospital discharge or death</td>
</tr>
<tr>
<td>Roessler et al. 2011&lt;sup&gt;26&lt;/sup&gt;; Germany</td>
<td>RCT (n = 49)&lt;sup&gt;§&lt;/sup&gt;</td>
<td>Adults presenting with ARF due to presumed ACPO, COPD, or pneumonia with signs of hypoxemia (SpO&lt;sub&gt;2&lt;/sub&gt; &lt; 90%) or ventilator failure (SpO&lt;sub&gt;2&lt;/sub&gt; &lt; 90% with RR &gt; 20 breaths/min, at rest)</td>
<td>BiPAP;&lt;sup&gt;∥&lt;/sup&gt; 5 to 20 cm H&lt;sub&gt;2&lt;/sub&gt;O, PEEP 5 to 15 cm H&lt;sub&gt;2&lt;/sub&gt;O, FiO&lt;sub&gt;2&lt;/sub&gt; 1.0 by face mask (n = 24) Provider: physician</td>
<td>CMT including supplementary oxygen (n = 25) In-hospital NIV use: allowed (n = 4)</td>
<td>Treatment success&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>30 days</td>
</tr>
</tbody>
</table>

Note: NR = Not reported, ACPO = Acute Cor Pulmonale, RCT = Randomized Controlled Trial, CPAP = Continuous Positive Airway Pressure, CMT = Comprehensive Medical Therapy, NIV = Non-Invasive Ventilation, RR = Respiratory Rate, SpO<sub>2</sub> = Oxygen Saturation, BiPAP = Bilevel Positive Airway Pressure, EPAP = Expiratory Positive Airway Pressure, IPAP = Inspiratory Positive Airway Pressure, PEEP = Positive End-expiratory Pressure, FiO<sub>2</sub> = Fraction of inspired oxygen.
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Craven et al. 2000&lt;sup&gt;29&lt;/sup&gt;; United States</td>
<td>Quasi-RCT (n = 62)**</td>
<td>Adults experiencing CHF with presumed ACPO (dyspnea with increased RR, HR, sweating, peripheral edema)</td>
<td>BiPAP; by face mask (pressure level NR) (n = 37)</td>
<td>CMT with oxygen (no further details provided) (n = 25)</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Provider: paramedic&lt;sup&gt;††&lt;/sup&gt;</td>
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<td></td>
<td></td>
<td></td>
<td>BiPAP; 12 cm H&lt;sub&gt;2&lt;/sub&gt;O, PEEP 5 cm H&lt;sub&gt;2&lt;/sub&gt;O, FiO&lt;sub&gt;2&lt;/sub&gt; 0.6 by face mask (n = 10)</td>
<td>CMT with oxygen at 8 L/min by face mask (n = 13)</td>
<td>Oxygen saturation</td>
<td>Until time of hospital discharge or death</td>
</tr>
<tr>
<td>Weitz et al. 2007&lt;sup&gt;30&lt;/sup&gt;; Germany</td>
<td>Quasi-RCT (n = 23)</td>
<td>Adults with presumed ACPO (severe dyspnea; SpO&lt;sub&gt;2&lt;/sub&gt; &lt; 90%)</td>
<td>BiPAP; 12 cm H&lt;sub&gt;2&lt;/sub&gt;O, PEEP 5 cm H&lt;sub&gt;2&lt;/sub&gt;O, FiO&lt;sub&gt;2&lt;/sub&gt; 0.6 by face mask (n = 10)</td>
<td>CMT with oxygen</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Provider: physician&lt;sup&gt;‡‡&lt;/sup&gt;</td>
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</tbody>
</table>

ACPO = acute cardiopulmonary edema; ARF = acute respiratory failure; BiPAP = bilevel inspiratory positive airway pressure; BNP = B-type natriuretic peptide; CMT = conventional medical treatment; COPD = chronic obstructive pulmonary disease; CPAP = continuous positive airway pressure; EPAP = expiratory positive airway pressure; FiO<sub>2</sub> = fractional inspired oxygen; HR = heart rate; IPAP = inspiratory positive airway pressure; NIMV = noninvasive mechanical ventilation; NIPSV = noninvasive pressure support ventilation; NIV = noninvasive ventilation; NR = not reported; PEEP = positive end-expiratory pressure; RCT = randomized controlled trial; RR = respiratory rate, SOT = standard oxygen therapy; SpO<sub>2</sub> = oxygen saturation.

<sup>*Of the 124 patients randomized in the study, two patients in the CPAP group refused full consent and were excluded from analysis.</sup>

<sup>†Treatment success was defined as a respiratory rate < 25 breaths/min with SpO<sub>2</sub> > 90% after an hour of study inclusion.</sup>

<sup>‡Dyspnea clinical score consisted of four items yielding a total score of 10. Dyspnea: auscultation rates intensity and accessory muscle use were rated 0 (absent) to 3 (severe/important). The remaining criterion was based on the presence of cyanosis, rated as 0 (no) or 1 (yes).</sup>

<sup>§Of the 51 patients included in the study, two patients were excluded from the analysis because they were previously dependent on home oxygen.</sup>

<sup>||NIV was initially started with FiO<sub>2</sub> and CPAP; however, this was quickly changed to BiPAP, if CPAP was tolerated (22 of 24 patients in the intervention group).</sup>

<sup>¶Treatment was considered to be inefficient if the following occurred while on NIV or CMT: If SpO<sub>2</sub> < 85% or dropped to ≤85% and/or if the respiratory rate was ≤30 or had increased to 30 breaths/min or more.</sup>

<sup>**Of the 71 patients enrolled in the study, 62 patients completed the study.</sup>

<sup>††Medical responders were emergency medical technicians (certified at cardiac technician or paramedic level) trained in advanced life support.</sup>

<sup>‡‡The emergency team was made up of one physician and two paramedics.</sup>
Mixed Individual Patient Data and Aggregate Data Network Meta-analysis. Potential treatment effect modifiers were identified from separate analyses of each study adjusting treatment effect for age, sex, primary diagnosis, provider, and various measures of severity of acute respiratory failure. Age, sex, primary diagnosis, and respiratory rate were identified as potential modifiers of the effect of treatment on mortality and sex, respiratory rate, $\text{SpO}_2$, $\text{PaO}_2$, and $\text{PaCO}_2$ as potential modifiers of the effect of treatment on intubation rate to be included in the network meta-regression. Data on prehospital time delay were not well defined or...
### Table 2
Mortality in Prehospital NIV Patients With Acute Respiratory Failure With Continuous Treatment Effect Modifiers:* Posterior Results for the Odds of Death Relative to Standard Care (Random Effects)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Potential Treatment Effect Modifier</th>
<th>Respiratory Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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<tr>
<td>Data source</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Individual patient data</td>
<td>Ducros, Frontin, Roessler, Plaisance, Austin and Wills</td>
<td></td>
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<tr>
<td>Aggregate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coefficient of treatment effect modifier, OR (95% CrI)</td>
<td>1.04 (0.92-1.18)</td>
<td>0.88 (0.70-1.04)</td>
</tr>
<tr>
<td>Treatment effect at the mean value of the treatment effect modifier, OR (95% CrI)</td>
<td>2.44 (0.76-8.71)</td>
<td>2.66 (0.59-15.19)</td>
</tr>
<tr>
<td>Between-study SD (95% CrI)</td>
<td>0.31 (0.02-0.87)</td>
<td>0.30 (0.01-0.89)</td>
</tr>
<tr>
<td>Deviance information criterion (model with treatment effect modifier vs. model without treatment effect modifier)</td>
<td>481.80 vs. 470.54</td>
<td>455.99 vs. 451.62</td>
</tr>
</tbody>
</table>

BiPAP = bi-level inspiratory positive airway pressure; CPAP = continuous positive airway pressure; CrI = credible interval; NIV = noninvasive ventilation.

*Each potential treatment effect modifier was analyzed separately in the model.

### Table 3
Mortality in Prehospital NIV Patients With Acute Respiratory Failure With Binary Treatment Effect Modifiers:* Posterior Results for the Odds of Death Relative to Standard Care (Random Effects)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Potential Treatment Effect Modifier</th>
<th>Sex</th>
<th>ACPO†</th>
<th>COPD†</th>
<th>Provider</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Data source</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Individual patient data</td>
<td>Ducros, Frontin, Roessler, Plaisance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aggregate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coefficient of treatment effect modifier, OR (95% CrI)</td>
<td>0.19 (0.01-2.44)</td>
<td>1.45 (0.25-9.44)</td>
<td>0.19 (0.01-1.70)</td>
<td>0.57 (0.06-3.59)</td>
<td></td>
</tr>
<tr>
<td>Treatment effect at the mean value of the treatment effect modifier, OR (95% CrI)</td>
<td>1.30 (0.25-7.13)</td>
<td>0.72 (0.03-1.92)</td>
<td>1.43 (0.32-6.36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between-study SD (95% CrI)</td>
<td>0.18 (0.04-0.74)</td>
<td>1.58 (0.02-0.87)</td>
<td>2.13 (0.01-0.89)</td>
<td>0.80 (0.01-0.89)</td>
<td></td>
</tr>
<tr>
<td>Deviance information criterion (model with treatment effect modifier vs. model without treatment effect modifier)</td>
<td>353.39 vs. 358.43</td>
<td>210.65 vs. 208.56</td>
<td>207.89 vs. 208.46</td>
<td>77.95 vs. 76.32</td>
<td></td>
</tr>
</tbody>
</table>

ACPO = acute cardiopulmonary edema; BiPAP = bi-level inspiratory positive airway pressure; COPD = chronic obstructive pulmonary disease; CPAP = continuous positive airway pressure; CrI = credible interval.

*Each potential treatment effect modifier was analyzed separately in the model.
†Primary diagnosis.
reported so this was not explored as a potential treatment effect modifier.

Tables 2 and 3 give the results for mortality. The individual patient data and aggregate data network meta-regression suggested that sex was a modifier of the effect of treatment with CPAP, compared to standard care on mortality (OR for males relative to females = 0.18; 95% CrI = 0.04 to 0.74). There was insufficient evidence that sex was a modifier of the effect of treatment with BiPAP compared to standard care on mortality.

### Tables 4 and 5

Tables 4 and 5 give the results for intubation rate. The individual patient data and aggregate data network meta-regression suggested that none of the covariates were modifiers of treatment effect.

### Safety and Adverse Events

Safety information was inconsistently recorded and reported. Three studies reported that no adverse events were identified, one study reported one case of vomiting that resolved spontaneously, and one study reported so this was not explored as a potential treatment effect modifier.

---

<table>
<thead>
<tr>
<th>Variable</th>
<th>Potential Treatment Effect Modifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>SpO₂</td>
</tr>
<tr>
<td>Data source</td>
<td></td>
</tr>
<tr>
<td>Aggregate</td>
<td>Thompson29</td>
</tr>
<tr>
<td>Coefficient of treatment effect modifier, OR (95% CrI)</td>
<td>0.94 (0.77-1.12)</td>
</tr>
<tr>
<td>BiPAP</td>
<td>0.99 (0.90-1.10)</td>
</tr>
<tr>
<td>CPAP</td>
<td>0.50 (0.10-2.33)</td>
</tr>
<tr>
<td>Treatment effect at the average value of the treatment effect modifier, OR (95% CrI)</td>
<td>0.35 (0.15-0.83)</td>
</tr>
<tr>
<td>Between study SD (95% CrI)</td>
<td>0.29 (0.01-0.91)</td>
</tr>
<tr>
<td>Deviance information</td>
<td>320.76 vs. 318.67</td>
</tr>
</tbody>
</table>

---

<table>
<thead>
<tr>
<th>Variable</th>
<th>Potential Treatment Effect Modifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>Sex</td>
</tr>
<tr>
<td>Data source</td>
<td></td>
</tr>
<tr>
<td>Individual patient data</td>
<td>Ducros,22 Frontin,23 Plaisance,25 Roessler26</td>
</tr>
<tr>
<td>Aggregate</td>
<td>Thompson28 Craven29</td>
</tr>
<tr>
<td>Coefficient of treatment effect modifier, OR (95% CrI)</td>
<td>3.42 (0.26-43.80)</td>
</tr>
<tr>
<td>BiPAP</td>
<td>3.61 (0.78-19.11)</td>
</tr>
<tr>
<td>CPAP</td>
<td>3.05 (0.21-43.80)</td>
</tr>
<tr>
<td>Treatment effect at the mean value of the treatment effect modifier, OR (95% CrI)</td>
<td>0.37 (0.06-1.98)</td>
</tr>
<tr>
<td>BiPAP</td>
<td>0.37 (0.06-1.98)</td>
</tr>
<tr>
<td>CPAP</td>
<td>0.55 (0.21-1.43)</td>
</tr>
<tr>
<td>Between-study SD (95% CrI)</td>
<td>0.21 (0.01-0.74)</td>
</tr>
<tr>
<td>Deviance information</td>
<td>298.76 vs. 293.92</td>
</tr>
</tbody>
</table>

---

*Each potential treatment effect modifier was analyzed separately in the model."
reported vomiting as the only adverse event in both intervention and comparator groups (two of 60 vs. three of 62, respectively).

**Risk of Publication Bias**

For completeness and descriptive purposes, funnel plots were drawn to explore publication bias. There was no obvious indication of asymmetry, although the number of studies available was small and less than recommended for statistical hypothesis testing\(^3\) (Data Supplement S4, available as supporting information in the online version of this paper).

**DISCUSSION**

Prehospital CPAP appears to reduce mortality and intubation rate in acute respiratory failure. The effectiveness of prehospital BiPAP is uncertain, with estimates of the effect on mortality and intubation, including the possibility of either worthwhile benefit or potential harm. The network meta-analysis using a mixture of individual patient data and aggregate data suggested that male sex was a significant modifier of the effect of treatment effect on mortality, with CPAP being more effective in males. It could be postulated that muscle mass allows CPAP to have an enhanced effect in males, but given that this was one of a number of associations explored, it should be interpreted with caution. We found no such association in the analysis of intubation data.

Two previous meta-analyses of prehospital NIV have been published.\(^13\)\(^14\) Williams et al.\(^13\) only evaluated prehospital CPAP and included nonrandomized studies. They reported that CPAP was associated with lower mortality and fewer intubations, with similar ORs to ours. The inclusion of nonrandomized studies may be inappropriate, given their high risk of bias. Our decision to include quasi-randomized trials could be criticized for similar reasons, but sensitivity analysis showed similar results when these were excluded. Mal et al.\(^13\) evaluated prehospital CPAP and BiPAP, but combined results from studies of these different modalities. They reported that NIV was associated with a reduction in mortality (relative risk = 0.58; 95% CI = 0.35 to 0.95) and need for invasive ventilation (relative risk = 0.37; 95% CI = 0.24 to 0.58). Our analysis showed that this finding is confirmed for prehospital CPAP but not for prehospital BiPAP.

**LIMITATIONS**

Although our review is the most comprehensive to date, it is possible that we may have missed studies that were neither registered nor published, resulting in publication bias. There were relatively few studies available for analysis, and the between-study variability was uncertain. The analysis of BiPAP in particular involved fewer studies and fewer patients (190 vs. 610 receiving CPAP). Patients eligible for prehospital NIV might be expected to receive in-hospital NIV if prehospital treatment were not available, but this was only clearly mandated in one study. Thus some of the studies may be more appropriately considered as evaluations of NIV per se, rather than evaluations of prehospital versus in-hospital NIV. Prehospital NIV was typically delivered by physicians or paramedics with online physician support in the studies, so findings may not be generalizable to prehospital systems based on paramedics working without physician support. Safety and adverse events were inconsistently reported so we are unable to draw reliable conclusions on these issues. Finally, we did not examine cost-effectiveness, so even if prehospital CPAP is considered clinically effective, it may not be cost-effective.

**CONCLUSIONS**

Prehospital continuous positive airway pressure can reduce mortality and intubation rates for patients with acute respiratory failure, although the available evidence may not be generalizable to some prehospital systems. In particular, existing studies have not all compared prehospital continuous positive airway pressure to in-hospital noninvasive ventilation and thus may not be generalizable to systems where in-hospital noninvasive ventilation is standard practice. The substantial cost of implementing prehospital continuous positive airway pressure means that evidence of cost-effectiveness is required before implementation can be recommended. The available evidence does not currently support the use of prehospital bilevel inspiratory positive airway pressure. Further research is required in the form of a large pragmatic study and economic analysis comparing prehospital continuous positive airway pressure to in-hospital noninvasive ventilation for patients with acute respiratory failure.

We thank Gavin Perkins, Matt Ward, and Jerry Penn-Ashman for providing expert clinical advice and Kathryn MacKellar for clerical assistance. We thank Rebecca Harvey for creating the forest plots and funnel plots.

**References**

4. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1767–847.


Supporting Information

The following supporting information is available in the online version of this paper:

Data Supplement S1. Literature search strategies.

Data Supplement S2. Methodological quality graph: review authors’ judgments about each methodological quality item as percentages across all included studies.

Data Supplement S3. Methodological quality summary: review authors judgments about each methodological quality item for each included study.

Data Supplement S4. Funnel plots of sample treatment effects.