Effect of Out-of-Hospital Noninvasive Positive-Pressure Support Ventilation in Adult Patients With Severe Respiratory Distress: A Systematic Review and Meta-analysis

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Study objective: Noninvasive positive-pressure ventilation (NIPPV) is increasingly being used by emergency medical services (EMS) for treatment of patients in respiratory distress. The primary objective of this systematic review is to determine whether out-of-hospital NIPPV for treatment of adults with severe respiratory distress reduces inhospital mortality compared with "standard" therapy. Secondary objectives are to examine the need for invasive ventilation, hospital and ICU length of stay, and complications.

Methods: Electronic searches of MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and Cumulative Index to Nursing and Allied Health Literature were conducted and reference lists of relevant articles hand searched. Randomized controlled trials comparing out-of-hospital NIPPV with standard therapy in adults (aged ≥16 years) with severe respiratory distress published in English were included. Two reviewers independently screened abstracts, assessed quality of the studies, and extracted data. Data were pooled with random-effects models and reported as risk ratios (RRs) with 95% confidence intervals (CIs) and number needed to treat (NNT).

Results: Seven randomized controlled trials were included, with a combined total of 632 patients; 313 in the standard therapy group and 319 in the NIPPV group. In patients treated with NIPPV, the pooled estimate showed a reduction in both inhospital mortality (RR 0.58; 95% CI 0.35 to 0.95; NNT=18) and need for invasive ventilation (RR 0.37; 95% CI 0.24 to 0.58; NNT=8). There was no difference in ICU or hospital length of stay.

Conclusion: Out-of-hospital administration of NIPPV appears to be an effective therapy for adult patients with severe respiratory distress. [Ann Emerg Med. 2014;63:600-607.]

Please see page 601 for the Editor's Capsule Summary of this article.

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INTRODUCTION

Severe dyspnea is a common presenting complaint to emergency medical services (EMS) providers. Dyspnea can result from a variety of conditions, including acute cardiogenic pulmonary edema, acute exacerbation of chronic obstructive pulmonary disease, acute asthma exacerbation, and pneumonia. Out-of-hospital treatment of patients in severe respiratory distress presents unique challenges. These patients often require positive-pressure ventilation, but may have factors that make invasive ventilation by intubation or insertion of a supraglottic airway device difficult. Examples of such factors include intact airway reflexes, environmental challenges, and intubation's being a low-frequency skill for most paramedics.[1-3] Additionally, "standard" out-of-hospital therapy for severe dyspnea is diverse, depending on the region of the world, ranging from simple supplemental oxygen therapy to diuretic and ionotropic infusions. The approaches currently used are varied and lack evidence to support any particular practice patterns.

Inhospital treatment of acute cardiogenic pulmonary edema and acute exacerbation of chronic obstructive pulmonary disease with noninvasive positive-pressure ventilation (NIPPV), which includes continuous and bilevel pressure modalities, has been studied extensively.[4-9] A recent Cochrane review of 21 studies involving 1,071 adult patients with acute cardiogenic pulmonary edema reported significantly reduced inhospital mortality (risk ratio [RR] 0.6; 95% confidence interval [CI] 0.45 to 0.84) and intubation (RR 0.53; 95% CI 0.34 to 0.83) when NIPPV was compared with standard medical care.[4] A second Cochrane review of 14 studies involving 758 patients with acute exacerbation of chronic obstructive pulmonary

Editor's Capsule Summary

What is already known on this topic

Out-of-hospital providers have few options for treating severe respiratory distress.

What question this study addressed

Does out-of-hospital noninvasive positive-pressure ventilation (NIPPV) reduce mortality?

What this study adds to our knowledge

In this meta-analysis of 7 randomized controlled trials including 632 adults, NIPPV was associated with reduced mortality and a reduced need for intubation.

How this is relevant to clinical practice

This meta-analysis supports the expanded use of out-of-hospital NIPPV for severe respiratory distress in adults.

disease on the use of NIPPV showed similarly impressive results, with reductions in hospital mortality (RR 0.52; 95% CI 0.35 to 0.76) and need for intubation (RR 0.41; 95% CI 0.33 to 0.53).[7]

A number of commercial systems are available that allow NIPPV to be administered out-of-hospital relatively easily without large ventilators.[10-13] NIPPV is increasingly being used by EMS providers for the treatment of severe respiratory distress in the out-of-hospital setting.[14-23] The primary objective of our systematic review was to determine whether out-of-hospital–administered NIPPV for the treatment of adults (aged ≥16 years) with severe respiratory distress reduces inhospital mortality compared with standard therapy. Our secondary objectives included hospital length of stay, ICU length of stay, need for invasive ventilation, and complications arising from the use of NIPPV.

MATERIALS AND METHODS

The systematic literature searches were conducted in MEDLINE (1946 to December 2012), EMBASE Classic and EMBASE (1947 to week 48, 2012), Cumulative Index to Nursing and Allied Health Literature (1982 to December 2012), and Cochrane Central Register of Controlled Trials (December 2012) by a research librarian with formal training in electronic literature searching.

Only randomized controlled trials comparing the use of out-of-hospital NIPPV with standard therapy in adults (aged ≥16 years) in severe respiratory distress with a suspected diagnosis of acute cardiogenic pulmonary edema, acute exacerbation of chronic obstructive pulmonary disease, acute asthma exacerbation, or pneumonia were included in this review.

A sensitive search strategy (Appendix E1, available online at http://www.annemergmed.com) included a combination of subject headings and free text words using various spelling and endings, such as but not limited to the following terms: "out-of-hospital," "pre-hospital," "emergency medical services," "paramedic," "emergency care," "continuous positive airway pressure," "CPAP," "nCPAP," "bilevel positive airway pressure," "BIPAP," "non-invasive ventilation," "NIV," "non-invasive positive pressure ventilation," "NIPPV," "NPPV," "positive pressure ventilation," "non-invasive mechanical ventilation," "pulmonary edema," "oedema," "chronic obstructive pulmonary disease," "COPD," "heart failure," "asthma," "respiratory insufficiency," and "respiratory distress."

Because NIPPV is a general term for a variety of noninvasive modalities with various terminologies, studies that reported the use of continuous positive airway pressure (CPAP), noninvasive CPAP, bilevel positive airway pressure (BiPAP), biphasic positive airway pressure, biphasic CPAP, bilevel noninvasive pressure support ventilation, and noninvasive pressure support ventilation were included.

The searches were restricted to studies published in the English language. An optimized hedges filter and keywords were used to refine search results to randomized controlled trials and systematic reviews published on the topic. The search strategies were modified for each database with prespecified terms, search filters, and fields. Reference lists of retrieved studies were hand searched for relevant citations, and the regulatory Web site clinicaltrials.gov was also searched to identify ongoing or unpublished trials. Two authors independently screened the search output to identify potentially eligible trials, the full texts of which were retrieved and assessed for inclusion (Figure 1). Individual study authors were contacted to retrieve additional information and clarification when needed.

Outcome Measures

Our primary outcome of interest was inhospital mortality. Our secondary outcomes included ICU length of stay, hospital length of stay, need for invasive ventilation, and complications arising from the use of NIPPV.

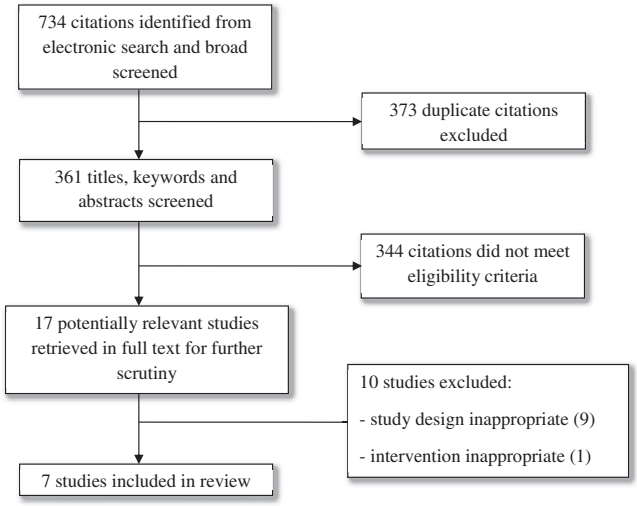

Figure 1. Flow diagram of included studies.

Data Collection and Processing

Using a standardized data collection form, 2 authors independently extracted data on age and sex of participants, sample size, condition being treated, type of NIPPV device, duration and dose of therapy, type of comparator, and outcome data. Two authors independently assessed risk of bias of the included trials by using the Cochrane Collaboration's tool for assessing risk of bias, as described in section 8.5 of the *Cochrane Handbook for Systematic Reviews of Interventions*.[24] Discrepancies in quality assessment scores were resolved by discussion. The following domains were assessed as having a low, unclear (uncertain), or high risk of bias: sequence generation, allocation concealment, blinding of participants/personnel, blinding of outcomes assessment, incomplete outcome data, and selective outcome reporting.

Primary Data Analysis

Individual study results were combined with Review Manager 5.0.18 (Nordic Cochrane Centre, Copenhagen, Denmark). Where appropriate, data were pooled with random-effects models to account for both within-study and between-study heterogeneity and reported as RRs with 95% CIs. RRs were computed such that a value less than 1 indicated that out-of-hospital treatment with NIPPV was better than standard therapy. The number needed to treat (NNT) was calculated to help interpret the clinical significance of the results. Statistical significance was defined as $P<.05$ or 95% CI of the RR that excluded unity. ICU and hospital length of stay could not be pooled because of the inconsistent reporting of mean values, so these outcomes have been reported descriptively.

Statistical heterogeneity was assessed with both a χ^2 test and the I^2 statistic, which describes the percentage of variability in the effect estimates that is due to underlying differences between the studies rather than chance.[25] I^2 values of greater than or equal to 75% indicated substantial heterogeneity. To explain possible heterogeneity, a priori subgroup analyses were planned to investigate type and severity of disease, type of NIPPV device and dose or duration of therapy, and differences in standard therapy.

RESULTS

Our search strategy yielded 734 potentially relevant clinical citations from multiple databases. After elimination of duplicate citations and reports that did not satisfy the selection criteria, 17 full-text articles were retrieved (Figure 1). After screening for eligibility, 7 randomized controlled trials were included in the review, with a combined total of 632 patients, 313 in the standard therapy group and 319 in the NIPPV group.[14-20] The extent of agreement between reviewers during final selection of included studies was assessed with Cohen's κ statistic. There was perfect agreement between the reviewers ($\kappa=1.0$) for selection of included trials.

Six of the included trials used a CPAP device and 1 trial used a BiPAP device (Table 1). Six studies included patients with suspected acute cardiogenic pulmonary edema (n=522), 3 studies included patients with suspected acute exacerbation of chronic obstructive pulmonary disease (n=81), 2 trials included patients with suspected pneumonia (n=19), and 1 study included patients with severe asthma (n=10). The authors of the studies who reported median values for ICU and hospital length of stay were contacted to retrieve original data so means could be calculated and potentially pooled. Two authors provided additional information and clarification. However, ICU and hospital length of stay could not be pooled because of insufficient data, so these outcomes have been reported descriptively (Table 2).

Overall, 5 studies (71.4%) were judged to be of low risk of bias with respect to random sequence generation and 2 (28.6%) were unclear owing to lack of information (Table 3). Allocation

Table 1. Characteristics of included trials.

Trial	Type of Disease	NIPPV Device, Dose, cm H_2O	Standard Care	Outcomes	STD n	TX n
Plaisance (2007) France[16]	ACPE	CPAP, 7.5	Diuretics, NTG, CCB, ionotropes, O_2	**DCS**, **ABG**, ETT, death	61	63
Frontin (2011) France[15]	ACPE	CPAP, 10	Diuretics, nitrates, O_2	**Vitals**, ETT, death, ICU LOS, hospital LOS	62	60
Schmidbauer (2011) Germany[17]	AECOPD	CPAP, unclear	O_2	DCS, ETT, ICU LOS, RR, O_2	18	18
Thompson (2008) Canada[18]	Severe resp distress	CPAP, 10	Diuretics, NTG, morphine, bronchodilators, O_2	**ETT**, death, ICU LOS, hospital LOS	35	36
Weitz (2007) Germany[19]	ACPE	BiPAP, 12.5/5	Diuretics, NTG, morphine, O_2	**O_2 sat**	13	10
Ducros (2011) France[14]	ACPE	CPAP, 7.5–10	Diuretics, nitrates, ionotropes, O_2	**Death**, **ETT**, ICU LOS, med doses, BNP/TnI	100	107
Roessler (2012) Germany[20]	ACPE, AECOPD, pneumonia	CPAP, 5–20	Bronchodilators, dexamethasone, opiates, Lasix, O_2	**Effectiveness of treatment**, 90-day survival, 28-day survival, SpO_2, RR, ICU LOS, hospital LOS	25	24

STD, standard; *TX*, treatment; *ACPE*, acute cardiogenic pulmonary edema; *CPAP*, continuous positive airway pressure; *NTG*, nitroglycerin; *CCB*, calcium channel blocker; *DCS*, dyspnea clinical score; *ABG*, arterial blood gas; *ETT*, endotracheal intubation; *LOS*, length of stay; *AECOPD*, acute exacerbation of chronic obstructive pulmonary disease; *ICU*, intensive care unit; *RR*, respiratory rate; *BiPAP*, bi-level positive airway pressure; *BNP*, brain natriuretic peptide; *TnI*, Troponin-I; *SpO_2*, blood oxygen saturation.
Bold indicates primary outcome.

Table 2. Hospital and ICU LOS as reported by included trials.

	Hospital LOS			ICU LOS		
Trial	**Standard Care**	**NIPPV**	***P* Value**	**Standard Care**	**NIPPV**	***P* Value**
Frontin (2011)[15]	Median 6 days (IQR 2,9)	Median 6 days (IQR 3, 8)	.50	Median 8.2 h (IQR 5.3, 14.5)	Median 8 h (IQR 5.2, 12.5)	.27
Schmidbauer (2011)[17]	Median 7.7 days (IQR 3.1, 14.6)	Median 2.5 days (IQR 1.0, 5.5)	.02	Median 13 h (IQR 7, 20)	Median 8 h (IQR 3, 14)	.16
Thompson (2008)[18]	Median 9 days	Median 7 days	nr	Median 3 days	Median 6.5 days	nr
Weitz (2007)[19]	Mean (SD) 12.5 (1.8) days	Mean (SD) 8.2 (2.3) days	nr	Mean (SD) 2.3 (0.6) days	Mean (SD) 1.7 (0.5) days	nr
Ducros (2011)[14]	nr	nr	nr	Median 2 days (IQR 1, 3)	Median 2 days (IQR 1, 3)	.67
Roessler (2012)[20]	Mean (SD) 17.4 (18) days	Mean (SD) 13.9 (14.4) days	.50	Mean (SD) 3.7 (6.4) days	Mean (SD) 1.3 (2.6) days	.03

IQR, Interquartile range; *nr*, not reported.

was adequately concealed in 5 studies (71.4%) and unclear in 2 (28.6%), once again because of insufficient information for judgment. There was no blinding of participants or personnel performed in any of the included trials because sham NIPPV therapy is extremely difficult and expensive to administer. There was minimal loss to follow-up because 4 studies (57.1%) had complete follow-up and 3 studies (42.9%) reported a rate of loss to follow-up ranging from 2.8% to 3.9%, for a total of 8 of 632 patients (1.2%) in the data set. Overall, 5 of the studies (71.4%) were judged to be of relatively low risk of bias and 2 (28.6%) were judged unclear. The 2 studies that were unclear included a total of 59 (9.3%) patients.

Data on inhospital mortality were available for all 7 included trials, involving a total of 632 patients, 313 in the standard therapy group and 319 in the NIPPV group. There was a significant reduction in inhospital morality with the use of out-of-hospital NIPPV (RR 0.58; 95% CI 0.35 to 0.95; NNT 18), with no statistical heterogeneity among the studies (Figure 2; Table 4). Six of the included trials reported the outcome of need for invasive ventilation (Table 1). The pooled estimate showed a significant reduction of need for invasive ventilation with the use of out-of-hospital NIPPV (RR 0.37; 95% CI 0.24 to 0.58; NNT 8), with no statistical heterogeneity between the studies (Figure 3; Table 4). ICU and hospital length of stay could not be pooled because of inconsistent reporting of means (Table 2). Five of the included trials reported complication rates.[14-16,19,20] Three studies reported no complications with NIPPV.[16,19,20] In the 2 studies that reported complications, 3 patients (1.0%) receiving NIPPV experienced emesis.[14,15] No other complications were reported.

LIMITATIONS

As with any meta-analysis, the conclusions can only be as strong as the quality and consistency of trials that are included. There are a few important differences that existed between the studies included in this review.

Although our meta-analysis did not demonstrate statistically significant heterogeneity across the 7 studies included in the analysis, there is a significant amount of clinical heterogeneity warranting further discussion. The majority (>97%) of patients included in our review had subsequent diagnoses of acute cardiogenic pulmonary edema, acute exacerbation of chronic obstructive pulmonary disease, or asthma. There was 1 study

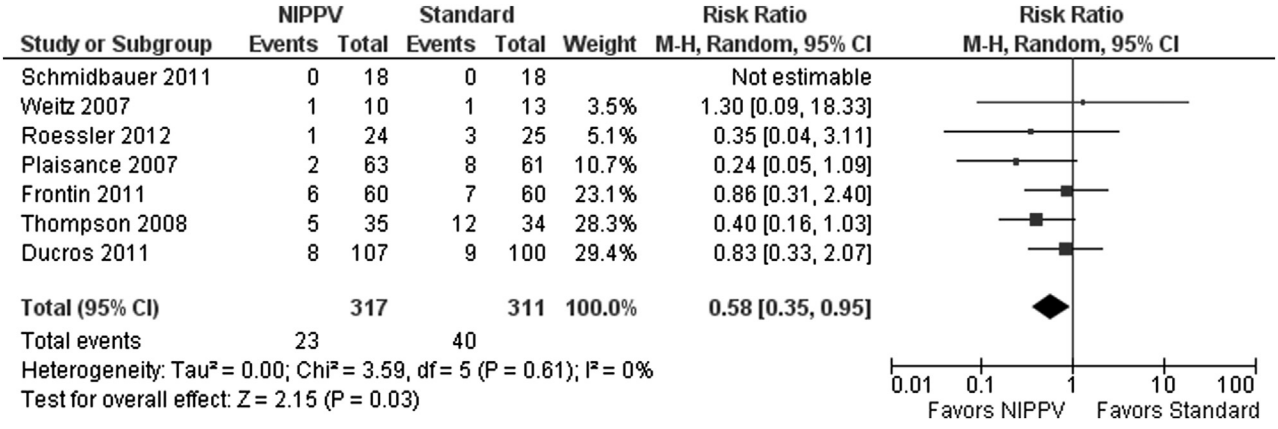

Figure 2. The use of NIPPV compared with standard therapy for inhospital mortality.

Table 3. Risk of bias summary for included trials.

Trial	Random Sequence Generation	Allocation Concealment	Blinding of Pts/Personnel	Blinding of Outcome Assessment	Lost to Follow-up (%)	Free of Selective Outcome Reporting
Plaisance (2007)[16]	Yes	Yes	No	No	0	Yes
Frontin (2011)[15]	Yes	Yes	No	No	0	Yes
Schmidbauer (2011)[17]	Yes	Yes	No	No	0	Unclear
Thompson (2008)[18]	Yes	Yes	No	No	2.8	Yes
Weitz (2007)[19]	Unclear	Unclear	No	No	0	Unclear
Ducros (2011)[14]	Unclear	Unclear	No	No	2.9	Yes
Roessler (2012)[20]	Yes	Yes	No	No	3.4	Yes
Summary score	Low risk of bias	Low risk of bias	High risk of bias	High risk of bias	Low risk of bias	Low risk of bias

that enrolled patients with broader inclusion criteria of "severe respiratory distress," which included patients with subsequent diagnoses of pneumonia and acute coronary syndrome.[18] Although the underlying disease may have been different, the inclusion criteria in each randomized controlled trial were similar because patients were required to present with hypoxic respiratory failure (SpO_2 <90%) and tachypnea. EMS providers are often faced with this clinical situation in which patients' conditions are deteriorating and require urgent intervention, but a diagnosis may not be immediately evident without ancillary testing. It appears that patients with undifferentiated dyspnea can be treated effectively with NIPPV, with a low likelihood of harm, given the right clinical situation and absence of obvious contraindications. A priori, we planned to perform subgroup analyses; however, the number of patients in each of the clinical subgroups was too small to generate appropriate and meaningful analyses.

Within each of the included randomized controlled trials, the definition of standard therapy differed, as did the level of training of the most responsible EMS provider. Six of the studies took place in Europe, where it is common to find physicians on ambulances, and 1 took place in Canada with advanced care paramedics (Table 1). The presence of a qualified anesthesiologist or emergency physician is an important consideration because their level of experience and training would affect the decision to intubate a patient in extremis compared with that of a paramedic. Also, in countries where paramedics function under strict medical directives, intubation may not be an option in certain scenarios; thus, the results of our meta-analysis may not be reproducible in these settings.

Additionally, the definitions of standard therapy were broad, ranging from simple oxygen administration to diuretic and inotrope infusions (Table 1). Even when NIPPV was compared with the most aggressive out-of-hospital therapy, significant reductions were found in the need for invasive ventilation.[14,16] Considering these results and the investment necessary to develop protocols and train EMS providers to administer and monitor advanced intravenous medications, EMS agencies may better use their resources to train those same providers to administer NIPPV. In some regions of the world, NIPPV is already being administered safely by primary (basic) care paramedics.[26]

There was no standard modality for administering positive-pressure ventilation across the 7 randomized controlled trials included in this review (Table 1). Six of the 7 included trials used CPAP in the treatment arm of the study[14-18,20] and 1 used BiPAP.[19] Four different commercial NIPPV systems were used to generate positive pressure, including an external pressure regulator (WhisperFlow,[14,18] Downflow[16]), turbulent flow valve (Boussignac[15]), and portable ventilator (Oxylog 3000[17,19,20]).

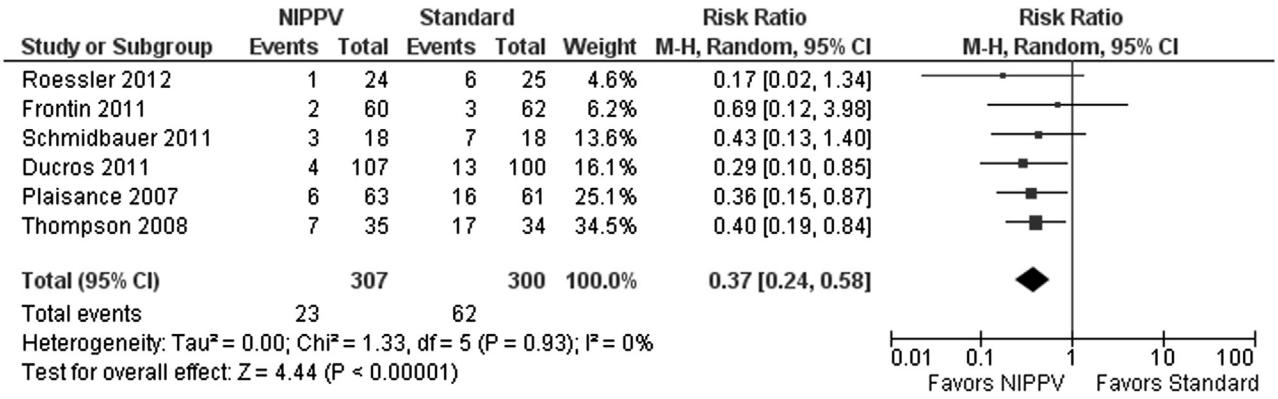

Figure 3. The use of NIPPV compared with standard therapy for need for invasive ventilation.

Table 4. Summary of findings.*

Outcomes	No. of Participants (Studies)	Quality of the Evidence (GRADE)	NNT (95% CI)	Relative Effect (95% CI)	Anticipated Absolute Effects	
					Risk With Standard Therapy	Risk Difference With NIPPV (95% CI)
Inhospital mortality	628 (7)	⊕⊕⊕⊖ Moderate† because of inconsistency	18 (9.7–109.2)	RR 0.58 (0.35–0.95)	129/1,000	54 fewer per 1,000 (from 6 fewer to 84 fewer)
Intubation	607 (6)	⊕⊕⊕⊕ High	8 (5.4–12.9)	RR 0.37 (0.24–0.58)	207/1,000	130 fewer per 1,000 (from 87 fewer to 157 fewer)

*The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). GRADE Working Group grades of evidence: High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important influence on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important influence on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.
†Although the CIs overlapped, 1 of 7 (Weitz) favored standard therapy.

Although analysis is beyond the scope of this review, each system has its strengths and weaknesses with respect to ease of paramedic use, cost, maximum therapy length because of oxygen requirements, and compatibility with existing hospital hardware.[27] Each of these points must be taken into consideration before an EMS system invests in any one particular unit.

Similar to the use of NIPPV in the hospital setting, there is no accepted standard dose for the initiation or length of therapy with NIPPV. The CPAP doses reported in the included trials ranged from 5 to 20 cm H_2O, and the one study in which BiPAP was used reported a dose of 12.5/5 cm H_2O (Table 1). Additionally, the length of out-of-hospital therapy ranged from 30 to 60 minutes. It is unclear from the current out-of-hospital evidence whether there is a minimum length of therapy required for benefit or, conversely, a maximum length after which there would be risk of harm.

Although we derived our search strategy to be comprehensive and thorough, it is possible that trials of out-of-hospital NIPPV with negative or inconclusive results were excluded from our review. This publication bias, or "file-drawer problem," refers to the tendency for negative or inconclusive results to remain unpublished by their authors. The pooled estimates presented in this review are based on published trials and may not be truly representative of all valid studies undertaken.

DISCUSSION

The results of this systematic review and meta-analysis suggest that the use of out-of-hospital NIPPV reduces the risk of inhospital mortality and need for invasive ventilation compared with standard therapy for the treatment of adult patients with severe respiratory distress. The use of out-of-hospital NIPPV in patients presenting with undifferentiated dyspnea does not appear to increase complication rates.

Acute cardiogenic pulmonary edema and acute exacerbation of chronic obstructive pulmonary disease are associated with substantial worldwide patient morbidity and mortality; thus, it is important to administer effective therapies as early as possible.[28,29] Previous inhospital meta-analyses demonstrate that the use of NIPPV in patients with acute cardiogenic pulmonary edema significantly reduces both hospital mortality (NNT=14) and need for mechanical ventilation (NNT=8), with no appreciable increase in complications such as intolerance of therapy or myocardial infarction.[4] A similar benefit is reported for patients with acute exacerbation of chronic obstructive pulmonary disease, in which inhospital treatment using NIPPV reduces the risk of mortality (NNT=10) and need for mechanical ventilation (NNT=4) compared with standard therapy.[7] Our results are consistent with the previously published inhospital data and demonstrate that NIPPV is a safe and effective therapy for patients in severe respiratory distress when administered in the out-of-hospital setting.

With respect to the treatment of patients with severe asthma exacerbation, NIPPV has traditionally been a contraindicated therapy because there are concerns of increasing airway pressures and subsequent barotrauma.[30] However, a few small studies of inhospital patients, including 1 randomized controlled trial, have examined its use for patients with status asthmaticus, and the limited evidence suggests that NIPPV may be benefical.[31-34] In our out-of-hospital systematic review, there was only 1 trial that included asthma patients (n=10), and the authors did not report any occurrence of pneumothoraces or worsening dyspnea.[18] Although additional inhospital and out-of-hospital randomized controlled trials evaluating the use of NIPPV in severe asthma are needed, specifically examining out-of-hospital safety, there may be a subset of patients who benefit from its early application.

Although a number of narrative and systematic reviews[27,35,36] have been previously published examining the use of out-of-hospital NIPPV for the treatment of adults in respiratory distress, to our knowledge none have included a meta-analysis of results pertaining to only high-quality randomized controlled trials. Simpson and Bendall[35] and Williams et al[36] published extensive reviews of the evidence for out-of-hospital use of NIPPV for patients with pulmonary edema. Simpson and Bendall[35] summarized the results of 12 primary studies documenting the use of NIPPV, either CPAP or BiPAP, for out-of-hospital management of acute cardiogenic pulmonary edema. The authors concluded that administration of NIPPV appears to be a safe and feasible therapy resulting in faster improvement in physiologic status and may decrease the need for intubation compared with delayed NIPPV administration in the emergency department.

However, the majority of articles included in the review were noncomparative descriptive studies. Only 3 were randomized controlled trials, and none addressed inhospital mortality as a primary outcome measure.[35]

In a recent systematic review by Williams et al,[36] CPAP therapy in the out-of-hospital environment was found to be beneficial to patients with acute pulmonary edema. It was also shown to improve patient vital signs during out-of-hospital transport and reduce rates of intubation and short-term mortality. However, only patients with acute pulmonary edema were included in the review.

In a thorough and comprehensive review on NIPPV, Daily and Wang[27] concluded that NIPPV is a feasible out-of-hospital therapeutic option for acute dyspnea. Although the majority of studies included in their review focused on patients with acute pulmonary edema, studies suggesting that NIPPV may prove useful with other reversible disease processes such as chronic obstructive pulmonary disease or asthma exacerbations were also included. The authors did not attempt a meta-analysis.

Future research about the out-of-hospital administration of NIPPV for severe respiratory distress should aim to delineate its safety and efficacy profile in expanded disease processes such as asthma and pneumonia. Also, current literature is available only for EMS systems using NIPPV with advanced care paramedics or ambulances with physician assistance. There are no published randomized controlled trials of NIPPV's being used by basic/primary care paramedics, to our knowledge. Last, no studies have been conducted in the out-of-hospital setting to evaluate its use in the pediatric population; therefore, no recommendations can be made for this age group.

Out-of-hospital administration of NIPPV appears to be an effective therapy for adult patients with severe respiratory distress. When EMS providers are faced with a patient presenting with undifferentiated dyspnea who is likely to require intubation, a trial of out-of-hospital NIPPV appears to be an effective and safe therapy that may decrease need for invasive ventilation and mortality, given there are no contraindications to its use. In light of this evidence, it is reasonable to consider NIPPV for the treatment of adults with severe respiratory distress in the out-of-hospital setting. EMS agencies and individual out-of-hospital care providers should incorporate NIPPV into the treatment of severe respiratory distress if feasible.

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Author contributions: SM, SM, AD, and ML conceived the study idea and designed the study protocol. AI performed the literature search. SM and SM independently screened the titles and abstracts, assessed the quality of the studies, and independently extracted data. SM and SM performed the statistical analysis. SM and SM drafted the study manuscript and all authors contributed substantially to its revision. The primary author SM takes responsibility for the paper as a whole.

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APPENDIX E1.

OVID MEDLINE 1946 TO DECEMBER 2012.

1. exp Emergency Medical Services/ or Emergency Medical Technicians/
2. (emergenc$ or emergicent$ or ems).af.
3. (prehospital$ or pre-hospital$ or ambulance$ or out-of-hospital$ or paramedic$ or para medic$ or para-medic$).tw.
4. ((patient$ adj transport$) or (mobile adj2 unit$)).tw.
5. or/1-4
6. exp Respiration, Artificial/ or exp Ventilators, Mechanical/ or Positive-Pressure Respiration/
7. (pressure$ and (positive$ or end-expiratory$ or bilevel or bi-level or biphasic or BIPAP)).tw.
8. ((positive-pressure$ or positive pressure$) and (ventilation$ or respiration$)).tw.
9. (ventilat$ adj5 (NIV or NPPV or NIPPV or NPSV or NIPSV or non invasive or noninvasive or non-invasive or cpap or ncpap or aprv or peep or ipap or airway pressure$ or mechanical$ or artificial$ or assisted$ or pulmonary$)).tw.
10. (NIV or NPPV or NIPPV or NPSV or NIPSV or non invasive or noninvasive or non-invasive or cpap or ncpap or aprv or peep or ipap or airway pressure$ or mechanical$ or artificial$ or assisted$ or pulmonary$).ab. /freq=2 and ventilat$.tw.
11. ventilat$.ab. /freq=2 and (NIV or NPPV or NIPPV or NPSV or NIPSV or non invasive or noninvasive or non-invasive or cpap or ncpap or aprv or peep or ipap or airway pressure$ or mechanical$ or artificial$ or assisted$ or pulmonary$).mp.
12. ventilat$.ti. and (NIV or NPPV or NIPPV or NPSV or NIPSV or non invasive or noninvasive or non-invasive or cpap or ncpap or aprv or peep or ipap or airway pressure$ or mechanical$ or artificial$ or assisted$ or pulmonary$).tw.
13. ((non-invasive or non invasive) and (positive-pressure$ or positive pressure$)).tw.
14. (respiration$ adj2 (artificial$ or assisted$)).tw.
15. or/6-14
16. Pulmonary Edema/ or Pulmonary Disease, Chronic Obstructive/ or exp Bronchitis, Chronic/ or exp Pulmonary Emphysema/ or exp Asthma/ or Respiratory Sounds/ or Bronchial Spasm/ or exp Bronchoconstriction/ or Bronchial Hyperreactivity/ or Respiratory Hypersensitivity/
17. exp Heart Failure/ or exp Myocardial Infarction/ or Ventricular Dysfunction, Left/ or exp Respiratory Insufficiency/ or Respiratory Distress Syndrome, Adult/
18. (heart failure$ or respiratory distress or wet lung).tw.
19. ((lung$ or respirat$ or pulmonary$ or airway$ or airflow$) and (chronic$ adj2 obstruct$)).tw.
20. (edema$ or oedema$ or asthma$ or bronchiti$ or emphysema$ or copd or coad or cobd or wheez$ or bronchospas$ or bronchoconstrict$ or (bronch$ adj2 spasm$) or (bronch$ adj2 constrict$)).tw.
21. or/16-20
22. 5 and 15 and 21
23. limit 22 to english language
24. 23 not (Animal/ not (Human/ and Animal/))
25. 24 not (letter not randomized controlled trial).pt.
26. 24 not (news not randomized controlled trial).pt.
27. 25 or 26
28. limit 27 to (case reports or editorial)
29. 27 not 28
30. random$.tw.
31. 29 and 30
32. limit 29 to "therapy (best balance of sensitivity and specificity)"
33. 31 or 32
34. limit 33 to review
35. 33 not 34
36. meta analysis.mp,pt. or MEDLINE.tw. or systematic review.tw.
37. 29 and 36
38. 35 or 37