Effective Health Care Program

Comparative Effectiveness Review
Number 68

Noninvasive Positive-Pressure Ventilation (NPPV) for Acute Respiratory Failure

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Noninvasive Positive-Pressure Ventilation (NPPV) for Acute Respiratory Failure

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting comparative effectiveness reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input from are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Noninvasive Positive-Pressure Ventilation (NPPV) for Acute Respiratory Failure

Structured Abstract

Objectives: Noninvasive positive-pressure ventilation (NPPV) is a form of mechanical ventilatory support delivered to patients with acute respiratory failure through a noninvasive interface. In patients with a range of etiologies for acute respiratory failure, NPPV has the potential to reduce complications and improve outcomes compared to invasive ventilation.

Data Sources: We searched PubMed®, Embase®, and the Cochrane Database of Systematic Reviews for English-language studies published since 1990 that compared NPPV versus supportive care or invasive ventilation, bilevel positive airway pressure (BPAP) versus continuous positive airway pressure (CPAP), NPPV versus conventional weaning from invasive ventilation, or NPPV versus supportive care to prevent or treat acute respiratory failure postextubation.

Review Methods: Two investigators screened each abstract and full-text article for inclusion, abstracted data, and performed quality ratings, efficacy-effectiveness ratings, and evidence grading. Random-effects models were used to compute summary estimates of effect.

Results: Forty-four studies (4,122 subjects) compared NPPV to supportive care, 5 (405 subjects) compared NPPV to invasive ventilation, 12 (1,520 subjects) compared BPAP to CPAP, and 12 (1,463 subjects) evaluated NPPV for weaning or in patients postextubation. Most studies were conducted in patients with acute respiratory failure due to congestive heart failure or severe exacerbations of chronic obstructive pulmonary disease (COPD). BPAP was the most common NPPV modality.

Compared with supportive care, NPPV reduced hospital mortality (odds ratio [OR] 0.56; 95% confidence interval [CI], 0.44 to 0.72), intubation rates (OR 0.31; 0.23 to 0.41), and hospital-acquired pneumonia. Outcomes did not differ for the major NPPV modalities. Compared with conventional weaning from invasive ventilation, NPPV was associated with a lower hospital mortality (OR 0.17; 0.05 to 0.65) and decreased rates of hospital-acquired pneumonia (OR 0.14; 0.04 to 0.48) in patients with COPD. When used to prevent recurrent respiratory failure postextubation, NPPV decreased mortality (OR 0.60; 0.34 to 1.04) and reintubation (OR 0.43; 0.24 to 0.77) only in those at high risk.

Effects on mortality were smaller for studies with more characteristics of effectiveness trials, but did not differ for intubation rates. Effects did not differ by clinical setting or global geographical region.

Conclusions: For patients with acute respiratory failure due to severe exacerbations of COPD or congestive heart failure, NPPV improves outcomes compared to supportive care alone. Current evidence suggests potential benefit for patients with acute respiratory failure who are postoperative or post-transplant, and in selected populations, as a method to facilitate weaning

from invasive ventilation or prevent recurrent respiratory failure postextubation. Limited evidence shows similar treatment effects across different settings and the possibility of less benefit in trials designed to replicate usual clinical practice.

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Executive Summary

Background

Acute respiratory failure is a life-threatening condition characterized by an inability to maintain normal levels of oxygen and/or carbon dioxide gas exchange due to dysfunction of the respiratory system. In its most basic sense, the respiratory system comprises a gas exchanging organ (lung) and a ventilatory pump (respiratory muscles and controllers, chest wall). Respiratory failure is classified based on failure of one or both of these elements, as well as the timing of such failure. Acute respiratory failure develops over minutes to several days. Respiratory failure is deemed chronic when derangements occur over several days or longer. Acute-on-chronic respiratory failure occurs when a patient with chronic respiratory failure suffers an acute deterioration in gas exchange; this is most commonly seen in patients with severe chronic obstructive pulmonary disease (COPD).

The epidemiology of acute respiratory failure is not fully known. In the United States, millions of patients are admitted to the intensive care unit (ICU) each year, and acute respiratory failure is the most common cause.[1] Acute respiratory failure is severe enough to require life support with invasive mechanical ventilation for approximately 800,000 Americans a year, a high proportion of whom do not survive the episode.[2] Epidemiological studies have estimated the annual incidence of acute respiratory failure to be between 77.6 and 430 patients per 100,000.[1,3-5] The estimated health care costs related to critical care are approximately 0.7 percent of the annual gross domestic product, and the human and financial costs are only expected to increase with an aging population.[6-9]

Supplemental oxygen is a mainstay of therapy for acute respiratory failure. In severe cases, acute respiratory failure requires respiratory support with invasive mechanical ventilation. Invasive ventilation (also known as conventional mechanical ventilation) is a form of life support in which positive pressure delivers a mixture of air and oxygen through an endotracheal or tracheostomy tube to central airways, which then flows distally to the alveoli. Despite the benefits of invasive ventilation in patients with respiratory failure, up to 40 percent of such patients die in the hospital; some of these deaths are directly attributable to the complications of invasive ventilation and artificial airways.[10-13] In addition, many survivors of acute respiratory failure require prolonged invasive ventilation and suffer persistent decrements in quality of life and functional independence.[14-16]

An increasingly recognized option in the management of selected cases of acute respiratory failure is to employ noninvasive positive-pressure ventilation (NPPV). NPPV refers to a form of mechanical support in which positive pressure delivers a mixture of air and oxygen throughout the respiratory tree via a noninvasive interface. Patient-ventilator interfaces for NPPV include a face mask, nasal mask or plugs, or a helmet that covers the head. NPPV collectively includes several modalities of noninvasive ventilation, which can be delivered via a standard ICU ventilator or a portable device. Continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BPAP) are the two most commonly used modes of NPPV. CPAP is applied throughout the respiratory cycle of a spontaneously breathing patient and is physiologically identical to constant positive end-expiratory pressure. BPAP delivers two pressure levels according to the respiratory cycle and improves ventilation, oxygenation, and alveolar recruitment. BPAP provides both an inspiratory positive airway pressure and a continuous expiratory positive airway pressure, and the difference between these reflects the volume of air

displaced with each breath. NPPV can provide modes nearly identical to standard ICU ventilators, such as pressure, volume, assist control, or even proportional assist ventilation.

The use of NPPV for support during the treatment of respiratory failure is attractive because it does not require either endotracheal intubation or moderate and/or deep sedation and can be safely initiated or discontinued as needed. It is also associated with few of the nosocomial complications recognized with endotracheal intubation, such as ventilator-associated pneumonia, critical illness-associated weakness, pneumothorax, delirium, and infections associated with the invasive monitoring typically required during invasive life support.[11,14] NPPV is not appropriate for some patients, such as those with cardiopulmonary arrest or shock, where greater airway control is required, or those with facial trauma, where the interface (e.g., mask) cannot be used appropriately.

NPPV has been evaluated in a large number of trials, often with clinically important benefits, but use of NPPV remains highly variable across institutions and geographical regions.[17-21] Surveys in the United States have shown high variability in estimated use across hospitals.[21] Barriers to use include a lack of physician knowledge, low rates of perceived efficacy, lack of standard protocols and team-based care at some hospitals, and, among older clinicians, little training or experience with NPPV.[22] A specific knowledge gap is uncertainty about the efficacy of NPPV for patients with acute respiratory failure for conditions other than COPD or acute cardiogenic pulmonary edema (ACPE). In addition, NPPV is a resource-intensive modality and requires a substantial amount of training and experience to implement successfully. As a result, some experts have questioned whether the benefits of NPPV seen in highly specialized settings are replicated in routine practice.

Objectives

The literature supporting the use of NPPV for respiratory failure in the acute-care setting has evolved over the last two decades.[12] Although there have been some exceptions, such as a 2010 meta-analysis examining NPPV in acute respiratory failure of multiple causes,[23] the use of NPPV has been most extensively studied in patients with acute respiratory failure due to COPD and congestive heart failure. In addition to these two well-studied uses, there is increasing interest in determining if NPPV is beneficial for other causes of acute respiratory failure (e.g., asthma) or can shorten the duration of invasive mechanical ventilation, either as a method to facilitate early extubation or to prevent extubation failure in high-risk groups.[23] Further, there is uncertainty about whether the beneficial effects demonstrated in randomized controlled trials (RCTs) are replicated in real-world settings where training, experience, organizational factors, and patient factors may differ substantially. Additionally, it is uncertain whether the effects of NPPV vary by clinician experience and training, the use of protocols, the setting in which NPPV initiation is applied, or by specific patient characteristics.

This comparative effectiveness review (CER) was commissioned by the Agency for Healthcare Research and Quality (AHRQ) to evaluate the evidence for NPPV versus other typical treatments for acute respiratory failure. We conducted a systematic review that is inclusive of all major causes of acute respiratory failure and includes studies of NPPV used for weaning from invasive ventilation. We anticipate that clinicians involved in medical and surgical critical care medicine, emergency medicine, and anesthesiology, along with developers of clinical practice guidelines, will be the primary audience for this report.

We constructed Key Questions (KQs) using the general approach of specifying the population of interest, the interventions, comparators, outcomes, timing of outcomes, and settings. The KQs considered in this CER are:

KQ 1: Is noninvasive positive-pressure ventilation (NPPV) associated with less morbidity (including from intubation), lower mortality, fewer adverse events, or lower medical utilization when compared with supportive medical therapy or invasive ventilation:

a. In adults with chronic obstructive pulmonary disease (COPD) and acute respiratory failure?
b. In adults with acute cardiogenic pulmonary edema (ACPE)?
c. In adults with acute respiratory failure due to other causes including: pneumonia, asthma, obesity-hypoventilation syndrome, and interstitial lung disease?
d. In adults with acute respiratory failure in selective settings including: postoperative setting and post-transplant setting?

KQ 2: Is NPPV with bilevel positive airway pressure (BPAP), compared with NPPV with continuous positive airway pressure (CPAP), associated with less morbidity, lower mortality, fewer adverse events, or lower medical utilization:

a. In adults with COPD and acute respiratory failure?
b. In adults with ACPE?
c. In adults with acute respiratory failure due to other causes including: pneumonia, asthma, obesity-hypoventilation syndrome, and interstitial lung disease?
d. In adults with acute respiratory failure in selective settings including: postoperative setting and post-transplant setting?

KQ 3: Is early extubation to NPPV, compared with usual care, associated with less morbidity, lower mortality, fewer adverse events, or lower medical utilization:

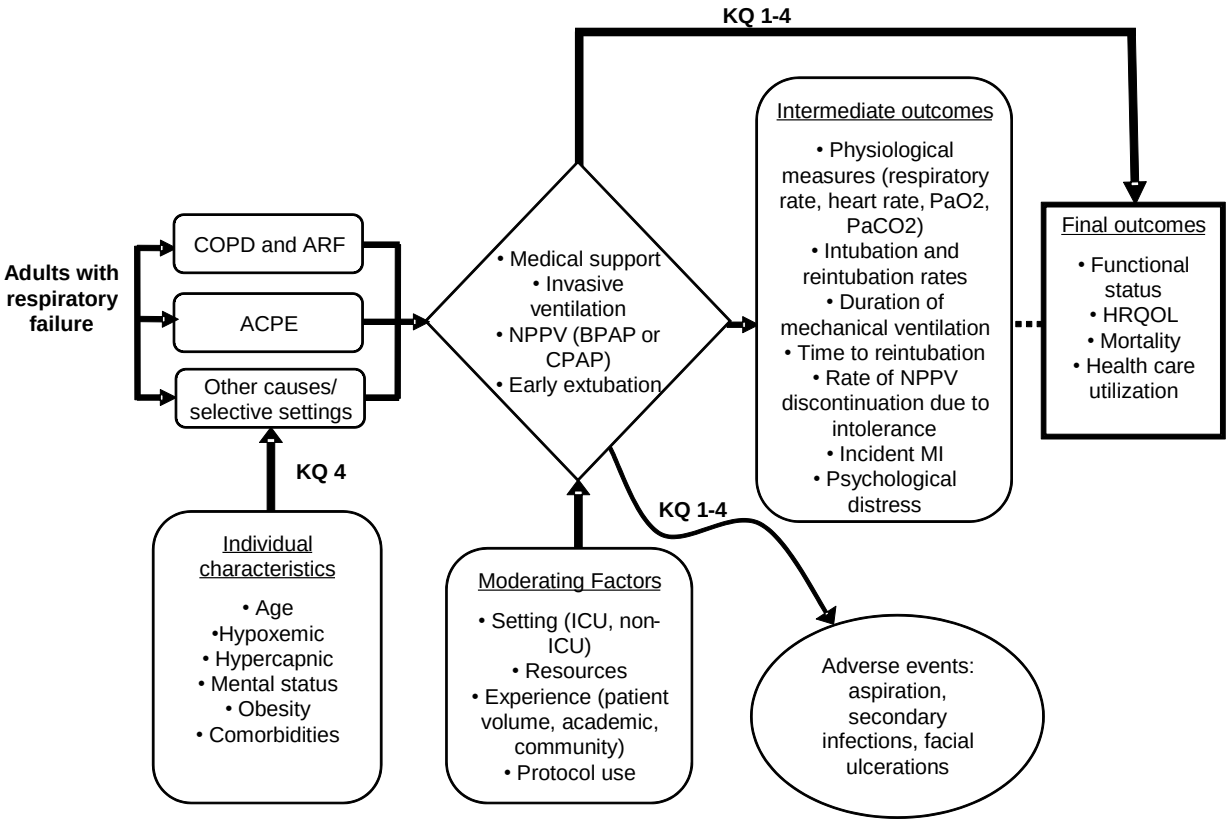
a. In adults with COPD and acute respiratory failure?
b. In adults with ACPE?
c. In adults with acute respiratory failure due to other causes including: pneumonia, asthma, obesity-hypoventilation syndrome, and interstitial lung disease?
d. In adults with acute respiratory failure in selective settings including: postoperative setting and post-transplant setting?

KQ 4: For KQs 1–3, do the effectiveness and risks of NPPV vary by setting and associated resources, experience and training of clinicians, and use of protocols or by patient characteristics (e.g., morbid obesity, mental-status changes, overall disease burden)?

Analytic Framework

Figure A shows the analytic framework for this project.

Figure A. Analytic framework



Abbreviations: ACPE = acute cardiogenic pulmonary edema; ARF = acute respiratory failure; BPAP = bilevel positive airway pressure; COPD = chronic obstructive pulmonary disease; CPAP = continuous positive airway pressure; HRQOL = health-related quality of life; ICU = intensive care unit; KQ = Key Question; MI = myocardial infarction; NPPV = noninvasive positive-pressure ventilation; PaCO2 = partial pressure of carbon dioxide in blood; PaO2 = partial pressure of oxygen in arterial blood

In general, the figure shows that this CER compares morbidity, mortality, adverse events, and health care utilization for patients receiving NPPV with supportive medical therapy or invasive ventilation (KQ 1), patients receiving NPPV with BPAP with NPPV with CPAP (KQ 2), and patients receiving early extubation to NPPV with those receiving weaning strategies that do not utilize NPPV (KQ 3). Subgroups considered for KQs 1–3 included adults with COPD and respiratory failure; adults with ACPE; adults with acute respiratory failure due to pneumonia,

asthma, obesity-hypoventilation syndrome, or interstitial lung disease; and adults with acute respiratory failure in postoperative or post-transplant settings. Adverse events considered are aspiration, secondary infections (including pneumonia and sinusitis), and facial ulcerations. Intermediate outcomes included physiological measures (respiratory rate, heart rate, partial pressure of oxygen in arterial blood [PaO2], and partial pressure of carbon dioxide in blood [PaCO2]); intubation and reintubation rates; duration of mechanical ventilation; time to reintubation; rate of NPPV discontinuation due to intolerance; incident myocardial infarction; and psychological distress. Final outcomes assessed are functional status, health-related quality of life, mortality (in-hospital and 30-day), and health care utilization (ventilator-dependent days, rate of ventilator dependence at hospital discharge, length of hospital stay, length of intensive care unit stay, and total hospital costs). The report also considers whether the effectiveness and risks outlined in KQs 1–3 vary by setting and associated resources, experience and training of the clinicians, use of protocols, or by patient characteristics (e.g., mental status, obesity, and comorbidities).

Methods

Input From Stakeholders

The methods for this CER follow those suggested in the ARHQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews (hereafter referred to as the Methods Guide).[24] During the topic refinement stage, we solicited input from a group of Key Informants (KIs) representing medical professional societies/clinicians in the areas of pulmonology, critical/intensive care, and respiratory therapy; scientific experts; payers; and Federal agencies to help define the KQs. These KQs were posted on AHRQ's Web site for public comment for 4 weeks, beginning in late December 2010. The comments received were considered in the revision of the KQs and in the development of the research protocol. We next convened a Technical Expert Panel (TEP) to provide input on defining populations, interventions, comparisons, and outcomes, as well as for identifying particular studies or databases to search. The TEP members provided the same range of viewpoints and expertise as are described for the KI group, with the addition of a methodologist with experience in trial efficacy-effectiveness assessment. The KIs and members of the TEP were required to disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Any potential conflicts of interest were balanced or mitigated. KIs and members of the TEP did not perform analyses of any kind or contribute to the writing of the report. All methods and analyses were guided by the protocol; certain methods map to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[25]

Data Sources and Selection

We searched PubMed®, Embase®, and the Cochrane Database of Systematic Reviews to identify relevant published literature. Our search strategies used the National Library of Medicine's medical subject headings (MeSH) keyword nomenclature and text words for NPPV and eligible study designs. We used validated search filters for randomized study designs where possible (the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version [2008 revision] in PubMed, and the Cochrane search

filter for identifying randomized trials in Embase[26]). We included studies conducted in adults and published in English from 1990 through our final search date of January 31, 2012. We limited studies to 1990 forward because standards of care have changed significantly since 1990. All searches were designed and conducted in collaboration with an experienced search librarian.

We supplemented the electronic searches with a manual search of citations from a set of key primary and review articles.[23,27-46] All citations were imported into an electronic bibliographic database (EndNote® Version X4; Thomson Reuters, Philadelphia, PA). As a mechanism to ascertain publication bias, we searched ClinicalTrials.gov to identify completed but unpublished studies.

We used two approaches to identifying relevant grey literature: (1) a request for scientific information packets submitted to device manufacturers; and (2) a request submitted to the U.S. Food and Drug Administration for any unpublished RCT data available for devices used to provide noninvasive positive-pressure ventilation.

Using the criteria described in Table A, two investigators independently reviewed each title and abstract for potential relevance to the Key Questions; articles included by either investigator underwent full-text screening. At the full-text screening stage, two investigators independently reviewed the full text of each article and indicated a decision to "include" or "exclude" the article for data abstraction. When the paired reviewers arrived at different decisions about whether to include or exclude an article, or about the reason for exclusion, we reached a final agreement through review and discussion among investigators. Articles meeting eligibility criteria were included for data abstraction.

Table A. Inclusion/exclusion criteria

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Population	Adults (age ≥ 18 years) with: • COPD and acute respiratory failure • ACPE • Acute respiratory failure due to other causes, including: pneumonia, asthma, obesity-hypoventilation syndrome, and interstitial lung disease • Acute respiratory failure in selective settings including: postoperative setting and post-transplant setting	• Population composed entirely of children (< 18 years of age) • Adult populations where NPPV is contraindicated, such as cardiopulmonary arrest, shock, and facial trauma
Interventions	• NPPV including CPAP, BPAP, and closely related noninvasive positive airway pressure modes delivered through any interface (e.g., face mask, nasal mask or plugs, or a helmet that covers the head)	• Invasive ventilation only

Table A. Inclusion/exclusion criteria (continued)

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Comparators	KQs 1, 2, and 4: • Supportive care, invasive ventilation, or another form of NPPV KQ 3: • Any approach to weaning that does not utilize NPPV	• No comparator
Outcomes	A clinical or utilization-related outcome of interest, including: • Intermediate outcomes: o Physiological measures such as respiratory rate, heart rate, PaO2, and PaCO2 (KQs 1–3) o Intubation (KQs 1, 2, 4) and reintubation (KQs 3, 4) rates; duration of mechanical ventilation (KQs 1–4); and time to reintubation (KQ 3) o Rates of discontinuing NPPV secondary to the patient being unable to tolerate the treatment (KQs 1–4) o Incident myocardial infarction (KQs 1–3) o Psychological distress (e.g., anxiety) assessed by using a validated measure • Final outcomes: o Functional status measured by using a validated questionnaire or performance-based measure at hospital discharge or the 30-day followup (KQs 1, 3, 4) o Health-related quality of life measured using a validated questionnaire at hospital discharge or the 30-day followup (KQs 1, 3, 4) o In-hospital and 30-day mortality rates (KQs 1–3) o Medical utilization (KQs 1–4), including ventilator-dependent days, rate of ventilator dependence at hospital discharge, length of hospital stay, length of ICU stay, and total hospital costs • Adverse events (KQs 1–4), including rates of: o Aspiration o Secondary infections (including pneumonia, sinusitis) o Facial ulcerations	• No relevant clinical or utilization-related outcome of interest reported (note that studies reporting only physiological measures such as respiratory rate, heart rate, PaO2, and PaCO2 were excluded)
Timing	• Studies of any duration	• None
Setting	Hospital settings, including: • ICUs • Emergency departments • Postoperative and post-transplant settings • General medical units	• Nonmedical settings such as home use • Long-term care settings such as nursing homes • Perioperative uses to prevent acute respiratory failure
Study design	RCTs	• Non-RCT study designs[a] • Not a clinical study (e.g., editorial, nonsystematic review, letter to the editor, case series)

Table A. Inclusion/exclusion criteria (continued)

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Publications	Published literature: • English-language only[b] • Published from 1990 on[c] • Peer-reviewed article Gray literature: • Report must be publicly available and have sufficient detail for abstraction (e.g., a full report similar in detail and quality to peer-reviewed literature)	• Non-English language publication[b] • Not published in peer-reviewed literature or one of the specified grey literature sources (Scientific Information Packets; FDA analyses) • Published before 1990[c]

[a]Although non-RCTs may be particularly pertinent to addressing effectiveness, confounding by indication makes it unlikely that these studies would yield a valid estimate of effect. English language: Given the high volume of literature available in English-language publications (including the majority of known important studies), and concerns about the applicability of non-English publication studies to settings in the United States, we excluded non-English articles.
[c]The rationale for this was that standards of care have changed significantly since 1990.
Abbreviations: Abbreviations: ACPE = acute cardiogenic pulmonary edema; BPAP = bilevel positive airway pressure; COPD = chronic obstructive pulmonary disease; CPAP = continuous positive airway pressure; FDA = U.S. Food and Drug Administration; ICU = intensive care unit; KQ = Key Question; NPPV = noninvasive positive-pressure ventilation; PaCO2 = partial pressure of carbon dioxide in blood; PaO2 = partial pressure of oxygen in arterial blood; RCT = randomized controlled trial

Data Extraction and Quality Assessment

The review team created forms for abstracting the data elements for the KQs. Based on their clinical and methodological expertise, a pair of researchers was assigned to abstract data from the eligible articles. One researcher abstracted the data, and the second reviewed the completed abstraction form alongside the original article to check for accuracy and completeness. Disagreements were resolved by consensus or by obtaining a third reviewer's opinion if consensus could not be reached by the first two investigators.

We designed the data abstraction forms for this project to collect the data required to evaluate the specified eligibility criteria for inclusion in this review, as well as demographic and other data needed for determining outcomes (intermediate, final, and adverse events outcomes). We used an efficacy-effectiveness instrument[47] to assess seven domains: population and setting, restrictiveness of eligibility criteria, health outcomes, flexibility of the intervention and study duration, assessment of adverse effects, adequate sample size for important health outcomes, and intention-to-treat approach to analyses. We rated each of the seven items as effectiveness (score = 1) or efficacy (score = 0); scores were summed and could range from 0 to 7. Final efficacy-effectiveness scores were based on the mean of two independent ratings. We classified the etiology of acute respiratory failure based on study inclusion criteria (e.g. acute respiratory failure secondary to COPD) and the description of included patients. When the etiology was mixed, we classified the study by a single condition if at least 70 percent of the sample had that condition; otherwise, the sample was described as "mixed." We prioritized abstraction of clinical outcomes reported for the duration of the ICU or hospital stay, along with any longer term outcomes. In addition, we described comparators (especially supportive therapy) as carefully as possible given the (sometimes limited) information provided in the study publications, as treatment standards may have changed during the period covered by this review. The safety outcomes were framed to help identify adverse events, including hospital-acquired pneumonia and facial ulcerations. Data necessary for assessing quality and applicability, as described in the Methods Guide,[24] were also abstracted.

To assess the risk of bias/methodological quality of individual studies, we used the key criteria for RCTs described in the Methods Guide[24] and adapted for this specific topic. These criteria include adequacy of randomization and allocation concealment, the comparability of groups at baseline, blinding, the completeness of followup and differential loss to followup, whether incomplete data were addressed appropriately, the validity of outcome measures, and conflict of interest. These general criteria were customized for each major outcome. To indicate the summary judgment of the quality of the individual studies, we used the summary ratings of good, fair, and poor, based on the studies' adherence to well-accepted standard methodologies and the adequacy of the reporting. For each study, one investigator assigned a summary quality rating, which was then reviewed by a second investigator; disagreements were resolved by consensus or by a third investigator if agreement could not be reached.

We graded the strength of evidence (SOE) for each outcome assessed using the approach described in the Methods Guide.[24,48] In brief, the approach requires assessment of four domains: risk of bias, consistency, directness, and precision. Additional domains considered were strength of association (magnitude of effect), and publication bias. For risk of bias we considered basic (e.g., RCT) and detailed study design (e.g., adequate randomization). For directness, we considered whether the interventions of interest were compared directly (i.e., head-to-head) and the directness of the specific outcome vis-à-vis our KQs. For example, we considered ICU length of stay to be an indirect outcome because it does not capture overall resource utilization, including the time and personnel required to implement NPPV. We used results from meta-analyses when evaluating consistency (forest plots, tests for heterogeneity), precision (confidence intervals), strength of association (odds ratio [OR]), and publication bias (funnel plots and test statistics). Optimal information size and considerations of whether the confidence interval crossed the clinical decision threshold using a therapy was also used when evaluating precision.[49] These domains were considered qualitatively, and a summary rating of "high," "moderate," or "low" SOE was assigned after discussion by two reviewers. In some cases, high, moderate, or low ratings were impossible or imprudent to make, for example, when no evidence is available or when evidence on the outcome is too weak, sparse, or inconsistent to permit any conclusion to be drawn. In these situations, a grade of "insufficient" was assigned. This four-level rating scale consists of the following definitions:

- High—High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate—Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- Low—Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
- Insufficient—Evidence either is unavailable or does not permit estimation of an effect.

Data Synthesis and Analysis

We began by summarizing key features of the included studies for each KQ. To the degree that data were available, we abstracted information on study design; patient characteristics; medical settings; type of NPPV, including the interface; and intermediate, final, and adverse events outcomes. We then determined the feasibility of completing a quantitative synthesis (i.e., meta-analysis). Based on the frequency of reported outcomes and the relative importance of

these outcomes, we determined that quantitative syntheses were indicated for: mortality, intubation or reintubation, myocardial infarction, and hospital-acquired pneumonia; other outcomes were summarized using descriptive statistics. Length of stay was analyzed qualitatively because the data reported for this outcome were often highly skewed, and because this outcome is biased due to the mortality benefit associated with NPPV treatment. For this qualitative synthesis, we focused our analysis on the larger studies that had greater power to detect a clinically and statistically significant difference in length of stay. We did not synthesize physiological outcomes because there were sufficient data to draw conclusions based on final outcomes and more clinically relevant intermediate outcomes. Other clinical outcomes that were reported infrequently, such as rates of sinusitis, facial ulceration, and discontinuation due to intolerance, are summarized descriptively.

For the outcomes selected for meta-analysis, we used random-effects models to synthesize the evidence quantitatively using the Comprehensive Meta-Analysis software (Version 2; Biostat, Englewood, NJ). When outcomes were reported at multiple time points, we used the longest in-hospital followup duration (e.g., in-hospital mortality instead of ICU mortality). We summarized binary or categorical outcomes using a weighted effect measure for proportions (e.g., OR) and 95 percent confidence intervals (CIs). When we found statistically significant effects, we calculated the risk difference by using the summary OR and median odds of events from the comparator arms of the included studies. If the summary OR varied substantially by study quality, we used the OR from the good-quality studies for this calculation. We tested for heterogeneity using graphical displays and test statistics (Q and I^2 statistics). When there were sufficient studies ($n \geq 10$), we assessed for publication bias using funnel plots and test statistics.[50] If these analyses suggested significant publication bias, we computed an adjusted summary estimate using Duval's trim-and-fill method.[51]

We hypothesized that the methodological quality of individual studies, efficacy-effectiveness score, the training or experience of the interventionists, the characteristics of the comparator, and patients' etiology of acute respiratory failure would be associated with the intervention effects. When there were sufficient studies, we performed subgroup analyses to examine these hypotheses. For these analyses, we categorized studies as mostly efficacy (score of 0–2), mixed efficacy-effectiveness (score of 3–5), and mostly effectiveness (score of 6–7). Since staffing and experience were reported rarely, we grouped studies by geographical region (primarily continents) as a proxy for experience and completed subgroup analyses for this classification.

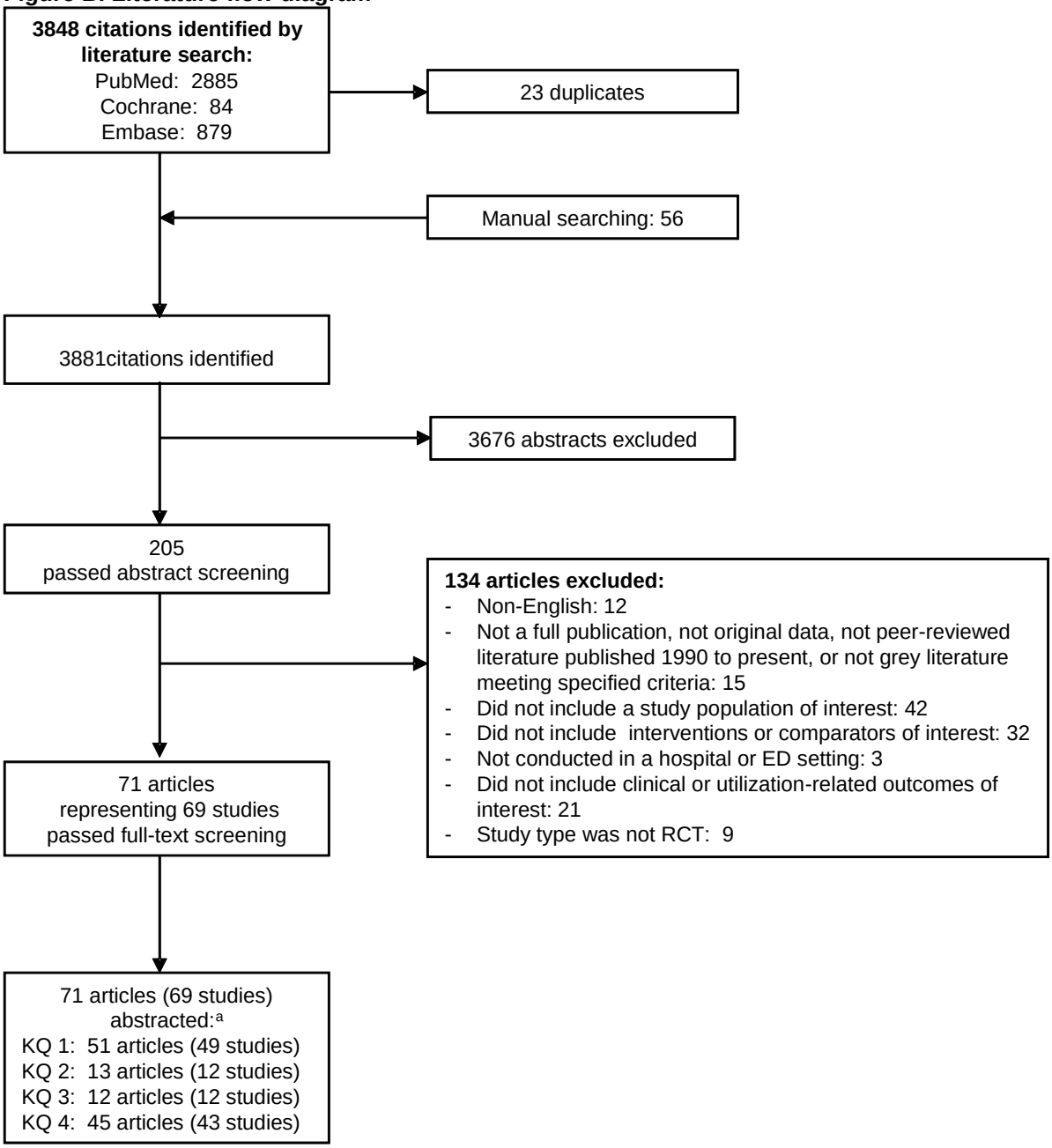
We conducted a secondary, mixed-treatment meta-analysis to address the effects of CPAP, BPAP, and invasive ventilation compared with supportive therapy by using both direct and indirect comparisons. Mortality is a dichotomous outcome and was fitted using multiple logistic regression analysis. Dummy variables were used for study differences, and treatment variables were used for the three treatment effects. A random-effects model was fitted using the EGRET® software (EGRET for Windows, 1999; Cytel Software Corporation, Cambridge, MA), which estimates both fixed-effect and random-effects parameters and automatically generates the dummy variables for each study ("Logistic-Normal Regression Model" option). Hasselblad 1998[52] describes the application of this methodology to meta-regression problems.

Results

Figure B depicts the flow of articles through the literature search and screening process. Searches of PubMed, Embase, and the Cochrane Database of Systematic Reviews yielded 3,848 citations, 23 of which were duplicate citations. Manual searching identified 56 additional

citations, for a total of 3,881 citations. After applying inclusion/exclusion criteria, we included 71 articles (representing 69 unique studies) for data abstraction. As indicated in Figure B, many articles/studies were relevant to more than one KQ. Our search of ClinicalTrials.gov did not find evidence for completed but unpublished studies relevant to our KQs.

Figure B. Literature flow diagram



[a]Some studies/articles were included for more than one KQ, so that numbers given in this box total to more than 71 articles/69 studies.Abbreviations: ED = emergency department; KQ = Key Question; RCT = randomized controlled trial

Key Question 1. NPPV Versus Supportive Care or Invasive Ventilation

Key points from the Results chapter are:

- In patients treated for acute respiratory failure, current evidence supports a reduction in mortality when NPPV plus supportive care is used versus supportive care alone. This evidence is strongest for patients with COPD and ACPE, but limited evidence supports an effect in the postoperative and post-transplant settings.
- In patients treated for acute respiratory failure, current evidence supports a reduction in intubation rates when NPPV plus supportive care is used versus supportive care alone. This evidence is strongest for patients with COPD, but also supports an effect in patients with ACPE and in the postoperative and post-transplant settings.
- In patients treated for acute respiratory failure, current evidence supports a reduction in hospital-acquired pneumonia when NPPV plus supportive care is used versus supportive care alone. This evidence is strongest for patients with COPD.
- The evidence does not support an increase in rate of myocardial infarction related to NPPV.
- Evidence for treatment effects of NPPV in acute respiratory failure is sparse in many other etiologic subgroups, including acute respiratory distress syndrome (ARDS) and asthma.
- Effects of NPPV on medical utilization are uncertain.
- Outcomes for psychological response, functional status, or health-related quality of life were not reported. Duration of mechanical ventilation was reported infrequently.

Forty-nine studies involving 4,527 patients met our inclusion criteria for KQ 1. Of the 49 studies, 40 compared NPPV plus supportive medical therapy with supportive medical therapy alone, 5 compared NPPV with invasive ventilation, and 4 were 3-arm trials comparing CPAP, BPAP, and supportive care. Forty-three studies reported mortality, 39 studies reported intubation rates, 7 studies reported myocardial infarction, and 8 studies reported rates of hospital-acquired pneumonia. No studies reported effects on health-related quality of life or anxiety associated with NPPV use. Most studies (60%) were conducted in Europe; six studies (12%) were conducted in the United States or Canada. Of the 49 studies, 22 (45%) were of good methodological quality, 21 (43%) were of fair quality, and 6 (12%) were of poor quality.

Approximately two-thirds of the studies reported a morbidity index (Acute Physiology And Chronic Health Evaluation [APACHE] II or Simplified Acute Physiology Score [SAPS]) that relies primarily on physiological measures. The median predicted mortality for enrolled patients was approximately 12 percent. Table B summarizes the findings and strength of evidence (SOE) for each major outcome. In brief, in patients treated for acute respiratory failure, there is high SOE supporting a reduction in both mortality and intubation when NPPV plus supportive care is used versus supportive care alone. This effect was established most strongly for patients with ACPE, or severe exacerbations of COPD. There is moderate SOE supporting a reduction in pneumonia associated with NPPV, but the evidence does not support a change in rate of myocardial infarction related to NPPV compared with supportive care alone. Evidence for treatment effects is sparse or absent in many diagnostic groups, including those with asthma, interstitial lung disease, perioperative and post-transplant settings. Outcomes for psychological response, functional status, or health related quality of life were not reported. Duration of mechanical ventilation was reported infrequently.

NPPV was compared with invasive ventilation in only 405 subjects. Compared with invasive ventilation, NPPV lowered hospital-acquired pneumonia (summary OR 0.15; 95% CI, 0.08 to 0.30; SOE = high) but did not reduce mortality or length of stay (SOE = low).

Table B. Summary of the strength of evidence for KQ 1—NPPV versus supportive care

Number of Studies (Subjects)	Domains Pertaining to SOE				Strength of Evidence
	Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	Effect Estimate (95% CI)
Hospital mortality					**High**
39 (4,111)	RCT/Good	Consistent	Direct	Precise	OR = 0.56 (0.44 to 0.72) RD = 64 fewer per 1000 (40 to 83)
Intubation rate					**High**
39 (3,792)	RCT/Good	Inconsistent	Direct	Precise	OR = 0.31 (0.24 to 0.41) RD = 217 fewer per 1000 (177 to 247)
Myocardial infarction					**Moderate**
7 (1,517)	RCT/Good	Consistent	Direct	Imprecise	OR = 1.11 (0.85 to 1.44) RD = not applicable
Medical utilization: Hospital length of stay					**Low**
11 (2,499)[a]	RCT/Good	Consistent	Indirect	Imprecise	No study found a statistically significant difference in LOS
Medical utilization: ICU length of stay					**Insufficient**
5 (523)[a]	RCT/Good	Inconsistent	Indirect	Imprecise	Not estimable; 2 of 5 studies found a statistically significant decrease in LOS
Hospital-acquired pneumonia					**Moderate**
9 (650)	RCT/Good	Consistent	Direct	Imprecise	OR = 0.27 (0.15 to 0.49) RD = 121 fewer per 1000 (81 to 144)

[a]Data are for larger studies with sufficient power to test for a 1-day difference in length of stay.
Abbreviations: CI = confidence interval; ICU = intensive care unit; NA = not applicable; OR = odds ratio; RCT = randomized controlled trial; RD = risk difference; SOE = strength of evidence

Key Question 2. BPAP Versus CPAP

Key points from the Results chapter are:

- Thirteen RCTs of varied quality showed no statistically significant difference between providing NPPV with BPAP compared with CPAP for the outcomes of:
    - Mortality
    - Need for endotracheal intubation
    - Myocardial infarction
- Current evidence is insufficient to determine if BPAP or CPAP have differential treatment effects for hospital or ICU length of stay, hospital-acquired pneumonia, psychological distress, functional status or health-related quality of life, and mortality rates beyond hospitalization.
- All studies but one included only participants with ACPE, although indirect comparisons included other diagnoses and supported these findings. This limits the applicability of these findings in patients with other causes of acute respiratory failure, such as COPD, as well as those in postoperative and post-transplant settings.

A total of 12 RCTs were included in our analyses for KQ 2. Ten studies enrolled patients from emergency departments, one from unclear settings, and one from a high-dependency unit.

The number of patients included in studies ranged from 26 to 1,156, with a total of 1,463 patients. Four studies included three treatment arms (BPAP, CPAP, and supportive care with supplemental oxygen), while the remainder compared BPAP with CPAP alone. Although we aimed to address a variety of populations, all but one study included only patients with ACPE. No studies included in these analyses addressed obesity hypoventilation syndrome, interstitial lung disease, or the perioperative or post-transplant setting. Seven studies were performed in Europe, two in Brazil, one in Tunisia, one in Canada, and one in Australia. Of these, four were of good quality, six were of fair quality, and two were of poor quality.

Table C summarizes the findings and strength of evidence for each major outcome. In brief, 12 RCTs of varied quality showed no statistically significant difference between providing NPPV with BPAP compared with CPAP, for the outcomes of mortality and need for endotracheal intubation (moderate strength of evidence) or myocardial infarction (low strength of evidence). There is currently insufficient evidence to determine if BPAP or CPAP have differential treatment effects for: hospital or ICU length of stay, hospital-acquired pneumonia, psychological distress, functional status, health-related quality of life, and mortality rates beyond hospitalization. All studies but one included only participants with ACPE. The applicability of these findings is uncertain in those with COPD and other causes of acute respiratory failure.

Table C. Summary of the strength of evidence for KQ 2—CPAP versus BPAP

Number of Studies (Subjects)	Domains Pertaining to SOE				Strength of Evidence
	Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	Effect Estimate (95% CI)
Hospital mortality					**Moderate**
10 (1,338)	RCT/Good	Consistent	Direct	Imprecise	OR = 0.89 (0.58 to 1.35) RD = NA
Intubation rate					**Moderate**
12 (1,463)	RCT/Good	Consistent	Direct	Imprecise	OR = 0.84 (0.51 to 1.38) RD = NA
Myocardial infarction					**Low**
7 (1,056)	RCT/Good	Inconsistent	Indirect	Imprecise	OR = 0.69 (0.34 to 1.40) RD = NA
Medical utilization: hospital length of stay					**Insufficient**
3 (278)[a]	RCT/Good	Consistent	Indirect	Imprecise	Not estimable; No study found a statistically significant difference in LOS
Medical utilization: ICU length of stay					**Insufficient**
0 (0)	NA	NA	NA	NA	Not estimable
Hospital-acquired pneumonia					**Insufficient**
0 (0)	NA	NA	NA	NA	Not estimable

[a]Data are for larger studies with sufficient power to test for a 1-day difference in length of stay.
Abbreviations: CI = confidence interval; ICU = intensive care unit; NA = not applicable; OR = odds ratio; RCT = randomized controlled trial; RD = risk difference; SOE = strength of evidence

Key Question 3. Early Extubation to NPPV

Key points from the Results chapter are:

- In eligible studies, BPAP was the only NPPV modality evaluated; no studies used CPAP.
- In patients with COPD who are intubated for acute respiratory failure, current evidence supports a reduction in mortality and hospital-acquired pneumonia when NPPV is used to facilitate extubation. These benefits were not observed in studies enrolling patients with mixed etiologies of acute respiratory failure.

- In patients intubated for acute respiratory failure and deemed at high risk for extubation failure, current evidence supports a reduction in reintubation rates and hospital-acquired pneumonia when NPPV is used to prevent extubation failure. A mortality benefit in this group was suggested but was not statistically significant.
- In patients who develop recurrent acute respiratory failure, current evidence does not support a reduction in mortality, reintubation rates, or hospital-acquired pneumonia rates for NPPV use compared with supportive care.
- Few studies had adequate sample sizes to address effects on length of stay. Available evidence does not support a reduction in hospital length of stay with BPAP versus usual care, but suggests a possible decrease in ICU length of stay with early extubation to BPAP. BPAP-assisted weaning was associated with shorter duration of invasive ventilation.
- No studies reported data on myocardial infarction, psychological response, functional status, or health-related quality of life.

Twelve studies involving 1,519 patients met our inclusion criteria for KQ 3. All studies were conducted in ICU settings and used BPAP as the NPPV mode. Ten studies included a mixed population of patients with a variety of diagnoses causing respiratory failure. Two studies included only patients with a diagnosis of COPD. The included studies described three general strategies for using NPPV in the management of ventilator weaning: five studies investigated the use of NPPV in facilitating early extubation (i.e., comparing "usual" weaning strategy with extubation prior to meeting extubation criteria but with the application of NPPV as a bridge to liberation from invasive mechanical ventilation); five studies described the use of NPPV versus supportive care in preventing recurrent acute respiratory failure postextubation; and two studies examined the use of NPPV versus supportive care in the treatment of recurrent acute respiratory failure postextubation. Eleven studies reported effects on reintubation, and 11 reported mortality; no study reported myocardial infarction rates. One study was conducted in Canada and one multicenter study included sites in the United States; all others were carried out in Europe or Asia. Of the 12 studies, 6 were of good methodological quality, 5 were of fair quality, and 1 was of poor quality.

Tables D, E, and F summarize the findings and strength of evidence for each major strategy. In mixed populations of patients intubated for acute respiratory failure, current evidence shows a nonstatistically significant reduction in mortality but no effects on reintubation rates when BPAP is used to facilitate early extubation versus usual care (low strength of evidence). However, early extubation to BPAP is associated with lower rates of hospital-acquired pneumonia (low strength of evidence). Effects did not differ significantly for patients at high risk for reintubation who received anticipatory (presymptomatic) BPAP postextubation compared with those with recurrent respiratory failure when NPPV was used postextubation only among symptomatic patients. There is insufficient evidence to determine whether use of BPAP postextubation is associated with lower hospital or ICU length of stay or myocardial infarction compared with supportive care. No included studies used CPAP in the NPPV mode.

When compared with conventional weaning, we found lower mortality in patients with COPD, and a nonstatistically significant reduction in mortality in studies enrolling patients with mixed etiologies of acute respiratory failure. Results were similar for hospital-acquired pneumonia rates. NPPV did not affect reintubation rates, an effect that was consistent across diagnostic subgroups. When used to prevent acute respiratory failure postextubation, NPPV

decreased mortality and reintubation only for patients at high-risk of recurrent respiratory failure. Only two studies evaluated NPPV to treat recurrent acute respiratory failure postextubation. These studies did not show a benefit for NPPV on any outcome.

Table D. Summary of the strength of evidence for KQ 3—NPPV-assisted ventilator weaning versus conventional weaning

Number of Studies (Subjects)	Domains Pertaining to SOE				Strength of Evidence
	Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	Effect Estimate (95% CI)
Hospital mortality—COPD					**Low**
2 (140)	RCT/Fair	Consistent	Direct	Imprecise	OR = 0.17 (0.05 to 0.65) RD = 129 fewer per 1000 (50 to 151)
Hospital mortality—mixed etiologies					**Insufficient**
3 (214)	RCT/Fair	Inconsistent	Direct	Imprecise	OR = 0.46 (0.06 to 3.59) RD = NA
Reintubation rate					**Low**
4 (303)	RCT/Good	Consistent	Direct	Imprecise	OR = 0.83 (0.48 to 1.44) RD = NA
Myocardial infarction					**Insufficient**
0 (none)	NA	NA	NA	NA	OR = not estimated
Medical utilization: hospital length of stay					**Insufficient**
2 (229)	RCT/	Consistent	Indirect	Imprecise	Not estimable; No study found a statistically significant difference in LOS
Medical utilization: ICU length of stay					**Insufficient**
3 (279)[a]	RCT/Good	Consistent	Indirect	Imprecise	Not estimable; 2 of 3 studies found a statistically significant decrease in LOS
Hospital acquired pneumonia—COPD					**Low**
2 (140)	RCT/Fair	Consistent	Direct	Imprecise	OR = 0.14 (0.04 to 0.48) RD = 167 fewer per 1,000 (33 to 233)
Hospital-acquired pneumonia—mixed etiologies					**Low**
3 (214)	RCT/Fair	Inconsistent	Direct	Imprecise	OR = 0.53 (0.19 to 1.46) RD = NA

[a]Data are for larger studies with sufficient power to test for a 1-day difference in LOS.
Abbreviations: CI = confidence interval; LOS = length of stay; NA = Not applicable; OR = odds ratio; RCT = randomized controlled trial; RD = risk difference; SOE = strength of evidence

Table E. Summary of the strength of evidence for KQ 3—NPPV versus supportive care to prevent respiratory failure postextubation

Number of Studies (Subjects)	Domains Pertaining to SOE				Strength of Evidence
	Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	Effect Estimate (95% CI)
Hospital mortality—high-risk group					**Low**
3 (365)	RCT/Good	Consistent	Direct	Imprecise	OR = 0.60 (0.34 to 1.04) RD = NA
Hospital mortality—average-risk group					**Insufficient**
1 (406)	RCT/Fair	NA	Direct	Imprecise	OR = 1.52 (0.25 to 9.21) RD = NA
Reintubation rate—high-risk group					**Low**
3 (365)	RCT/Good	Consistent	Direct	Imprecise	0.43 (0.24 to 0.77)
Reintubation rate—average-risk group					**Low**
2 (499)	RCT/Fair	Consistent	Direct	Imprecise	OR = 1.56 (0.89 to 2.76) RD = NA
Myocardial infarction					**Insufficient**
0 (none)	NA	NA	NA	NA	OR = not estimated
Medical utilization: hospital length of stay					**Insufficient**
3 (365)	RCT/Good	Consistent	Indirect	Imprecise	Not estimable; No study found a statistically significant difference in LOS
Medical utilization: ICU length of stay					**Insufficient**
3 (365)[a]	RCT/Good	Consistent	Indirect	Imprecise	Not estimable; No study found a statistically significant difference in LOS
Hospital acquired pneumonia					**Low**
2 (268)[a]	RCT/Fair	Consistent	Direct	Imprecise	OR = 0.52 (0.28 to 0.97) RD = 102 fewer per 1,000 (6 to 164)

[a]Data are for larger studies with sufficient power to test for a 1-day difference in LOS.

Abbreviations: CI = confidence interval; LOS = length of stay; OR = odds ratio; RCT = randomized controlled trial; RD = risk difference; SOE = strength of evidence

Table F. Summary of the strength of evidence for KQ 3—NPPV versus supportive care to treat respiratory failure postextubation

Number of Studies (Subjects)	Domains Pertaining to SOE				Strength of Evidence
	Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	Effect Estimate (95% CI)
Hospital mortality					**Low**
2 (302)	RCT/Good	Consistent	Direct	Imprecise	OR = 1.52 (0.78 to 2.97) RD = NA
Reintubation rate					**Low**
2 (302)	RCT/Good	Consistent	Direct	Imprecise	OR = 1.05 (0.66 to 1.67) RD = NA
Myocardial infarction					**Insufficient**
0 (none)	NA	NA	NA	NA	OR = not estimated
Medical utilization: hospital length of stay					**Insufficient**
1 (81) [a]	RCT/Good	NA	Indirect	Imprecise	Not estimable
Medical utilization: ICU length of stay					**Insufficient**
2 (302)[a]	RCT/Good	Consistent	Indirect	Imprecise	Not estimable; No study found a statistically significant difference in LOS
Hospital-acquired pneumonia					**Insufficient**
1 (81)	RCT/Good	NA	Direct	Imprecise	OR = 1.02 (0.42 to 2.48)

[a]Data are for larger studies with sufficient power to test for a 1-day difference in LOS.
Abbreviations: CI = confidence interval; LOS = length of stay; OR = odds ratio; RCT = randomized controlled trial; RD = risk difference; SOE = strength of evidence

Key Question 4. Variation by Subgroups

Key points from the Results chapter are:

- The effects of NPPV on intubation rates are stronger when NPPV is initiated in the ICU than when it is initiated in the ED, but these findings are based on indirect comparisons.
- Few studies reported details about clinical setting and associated resources, experience and training of clinicians, or the use of clinical protocols. With the exception of diagnosis at study entry, no studies reported results by patient characteristics.
- The pooled OR associated with NPPV for both mortality and intubation shows a stronger effect for efficacy trials compared with effectiveness trials, but only two effectiveness trials were included in the analysis, and the 95% CIs overlapped.
- The treatment effects for NPPV on mortality and intubation rates are consistent across studies conducted in the United States or Canada versus European countries versus other countries.
- With the exception of the clinical setting in studies that compared NPPV with usual supportive care or invasive ventilator support (KQ 1), too few studies reported sufficient data to evaluate whether effectiveness or risks of NPPV vary by setting or patient characteristics.

Of the 69 studies included in this report overall, 65 included information about the clinical setting in which NPPV was initiated, 3 provided specific information about the experience or training of study clinicians, 2 reported patients' mean body mass index, 16 reported data on patients' neurological or mental status, 17 reported a measure of disease burden, and 67 reported mean baseline acute physiology scores for predicted ICU mortality. We conducted subgroup

analysis for: the clinical setting, the geographical world region and efficacy-effectiveness category. Of the 49 studies that pertain to KQ 1, NPPV was initiated in the ED setting in 10 studies and in the ICU setting in 23 studies. In the remaining 16 studies, clinical setting was either not reported, or NPPV was initiated in another setting such as a general medicine ward or ambulance. The majority of studies were conducted in Europe. Most studies were classified as mixed efficacy-effectiveness studies; only two were classified as effectiveness studies.

Table G summarizes the findings and strength of evidence for each of these analyses. Because these subgroup comparisons were made across studies, and thus were indirect comparisons, the study design was classified as an observational approach. Effects on mortality were lower for effectiveness studies but did not differ for intubation rates. These analyses were limited by the paucity of effectiveness trials. The pooled estimate of effect did not differ significantly across different settings or different countries.

Table G. Summary of the strength of evidence for KQ 4—variability in treatment effect by study characteristics

Number of Studies (Subjects)	Domains Pertaining to SOE				Strength of Evidence
	Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	Summary of Effect
Different treatment effects by study effectiveness characteristics					**Low**
43 (4,467)[a]	Observational	Inconsistent	Direct	Imprecise	OR (95% CI) for mortality: Efficacy trial: 0.56 (0.31 to 1.02) Mixed trial: 0.52 (0.41 to 0.66) Effectiveness trial: 0.99 (0.66 to 1.49) OR (95% CI) for intubation: Efficacy trial: 0.29 (0.19 to 0.46) Mixed trial: 0.29 (0.21 to 0.41) Effectiveness trial: 0.58 (0.16 to 2.13)
Different treatment effects across clinical settings					**Low**
43 (4,467) [a]	Observational	Consistent	Direct	Imprecise	OR (95% CI) for mortality: ED: 0.72 (0.49 to 1.05) ICU: 0.48 (0.35 to 0.66) OR (95% CI) for intubation: ED: 0.50 (0.26 to 0.95) ICU: 0.23 (0.15 to 0.34)
Different treatment effects across geographical regions[b]					**Low**
43 (4,467)[a]	Observational	Consistent	Direct	Imprecise	OR (95% CI) for mortality: Europe: 0.58 (0.46 to 0.73) U.S./Canada: 0.58 (0.25 to 1.33) OR (95% CI) for intubation: Europe: 0.33 (0.22 to 0.48) U.S./Canada: 0.36 (0.20 to 0.66)

[a]39 studies and 3,792 patients for analyses of intubation rates.
[b]Geographical regions used were: U.S./Canada, Europe, and other
Abbreviations: KQ = Key Question; OR = odds ratio; SOE = strength of evidence; ED = emergency department; ICU = intensive care unit

Discussion

Key Findings

In this review, we included 69 trials that that compared NPPV with other common treatment strategies (supportive care and conventional mechanical ventilation). We also included trials that compared different types of NPPV with one another (CPAP vs. BPAP). We included common outcomes of interest such as mortality and adverse events, but also examined more difficult to measure issues such as resource utilization and efforts to shorten the duration of mechanical ventilation (by facilitating weaning from invasive ventilation, preventing extubation failure, and for treating recurrent respiratory failure).

Key findings with a high strength of evidence were decreased mortality and intubation rates for NPPV versus supportive care. This effect was established most strongly for patients with ACPE, or severe exacerbations of COPD, but more limited evidence showed a consistent effect across different populations including those with postoperative acute respiratory failure and acute respiratory failure in post-transplant patients. We found moderate strength of evidence for: a lack of treatment effect on myocardial infarction rates, reduced hospital-acquired pneumonia, and comparable effects for CPAP and BPAP. We found the evidence insufficient to estimate the effects of NPPV on utilization of medical resources due to inconsistent effects across studies, indirectness of the outcomes reported (length of stay), and imprecise results. Few studies reported effects beyond the duration of hospitalization and no studies reported effects on functional status or quality of life.

NPPV was compared with invasive ventilation in only 405 subjects, a finding itself likely related to widespread contemporary clinician belief that avoiding invasive ventilation is strongly desired. Compared with invasive ventilation, NPPV lowered hospital-acquired pneumonia but did not reduce mortality or length of stay.

Compared with studies evaluating NPPV for initial treatment of acute respiratory failure, fewer studies examined the effects of NPPV to assist in weaning from invasive ventilation or to prevent or treat recurrent acute respiratory failure postextubation. When compared with conventional weaning, we found low SOE for lower mortality in patients with COPD and a nonstatistically significant reduction in mortality in studies enrolling patient with mixed etiologies of acute respiratory failure. Results were similar for hospital-acquired pneumonia rates. NPPV did not affect reintubation rates, an effect that was consistent across diagnostic subgroups. Evidence was insufficient to estimate effects for other outcomes. When used to prevent acute respiratory failure postextubation, NPPV decreased mortality and reintubation (low SOE) only for patients at high-risk of recurrent respiratory failure. Only two studies evaluated NPPV to treat recurrent acute respiratory failure postextubation. These studies did not show a benefit for NPPV on any outcome. Evidence was insufficient to estimate effects for other outcomes.

We also sought to determine whether the effects of NPPV varied by clinical setting, the experience and composition of the treating clinicians, by patient characteristics, and by whether each individual study was primarily an efficacy or an effectiveness trial. In an exploratory analysis, treatment effects for death or intubation did not differ significantly if NPPV was initiated in an ICU versus in an ED. We used global geographical region as a proxy for experience with NPPV and found no significant difference in treatment effects across regions. Most studies were classified as mixed efficacy-effectiveness studies; only two were classified as predominately effectiveness studies. Effects on mortality were lower for effectiveness studies but

did not differ for intubation rates. These analyses were limited by the paucity of effectiveness trials.

Findings in Relation to What Is Already Known

Our results are generally consistent with previous systematic reviews[42,44,45] and clinical guidelines.[38,53,54] Previous reviews have found similar benefits on mortality and intubation rates in patients with respiratory failure due to ACPE[33,36,39,44,45] and severe exacerbations of COPD.[42,43] Our review spanned multiple conditions, finding consistent treatment effects across conditions, whereas prior reviews tend to be focused on a single cause of acute respiratory failure. Like others, we found few studies addressing acute respiratory failure in patients who are postoperative, post-transplant, or who have acute respiratory failure in the context of obesity-hypoventilation syndrome, acute respiratory distress syndrome, asthma or interstitial lung disease. As in other reviews, our study found comparable effects for CPAP and BPAP, but by incorporating indirect comparisons, we were able to strengthen this conclusion. Also of note, our review is the first to classify trials by efficacy and effectiveness characteristics, an analysis that highlights the paucity of effectiveness studies.

Mortality is increased with the duration of invasive mechanical ventilation and in patients who have recurrent respiratory failure following extubation from mechanical ventilation. This additional mortality risk is likely due to higher rates of delirium, lower mobility, and higher infection rates due to longer exposure to intravascular catheters and endotracheal tubes. Therefore, there is a potential role for NPPV in these clinical scenarios.[10,55-57] Our review has limitations when evaluating the role of NPPV as a method to facilitate weaning from invasive ventilation or to prevent or treat acute respiratory failure following extubation. We identified a relatively small number of trials that were analyzed in three subgroups depending on the specific clinical application of NPPV. For each clinical scenario, we conducted exploratory analysis by diagnostic group or risk of recurrent acute respiratory failure, indirect comparisons that are subject to confounding.

Our review also highlights the limited data for patients with acute respiratory failure not due to COPD or congestive heart failure, and the poor reporting of factors that may be related to treatment effects such as the experience of the treating clinicians and patient characteristics.

Applicability

Relatively few studies were conducted in the United States or Canada (n = 8), with most studies (57%) conducted in Europe. There is a longer clinical experience with NPPV in Europe compared with the U.S., leading us to hypothesize that outcomes may be better in European countries. However, our analyses showed treatment effects for NPPV that were consistent across studies conducted in the U.S. or Canada compared with European or other countries. Other study reporting issues also affect applicability. The study interventions were not well-described in the majority of the studies, a limitation that could impede dissemination and contribute to the knowledge deficits described in surveys of clinicians. Twelve of the 69 studies poorly described the patient population, and 9 reported only outcomes that occurred 72 hours or less after initiating NPPV or a control intervention. More consistent reporting of patient characteristics, including overall medical comorbidity, race, and body mass index, would facilitate evaluations of differential effects in these important subgroups.

Limitations of the Comparative Effectiveness Review Process

Our findings have limitations related to the literature and our approach. Important limitations of the literature include few studies in certain populations of high interest, incomplete reporting of outcomes related to resource utilization, and descriptions of the interventions that were often inadequate to permit replication. In addition, the limited reporting of adverse effects and myocardial infarction suggest the possibility of selective outcomes reporting. Limitations in reporting precluded any analyses of variability in treatment effects by patient characteristics. A patient-level meta-analysis was not possible in the current study, but would be useful approach to examine this issue. Our review methods also had limitations. Our study was limited to English-language publications, which may have contributed to different conclusions about the effects of NPPV on ventilator weaning compared with Burns et al.[31] Although we attempted to evaluate the impact of effectiveness versus efficacy studies, our approach consisted of indirect comparisons without adjustment for potential confounders. The approach was further limited by a simple rules-based approach to classifying certain items in the efficacy-effectiveness scale (e.g., university affiliation = highly trained) and few effectiveness studies.

Research Gaps and Recommendations for Future Research

We used the framework recommended by Robinson et al.[58] to identify gaps in evidence and classify why these gaps exist (Table H). Although we recommend multicenter RCTs to address some evidence gaps, we are aware that there are some particular challenges to conducting these RCTs. It is difficult to blind patients or treating clinicians to the treatment group. While lack of blinding is unlikely to bias ascertainment of mortality outcomes, it could introduce bias in the assessment of more subjective outcomes and a subtle bias into patient care. Therefore it is critical that supportive treatments be specified carefully and that outcomes be assessed by individuals who are blind to treatment assignment. Some studies included in our review reported effects on length of stay for the sample overall and the subgroup of survivors. In clinical applications where NPPV has a mortality advantage, length-of-stay analyses could be biased if analyses use all patients randomized. Studies should report length of stay for the sample overall and for the subgroup of survivors. Additionally, the application of NPPV among patients at the end of life needs further study. Many providers do not conceptualize NPPV as a form of life support, and this constitutes a potential threat to the patient-centeredness of care among those with do not attempt resuscitation orders. Finally, we recommend that authors provide more careful descriptions of the patient population, details of randomization and allocation concealment, and detailed intervention protocols to facilitate dissemination of effective treatments. An additional area of research that could facilitate the implementation of NPPV would be study of evidence-based treatment algorithms such as decision support aids or in-time electronic screening tools that could help identify patients early who could benefit from NPPV.

Table H. Evidence gaps and future research

Evidence Gap	Reason	Type of Studies To Consider
Patients		
Effects vs. supportive care in patients with asthma, interstitial lung disease, pneumonia, acute decompensated, obesity-hypoventilation syndrome and those who are postoperative or post-transplant	Insufficient or imprecise information	Multicenter RCTs
Uncertain benefit of NPPV to assist weaning	Imprecise information	Multicenter RCTs
Uncertain benefit of NPPV to prevent recurrent acute respiratory failure postextubation	Imprecise information	Multicenter RCTs
Whether NPPV treatment effects vary by patient characteristics	Insufficient information	Patient level meta-analyses Subgroup analyses from large, multicenter RCTs Improved reporting in trial publications
Outcomes		
Effects on resource utilization NPPV compared with supportive care for acute respiratory failure	Insufficient information; not the right information	Analyze effects on resource utilization from large trials Model effects on resource utilization
Effects on psychological response, functional status, or health-related quality of life	Insufficient information	Multicenter RCTs
Settings		
Effectiveness of NPPV as implemented in usual care (outside of RCTs)	Insufficient information	Observational studies
Uncertainty about the effects of training, staffing composition/ratios and use of algorithms on NPPV effectiveness	Insufficient information	Observational studies

Abbreviations: NPPV = noninvasive positive-pressure ventilation; RCT = randomized controlled trial

Conclusions

In summary, for patients with acute respiratory failure due to severe exacerbations of COPD or congestive heart failure, NPPV plus supportive care shows important reductions in mortality and intubation rates compared with supportive care alone. BPAP has been studied more rigorously, but direct comparisons of CPAP and BPAP in patients with ACPE show similar efficacy. Current evidence suggests potential benefit for patients with acute respiratory failure who are postoperative or post-transplant and as a method to facilitate weaning from invasive ventilation or prevent recurrent postextubation respiratory failure in those at high risk. However, the evidence for these indications is much weaker. Limited evidence shows similar treatment effects across different settings and the possibility of less benefit in trials designed to replicate usual clinical practice. There is a clear need for further studies in patient populations where NPPV has not been rigorously studied and to understand the role of training and effectiveness when used as part of routine clinical care.

Glossary

ACPE acute cardiogenic pulmonary edema
AHRQ Agency for Healthcare Research and Quality
APACHE Acute Physiology And Chronic Health Evaluation

BPAP	bilevel positive airway pressure
CER	comparative effectiveness review
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
ED	emergency department
ICU	intensive care unit
KQ	Key Question
MeSH	medical subject headings
NPPV	noninvasive positive-pressure ventilation
OR	odds ratio
PaCO2	partial pressure of carbon dioxide in blood
PaO2	partial pressure of oxygen in arterial blood
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomized controlled trial
SAPS	Simplified Acute Physiology Score
TEP	Technical Expert Panel
TOO	Task Order Officer

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Introduction

Background

Acute respiratory failure is the most common reason for admission to an intensive care unit (ICU), accounting for approximately 800,000 ICU admissions annually in the United States.[1,2] Epidemiological studies have estimated the annual incidence of acute respiratory failure to be between 77.6 and 430 patients per 100,000.[1,3-5] The estimated health care costs related to critical care are approximately 0.7 percent of the annual gross domestic product, and the human and financial costs are only expected to increase with an aging population.[6-9]

Until the past couple of decades, invasive mechanical ventilation has been the standard of care treatment for acute respiratory failure. Noninvasive positive-pressure ventilation (NPPV), a newer modality of respiratory support, has been evaluated in a large number of trials, often with clinically important benefits, but use of NPPV remains highly variable across institutions and geographical regions.[10-14] This comparative effectiveness review (CER) was commissioned by the Agency for Healthcare Research and Quality (AHRQ) to evaluate the evidence for NPPV versus other typical treatments for acute respiratory failure. We anticipate that clinicians involved in medical and surgical critical care medicine, emergency medicine, and anesthesiology, along with developers of clinical practice guidelines, will be the primary audience for this report.

Acute Respiratory Failure

Respiratory failure is a syndrome characterized by the inability to maintain normal gas exchange due to dysfunction of the respiratory system. In its most basic sense, the respiratory system is comprised of a gas exchanging organ (lung) and a ventilatory pump (respiratory muscles and controllers, chest wall). Respiratory failure is further classified based on failure of one or both of these elements, as well as the timing of such failure.

Type I (hypoxemic) respiratory failure represents a failure of the gas exchange organ and is characterized by a low partial pressure of oxygen in arterial blood (PaO2) with a normal or low partial pressure of carbon dioxide in arterial blood (PaCO2). Type I is the most common form of respiratory failure and generally involves filling or collapse of lung tissue in disorders such as pulmonary edema and pneumonia. Inability of the lungs and breathing muscles to pump air leads to type II respiratory failure, which is characterized by a high PaCO2, as seen in conditions such as asthma and neuromuscular disease. Respiratory failure is further defined by the timing of the development of respiratory dysfunction. Acute respiratory failure develops over minutes to several days. Respiratory failure is deemed chronic when derangements occur over several days or longer. Acute-on-chronic respiratory failure occurs when a patient with chronic respiratory failure suffers an acute deterioration in gas exchange; this is most commonly seen in patients with severe chronic obstructive pulmonary disease (COPD). Table 1 presents a limited list of causes of respiratory failure, as well as some of the general underlying physiological mechanisms.

Table 1. Sample causes of respiratory failure and associated physiological mechanisms

Type of Respiratory Failure (With Examples)	Comments
Type I (hypoxemic) respiratory failure CHF (cardiogenic pulmonary edema) Noncardiogenic pulmonary edema (e.g., ARDS) Pneumonia Aspiration Atelectasis Pneumothorax Trauma/contusion Pulmonary embolism Interstitial lung disease (e.g. idiopathic pulmonary fibrosis)	"Lung failure" may be due to ventilation-perfusion mismatch, anatomic or physiologic shunt, diffusion impairment, etc.
Type II (hypercapnic) respiratory failure Asthma COPD Neuromuscular weakness (e.g., ALS) Sedative drug toxicity/anesthesia Sleep disordered breathing Obesity hypoventilation syndrome Multiple rib fractures (e.g., flail chest) Kyphoscoliosis Brainstem stroke or trauma	"Respiratory pump" failure may be due to airflow obstruction, respiratory muscle weakness, mechanical chest wall defect, lack of respiratory drive, etc.

Abbreviations: ALS = amyotrophic lateral sclerosis; ARDS = acute respiratory distress syndrome; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease

These definitions, however, are not rigid, as many disease states demonstrate mixed physiology, and the workings of the lung and the ventilatory pump do not ultimately exist in isolation. For example, in actual clinical practice, almost *all* patients with acute respiratory failure are hypoxemic and are distinguished by a normal or low blood level of carbon dioxide (type I) as opposed to an elevated blood level of carbon dioxide (type II). Furthermore, traditional definitions of acute respiratory failure rely on arbitrary blood gas values and may not account for preexisting cardiopulmonary disease (as might be evidenced by polycythemia or cor pulmonale for chronic hypoxemic failure or renal compensation for chronic hypercapnic failure). More recent descriptions of acute respiratory failure incorporate clinical findings such as tachypnea, cyanosis, and use of accessory muscles, but may not fully appreciate the spectrum of presentations. For the purposes of this report, we used a more inclusive definition of acute respiratory failure, namely: *a significant change in a patient's baseline gas-exchange status (given the constellation of available clinical data) that occurs relatively suddenly (usually hours to days) and is potentially life-threatening, but which does not require emergent intubation.*

Treatment Strategies

Management of Respiratory Failure

The management of acute respiratory failure begins with efforts to identify the underlying etiology and an initial decision about the need for emergent invasive ventilation. Among the more common indications for emergent ventilation are cardiac arrest or shock, apnea, and need for airway protection (e.g., coma or seizures). For patients who do not require emergent ventilation, supportive care with supplemental oxygen is a mainstay of therapy. The use of medications (e.g., antibiotics, corticosteroids, beta-agonists, diuretics) is common but is dependent on identifying the underlying disorder. Unless a patient's condition is rapidly

reversible, these conservative measures often fail to improve gas exchange or decrease the work of breathing sufficiently to prevent further deterioration and death. In such cases, acute respiratory failure is severe enough to require respiratory support. Invasive ventilation (also known as conventional mechanical ventilation) is a form of life support in which positive pressure delivers a mixture of air and oxygen through an endotracheal or tracheostomy tube to central airways. Invasive ventilation offers multiple modes and settings and can provide variable levels of respiratory support. Despite the life-saving potential of invasive ventilation in patients with respiratory failure, up to 40 percent of patients die in the hospital; some of these deaths are directly attributable to the complications of invasive ventilation and artificial airways.[15-18] Additionally, many survivors of acute respiratory failure require prolonged invasive ventilation and suffer persistent decrements in quality of life and functional independence.[19-21]

NPPV as an Alternative Management Strategy

An increasingly recognized option in the management of patients who do not require emergent invasive ventilation for acute respiratory failure is NPPV. NPPV refers to a form of mechanical support in which positive pressure delivers a mixture of air and oxygen throughout the respiratory tree via a noninvasive interface. NPPV collectively includes several modalities of noninvasive ventilation, which can be delivered via a standard ICU ventilator or a portable device. Continuous positive airway pressure (CPAP) is applied throughout the respiratory cycle of a spontaneously breathing patient and is physiologically identical to constant positive end-expiratory pressure. Bilevel positive airway pressure (BPAP) delivers two pressure levels according to the respiratory cycle and improves ventilation, oxygenation, and alveolar recruitment. BPAP provides both an inspiratory positive airway pressure and a continuous expiratory positive airway pressure, and the difference between these reflects the volume of air displaced with each breath. NPPV can provide modes nearly identical to standard ICU ventilators, such as pressure, volume, assist control, or even proportional assist ventilation. Patient-ventilator interfaces for NPPV include a face mask, nasal mask or plugs, or a helmet that covers the head. Although the face mask may be less comfortable and more difficult to monitor for aspiration, it provides better physiological performance (less resistance to airflow and less air leak) when compared with nasal devices.[22,23]

The use of NPPV together with supportive care during the treatment of respiratory failure is attractive because it does not require either endotracheal intubation or moderate and/or deep sedation and can be safely initiated or discontinued as needed. It is also associated with few of the nosocomial complications recognized with endotracheal intubation, such as ventilator-associated pneumonia, critical illness-associated weakness, pneumothorax, delirium, and infections associated with the invasive monitoring that is typically required during invasive life support.[16,20] NPPV is not appropriate for some patients, such as those with cardiopulmonary arrest or shock, where greater airway control is required, or those with facial trauma, where the interface (e.g., mask) cannot be used appropriately.

Barriers to the Use of NPPV and Factors That May Affect Outcomes

Although NPPV has been a readily available modality since the early 1990s, use varies substantially across and within countries. Surveys in the United States have shown high variability in estimated use across hospitals.[14] Barriers to use include a lack of physician knowledge, low rates of perceived efficacy, lack of standard protocols and team-based care at some hospitals, and, among older clinicians, little training or experience with NPPV.[24] A specific

knowledge gap is uncertainty about the efficacy of NPPV for patients with acute respiratory failure for conditions other than COPD or ACPE.

NPPV is a resource-intensive modality and requires a substantial amount of training and experience to implement successfully. Optimal use requires coordination between respiratory therapists, nurses, and physicians to identify patients appropriate for NPPV treatment and to initiate and monitor response to treatment. Monitoring NPPV patients requires a significant time outlay for therapists because the severely ill patient does not have a protected airway. The patient receiving NPPV often requires more monitoring than one receiving invasive ventilation. In fact, there is a potential for harm if NPPV is applied or monitored improperly. Early in the course of NPPV, numerous adjustments must be made based on mask fit, patient-ventilator synchrony, and the ventilator settings themselves based on the patient's response to initial treatment. Since outcomes may be related to training and experience, some experts have questioned whether the beneficial effects of NPPV reported from randomized controlled trials (RCTs) are replicated when NPPV is used in routine practice. Differences in patient selection, the clinical setting and associated resources, use of protocols, and clinician training or experience could lead to important reductions in effectiveness when NPPV is implemented in more typical clinical settings.

Scope and Key Questions

Scope of This Review

The literature supporting the use of NPPV in the acute-care setting for respiratory failure has evolved over the last two decades.[17] Although there have been some exceptions, such as a 2010 meta-analysis examining NPPV in acute respiratory failure of multiple causes,[25] the use of NPPV has been most extensively studied in patients with acute respiratory failure due to COPD and congestive heart failure. Various professional societies have addressed NPPV in clinical practice guidelines; most of these address only the use of NPPV in COPD.[26] In addition to these two well-studied uses, there is increasing interest in determining if NPPV is beneficial for other causes of acute respiratory failure (e.g., asthma) or can shorten the duration of invasive mechanical ventilation, either as a method to facilitate early extubation or to treat or prevent extubation failure in high-risk groups.[25] Further, there is uncertainty about whether the beneficial effects demonstrated in RCTs are replicated in real-world settings where training, experience, organizational factors, and patient factors may differ substantially from the trials. For this reason, we conducted a systematic review that is inclusive of all major causes of acute respiratory failure and includes studies of NPPV used for weaning from invasive ventilation. Although real-world effects were of interest, we restricted our review to RCTs because RCTs give more valid estimates of comparative effectiveness. Further, our Technical Expert Panel (TEP) advised that observational studies were unsuitable for evaluating the comparative effectiveness of this treatment.

Key Questions

With input from the TEP, we constructed Key Questions using the general approach of specifying the population of interest, the interventions, comparators, outcomes, timing of outcomes, and settings (PICOTS; see the section on "Inclusion and Exclusion Criteria" in the Methods chapter for details). The Key Questions considered in this CER are:

KQ 1: Is noninvasive positive-pressure ventilation (NPPV) associated with less morbidity (including from intubation), lower mortality, fewer adverse events, or lower medical utilization when compared with supportive medical therapy or invasive ventilation:

a. In adults with chronic obstructive pulmonary disease (COPD) and acute respiratory failure?
b. In adults with acute cardiogenic pulmonary edema (ACPE)?
c. In adults with acute respiratory failure due to other causes including: pneumonia, asthma, obesity-hypoventilation syndrome, and interstitial lung disease?
d. In adults with acute respiratory failure in selective settings including: postoperative setting and post-transplant setting?

KQ 2: Is NPPV with bilevel positive airway pressure (BPAP), compared with NPPV with continuous positive airway pressure (CPAP), associated with less morbidity, lower mortality, fewer adverse events, or lower medical utilization:

a. In adults with COPD and acute respiratory failure?
b. In adults with ACPE?
c. In adults with acute respiratory failure due to other causes including: pneumonia, asthma, obesity-hypoventilation syndrome, and interstitial lung disease?
d. In adults with acute respiratory failure in selective settings including: postoperative setting and post-transplant setting?

KQ 3: Is early extubation to NPPV, compared with usual care, associated with less morbidity, lower mortality, fewer adverse events, or lower medical utilization:

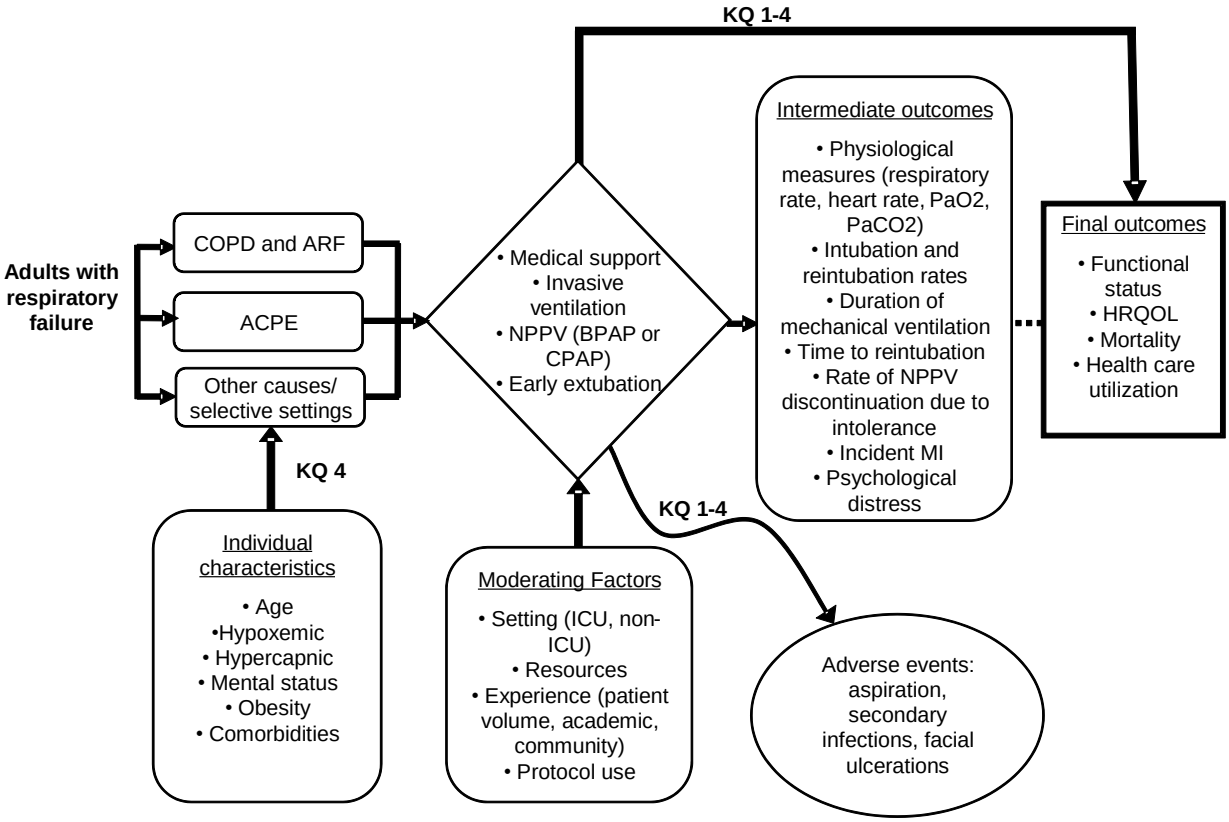
a. In adults with COPD and acute respiratory failure?
b. In adults with ACPE?
c. In adults with acute respiratory failure due to other causes including: pneumonia, asthma, obesity-hypoventilation syndrome, and interstitial lung disease?
d. In adults with acute respiratory failure in selective settings including: postoperative setting and post-transplant setting?

KQ 4: For KQs 1–3, do the effectiveness and risks of NPPV vary by setting and associated resources, experience and training of clinicians, and use of protocols or by patient characteristics (e.g., morbid obesity, mental-status changes, overall disease burden)?

Analytic Framework

Figure 1 shows the analytic framework for this project.

Figure 1. Analytic framework



Abbreviations: ACPE = acute cardiogenic pulmonary edema; ARF = acute respiratory failure; BPAP = bilevel positive airway pressure; COPD = chronic obstructive pulmonary disease; CPAP = continuous positive airway pressure; HRQOL = health-related quality of life; ICU = intensive care unit; KQ = Key Question; MI = myocardial infarction; NPPV = noninvasive positive-pressure ventilation; PaCO2 = partial pressure of carbon dioxide in blood; PaO2 = partial pressure of oxygen in arterial blood.

This figure depicts the KQs within the context of the PICOTS described above. In general, the figure shows that this CER compares morbidity, mortality, adverse events, and health care utilization for patients receiving NPPV with supportive medical therapy or invasive ventilation (KQ 1), patients receiving NPPV with BPAP with NPPV with CPAP (KQ 2), and patients receiving early extubation to NPPV with those receiving weaning strategies that do not utilize NPPV (KQ 3). Subgroups considered for KQs 1–3 included adults with COPD and respiratory failure; adults with ACPE; adults with acute respiratory failure due to pneumonia, asthma, obesity-hypoventilation syndrome, or interstitial lung disease; and adults with acute respiratory failure in postoperative or posttransplant settings. Adverse events considered are aspiration, secondary infections (including pneumonia and sinusitis), and facial ulcerations. Intermediate outcomes included physiological measures (respiratory rate, heart rate, PaO2, and PaCO2); intubation and reintubation rates; duration of mechanical ventilation; time to reintubation; rate of NPPV discontinuation due to intolerance; incident myocardial infarction; and psychological

distress. Final outcomes assessed are functional status, health-related quality of life, mortality (in-hospital and 30-day), and health care utilization (ventilator-dependent days, rate of ventilator dependence at hospital discharge, length of hospital stay, length of intensive care unit stay, and total hospital costs). The report also considers whether the effectiveness and risks outlined in KQs 1–3 vary by setting and associated resources, experience and training of the clinicians, use of protocols, or by patient characteristics (e.g., mental status, obesity, and comorbidities).

Methods

The methods for this comparative effectiveness review (CER) follow those suggested in the Agency for Healthcare Research and Quality (ARHQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews (hereafter referred to as the Methods Guide).[27] All methods and analyses were guided by a protocol, which was developed as described immediately below.

Topic Refinement and Review Protocol

During the topic refinement stage, we solicited input from a group of Key Informants (KIs) representing medical professional societies/clinicians in the areas of pulmonology, critical/intensive care, and respiratory therapy; scientific experts; payers; and Federal agencies to help define the Key Questions (KQs). These KQs were posted on AHRQ's Web site for public comment for 4 weeks, beginning in late December 2010. The comments received were considered in the revision of the KQs and in the development of the research protocol. We next convened a Technical Expert Panel (TEP) to provide input on defining populations, interventions, comparisons, and outcomes, as well as for identifying particular studies or databases to search. The TEP members provided the same range of viewpoints and expertise as are described for the KI group, with the addition of a methodologist with experience in trial efficacy-effectiveness assessment. The KIs and members of the TEP were required to disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Any potential conflicts of interest were balanced or mitigated. KIs and members of the TEP did not perform analyses of any kind or contribute to the writing of the report. All methods and analyses were guided by the protocol; certain methods map to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[28]

Literature Search Strategy

Search Strategy

We searched PubMed®, Embase®, and the Cochrane Database of Systematic Reviews to identify relevant published literature. Our search strategies used the National Library of Medicine's medical subject headings (MeSH) keyword nomenclature and text words for noninvasive positive-pressure ventilation (NPPV) and eligible study designs. We used validated search filters for randomized study designs where possible (the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version [2008 revision] in PubMed, and the Cochrane search filter for identifying randomized trials in Embase[29]). We included studies conducted in adults and published in English from 1990 on. We limited studies to 1990 forward because standards of care have changed significantly since 1990. Search dates and the exact search strings used for each database are given in Appendix A. All searches were designed and conducted in collaboration with an experienced search librarian.

We supplemented the electronic searches with a manual search of citations from a set of key primary and review articles.[25,30-49] All citations were imported into an electronic bibliographic database (EndNote® Version X4; Thomson Reuters, Philadelphia, PA).

As a mechanism to ascertain publication bias, we searched ClinicalTrials.gov to identify completed but unpublished studies (see Appendix A for search date and the exact search string used).

We used two approaches to identifying relevant grey literature: 1) a request for scientific information packets submitted to device manufacturers; and 2) a request submitted to the U.S. Food and Drug Administration for any unpublished randomized controlled trial (RCT) data available for devices used to provide noninvasive positive-pressure ventilation.

Inclusion and Exclusion Criteria

The PICOTS (population, interventions, comparators, outcomes, timing, and settings) criteria used to screen articles for inclusion/exclusion at both the title-and-abstract and full-text screening stages are detailed in Table 2. In general, our inclusion criteria were deliberately broad with respect to the definition of acute respiratory failure and etiologies of acute respiratory failure. We limited the setting to hospitals and emergency departments, settings where NPPV is a practical treatment option for acute respiratory failure. NPPV used for weaning was conceptualized broadly to include use for early extubation and to prevent or treat respiratory failure postextubation. We included studies of any duration, but required at least one of our specified final outcomes for inclusion.

Table 2. Inclusion/exclusion criteria

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Population	Adults (age ≥ 18 years) with: • COPD and acute respiratory failure • ACPE • Acute respiratory failure due to other causes including: pneumonia, asthma, obesity-hypoventilation syndrome, and interstitial lung disease • Acute respiratory failure in selective settings including: postoperative setting and post-transplant setting	• Population composed entirely of children (< 18 years of age) • Adult populations where NPPV is contraindicated, such as cardiopulmonary arrest, shock, and facial trauma
Interventions	• NPPV including CPAP, BPAP, and closely related noninvasive positive airway pressure modes delivered through any interface (e.g., face mask, nasal mask or plugs, or a helmet that covers the head)	• Invasive ventilation only

Table 2. Inclusion/exclusion criteria (continued)

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Comparators	KQs 1, 2 and 4: • Supportive care, invasive ventilation, or another form of NPPV KQ 3: • Any approach to weaning that does not utilize NPPV	• No comparator

Outcomes	A clinical or utilization-related outcome of interest, including:
	• Intermediate outcomes:
	  ○ Physiological measures such as respiratory rate, heart rate, PaO2, and PaCO2 (KQs 1–3)
	  ○ Intubation (KQs 1, 2, 4) and reintubation (KQs 3, 4) rates; duration of mechanical ventilation (KQs 1–4); and time to reintubation (KQ 3)
	  ○ Rates of discontinuing NPPV secondary to the patient being unable to tolerate the treatment (KQs 1–4)
	  ○ Incident myocardial infarction (KQs 1–3)
	  ○ Psychological distress (e.g., anxiety) assessed by using a validated measure
	
	• Final outcomes:
	  ○ Functional status measured by using a validated questionnaire or performance-based measure at hospital discharge or the 30-day followup (KQs 1, 3, 4)
	  ○ Health-related quality of life measured using a validated questionnaire at hospital discharge or the 30-day followup (KQs 1, 3, 4)
	  ○ In-hospital and 30-day mortality rates (KQs 1–3)
	  ○ Medical utilization (KQs 1–4), including ventilator-dependent days, rate of ventilator dependence at hospital discharge, length of hospital stay, length of ICU stay, and total hospital costs
	
	• Adverse events (KQs 1–4), including rates of:
	  ○ Aspiration
	  ○ Secondary infections (including pneumonia, sinusitis)
	  ○ Facial ulcerations
		• No relevant clinical or utilization-related outcome of interest reported (note that studies reporting only physiological measures such as respiratory rate, heart rate, PaO2, and PaCO2 were excluded)

Timing	• Studies of any duration	• None
Setting	Hospital settings, including: • ICUs • Emergency departments • Postoperative and posttransplant settings • General medical units	• Non-medical settings such as home use • Long-term care settings such as nursing homes • Perioperative uses to prevent acute respiratory failure

Table 2. Inclusion/exclusion criteria (continued)

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Study design	RCTs	• Non-RCT study designs[a] • Not a clinical study (e.g., editorial, nonsystematic review, letter to the editor, case series)
Publications	Published literature: • English-language only[b] • Published from 1990 on[c] • Peer-reviewed article Gray literature: • Report must be publicly available and have sufficient detail for abstraction (e.g., a full report similar in detail and quality to peer-reviewed literature)	• Non-English language publication[b] • Not published in peer-reviewed literature or one of the specified grey literature sources (Scientific Information Packets; FDA analyses) • Published before 1990[c]

[a]Although non-RCTs may be particularly pertinent to addressing effectiveness, confounding by indication makes it unlikely that these studies would yield a valid estimate of effect.
[b]English language: Given the high volume of literature available in English-language publications (including the majority of known important studies), and concerns about the applicability of non-English publication studies to settings in the United States, we excluded non-English articles.
[c]The rationale for this was that standards of care have changed significantly since 1990.
Abbreviations: Abbreviations: ACPE = acute cardiogenic pulmonary edema; BPAP = bilevel positive airway pressure; COPD = chronic obstructive pulmonary disease; CPAP = continuous positive airway pressure; FDA = U.S. Food and Drug Administration; ICU = intensive care unit; KQ = Key Question; NPPV = noninvasive positive-pressure ventilation; PaCO2 = partial pressure of carbon dioxide in blood; PaO2 = partial pressure of oxygen in arterial blood; RCT = randomized controlled trial

Study Selection

Using the criteria described in Table 2, two investigators independently reviewed each title and abstract for potential relevance to the KQs; articles included by either investigator underwent full-text screening. At the full-text screening stage, two investigators independently reviewed the full text of each article and indicated a decision to "include" or "exclude" the article for data abstraction. When the paired reviewers arrived at different decisions about whether to include or exclude an article, or about the reason for exclusion, we reached a final agreement through review and discussion among investigators. Full-text articles meeting eligibility criteria were included for data abstraction.

For citations retrieved by searching the grey literature or ClinicalTrials.gov, these procedures were modified such that a single screener initially reviewed all citations; final eligibility for data abstraction was determined by duplicate screening review. All screening decisions were made and tracked in a Distiller SR database (Evidence Partners Inc., Manotick, ON, Canada).

Data Extraction

The investigative team created forms for abstracting the data elements for the KQs. Based on their clinical and methodological expertise, a pair of researchers was assigned to abstract data from the eligible articles. One researcher abstracted the data, and the second reviewed the completed abstraction form alongside the original article to check for accuracy and completeness. Disagreements were resolved by consensus or by obtaining a third reviewer's opinion if consensus could not be reached by the first two investigators.

To aid in both reproducibility and standardization of data collection, researchers received data abstraction instructions directly on each form created specifically for this project within the DistillerSR database. The abstraction form templates were pilot-tested with a sample of included articles to ensure that all relevant data elements were captured and that there was consistency and reproducibility across abstractors.

We designed the data abstraction forms for this project to collect the data required to evaluate the specified eligibility criteria for inclusion in this review, as well as demographic and other data needed for determining outcomes (intermediate, final, and adverse events outcomes). We paid particular attention to describing the details of the intervention (e.g., NPPV interface); the training, experience, and disciplines of the treating clinicians; patient characteristics (e.g., etiology of acute respiratory failure); and study design (e.g., efficacy-effectiveness spectrum using a 7-item instrument[50]) that might affect outcomes.

We used the efficacy-effectiveness instrument (Appendix B) to assess seven domains: population and setting, restrictiveness of eligibility criteria, health outcomes, flexibility of the intervention and study duration, assessment of adverse effects, adequate sample size for important health outcomes, and intention-to-treat approach to analyses. We developed definitions for each domain that were specific to the literature reviewed. We rated each of the seven items as effectiveness (score = 1) or efficacy (score = 0); scores were summed and could range from 0 to 7. Final efficacy-effectiveness scores were based on the mean of two independent ratings, after resolving any scoring disagreements ≥ 2.

We classified the etiology of acute respiratory failure based on study inclusion criteria (e.g., acute respiratory failure secondary to COPD) and the description of included patients. When the etiology was mixed, we classified the study by a single condition if at least 70 percent of the sample had that condition; otherwise, the sample was described as "mixed."

We prioritized abstraction of clinical outcomes reported for the duration of the ICU or hospital stay, along with any longer term outcomes. Some outcomes were reported only in figures. In these instances, we used the Web-based software, EnGauge Digitizer (digitizer.sourceforge.net/) to convert graphical displays to numerical data. In addition, we described comparators (especially supportive therapy) as carefully as possible given the sometimes limited information provided in the study publications, as treatment standards may have changed during the period covered by this review. The safety outcomes were framed to help identify adverse events, including hospital-acquired pneumonia and facial ulcerations. We also abstracted the data necessary for assessing quality and applicability, as described in the General Methods Guide.[27] Appendix C provides a detailed listing of the data elements abstracted.

Quality (Risk of Bias) Assessment of Individual Studies

To assess the risk of bias/methodological quality of individual studies, we used the key criteria for RCTs described in the Methods Guide[27] and adapted for this specific topic. These criteria include adequacy of randomization and allocation concealment, comparability of groups at baseline, blinding, completeness of followup and differential loss to followup, whether incomplete data were addressed appropriately, validity of outcome measures, and conflict of interest. These general criteria were customized for each major outcome (see part Appendix C, section VII, for details).

To indicate the summary judgment of the quality of the individual studies, we used the summary ratings of good, fair, and poor, based on the studies' adherence to well-accepted standard methodologies and the adequacy of the reporting (Table 3). For each study, one

investigator assigned a summary quality rating, which was then reviewed by a second investigator; disagreements were resolved by consensus or by a third investigator if agreement could not be reached.

Table 3. Definitions of overall quality ratings

Quality Rating	Description
Good	A study with the least bias; results are considered valid. A good study has a clear description of the population, setting, interventions, and comparison groups; uses a valid approach to allocate patients to alternative treatments; has a low dropout rate; and uses appropriate means to prevent bias, measure outcomes, and analyze and report results.
Fair	A study that is susceptible to some bias but probably not enough to invalidate the results. The study may be missing information, making it difficult to assess limitations and potential problems. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses. The results of some fair-quality studies are possibly valid, while others are probably valid.
Poor	A study with significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; have large amounts of missing information; or have discrepancies in reporting. The results of a poor-quality study are at least as likely to reflect flaws in the study design as to indicate true differences between the compared interventions.

Data Synthesis

We began by summarizing key features of the included studies for each KQ. To the degree that data were available, we abstracted information on study design; patient characteristics; medical settings; clinician disciplines, experience, or training; type of NPPV, including the interface; and intermediate, final, and adverse events outcomes.

We then determined the feasibility of completing a quantitative synthesis (i.e., meta-analysis). Feasibility depended on the volume of relevant literature, the conceptual homogeneity of the studies, and the completeness of the reporting of results. Based on the frequency of reported outcomes and the relative importance of these outcomes, we determined that quantitative syntheses were indicated for: mortality, intubation or reintubation, myocardial infarction, and hospital-acquired pneumonia; other outcomes were summarized using descriptive statistics. Length of stay was analyzed qualitatively because the data reported for this outcome were often highly skewed, and because this outcome is biased due to the mortality benefit associated with NPPV treatment. For this qualitative synthesis, we focused our analysis on the larger studies that had greater power to detect a clinically and statistically significant difference in length of stay. We did not synthesize physiological outcomes because there were sufficient data to draw conclusions based on final outcomes and more clinically relevant intermediate outcomes. Other clinical outcomes that were reported infrequently, such as rates of sinusitis, facial ulceration and discontinuation due to intolerance, are summarized descriptively.

For the outcomes selected for meta-analysis, we used random-effects models to synthesize the evidence quantitatively using the Comprehensive Meta-Analysis software (Version 2; Biostat, Englewood, NJ). When outcomes were reported at multiple time points, we used the longest in-hospital followup duration (e.g., in-hospital mortality instead of ICU mortality). The majority of outcomes considered in this report were binary or categorical; we therefore summarized these outcomes using a weighted effect measure for proportions (e.g., odds ratio [OR]) and 95 percent confidence intervals (CIs). When we found statistically significant effects, we calculated the risk difference (RD) by using the summary OR and median odds of events from the comparator arms of the included studies (presented in the relevant strength of evidence summary table in the Discussion chapter). If the summary OR varied substantially by study

quality, we used the OR from the good-quality studies for this calculation. We tested for heterogeneity using graphical displays and test statistics (Q and I^2 statistics), while recognizing that the ability of statistical methods to detect heterogeneity may be limited. When there were sufficient studies ($n \geq 10$), we assessed for publication bias using funnel plots and test statistics (Appendix D).[51] If these analyses suggested significant publication bias, we computed an adjusted summary estimate using Duval's trim-and-fill method.[52]

We anticipated that intervention effects may be heterogeneous. We hypothesized that the methodological quality of individual studies, efficacy-effectiveness score, the training or experience of the interventionists, the characteristics of the comparator, and patients' etiology of acute respiratory failure would be associated with the intervention effects. When there were sufficient studies, we performed subgroup analyses to examine these hypotheses. For these efficacy-effectiveness-analyses, we categorized studies as mostly efficacy (score of 0–2), mixed efficacy-effectiveness (score of 3–5), and mostly effectiveness (score of 6–7). Gartlehner et al. reported a sensitivity of 72 percent and specificity of 83 percent using a threshold of 6 or higher to identify effectiveness studies.[50] Since European countries have a longer experience with NPPV, and few studies reported the training or experience of clinicians delivering NPPV, we used the global geographical location as a proxy for experience. In addition to these analyses, we summarized qualitatively any relevant subgroup analyses reported in the primary studies.

We conducted a secondary, mixed-treatment meta-analysis to address the effects of CPAP, BPAP (KQ 2), and invasive ventilation compared with supportive therapy by using both direct and indirect comparisons. Mortality is a dichotomous outcome and was fitted using multiple logistic regression analysis. Dummy variables were used for study differences, and treatment variables were used for the three-treatment effects (CPAP, BPAP, and supportive care). A random-effects model was fitted using the EGRET® software (EGRET for Windows, 1999; Cytel Software Corporation, Cambridge, MA) which estimates both fixed-effect and random-effects parameters and automatically generates the dummy variables for each study ("Logistic-Normal Regression Model" option). Hasselblad 1998[53] describes the application of this methodology to meta-regression problems.

Strength of the Body of Evidence

We graded the strength of evidence for each outcome assessed using the approach described in the Methods Guide.[27,54] In brief, this approach requires assessment of four domains: study quality (risk of bias), consistency, directness, and precision. Additional domains considered were strength of association (magnitude of effect) and publication bias. For risk of bias we considered basic (e.g., RCT) and detailed study design (e.g., adequate randomization). For directness, we considered whether the interventions of interest were compared directly (i.e., head-to-head) and the directness of the specific outcome vis-à-vis our Key Questions. For example, we considered ICU length of stay to be an indirect outcome because it does not capture overall resource utilization, including the time and personnel required to implement NPPV. We used results from meta-analyses when evaluating consistency (forest plots, tests for heterogeneity), precision (CIs), strength of association (OR), and publication bias (funnel plots and test statistics). Optimal information size (a method that considers whether the number of events are sufficient to protect against random error) and considerations of whether the CI crossed the clinical decision threshold using a therapy were also used when evaluating precision.[55] These domains were considered qualitatively, and a summary rating of "high," "moderate," or "low" strength of evidence was assigned after discussion by two reviewers. In some cases, high, moderate, or low

ratings were impossible or imprudent to make, for example, when no evidence was available or when evidence on the outcome was too weak, sparse, or inconsistent to permit any conclusion to be drawn. In these situations, a grade of "insufficient" was assigned. This four-level rating scale consists of the following definitions:

- High—High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate—Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- Low—Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
- Insufficient—Evidence either is unavailable or does not permit estimation of an effect.

Applicability

Systematic evidence reviews are conducted to summarize knowledge and to support clinicians, patients, and policymakers in making informed decisions. "Does this information apply?" is the core question for decisionmakers weighing the usefulness and value of a specific intervention or choosing among interventions. Interventions that work well in one context may not in another. The primary aim of assessing applicability is to determine whether the results obtained under research conditions are likely to reflect the results that would be expected in broader populations under "real-world" conditions. In this particular instance, we focused on application to populations cared for in hospital settings.

We assessed applicability directly in KQ 4 (effect of setting, experience, and patient characteristics) and by using the methods described in the Methods Guide.[27,56] In brief, the latter methods use the PICOTS (Population, Intervention, Comparator, Outcome, Timing, Setting) format as a way to organize information relevant to applicability. The most important issue with respect to applicability is whether the outcomes are different across studies that recruit different populations (e.g., age groups, exclusions for obesity) or use different methods to implement the intervention (e.g., strict clinical or training protocols). That is, important characteristics are those that affect baseline (control-group) rates of events, intervention-group rates of events, or both. We used a checklist to guide the assessment of applicability (Appendix C, section VIII). We used these data to evaluate the applicability to clinical practice, paying special attention to study eligibility criteria, demographic features of the enrolled population in comparison with the target population, characteristics of the intervention used in comparison with care models currently in use, and clinical relevance and timing of the outcome measures. We summarize issues of applicability qualitatively.

Peer Review and Public Commentary

The peer review process was our principal external quality-monitoring device. Nominations for peer reviewers were solicited from several sources, including the TEP and interested Federal agencies. Experts in pulmonology and critical care, along with individuals representing stakeholder and user communities, were invited to provide external peer review of the draft report; AHRQ and an associate editor also provided comments. The draft report was posted on AHRQ's Web site for public comment for 4 weeks, from January 20, 2012, to February 17, 2012. We have addressed all reviewer comments, revising the text as appropriate, and have

documented everything in a disposition of comments report that will be made available 3 months after the Agency posts the final report on AHRQ's Web site. A list of peer reviewers submitting comments on the draft report is provided in the front matter of this report.

Results

Introduction

In what follows, we begin by presenting the results of our literature searches. We then provide a brief description of the included studies. The remainder of the chapter is organized by Key Question (KQ). Under each KQ, we begin by listing the key points of the findings, followed by a brief description of included studies, followed by a more detailed synthesis of the evidence. The detailed syntheses are organized by major outcome: mortality, rates of intubation or reintubation, myocardial infarction, hospital-acquired pneumonia, length of stay, and other clinical outcomes. We conducted quantitative analyses (i.e., meta-analyses) where possible, as described in the Methods chapter. Results of these analyses are presented graphically in the form of forest plots, and in tabular format.

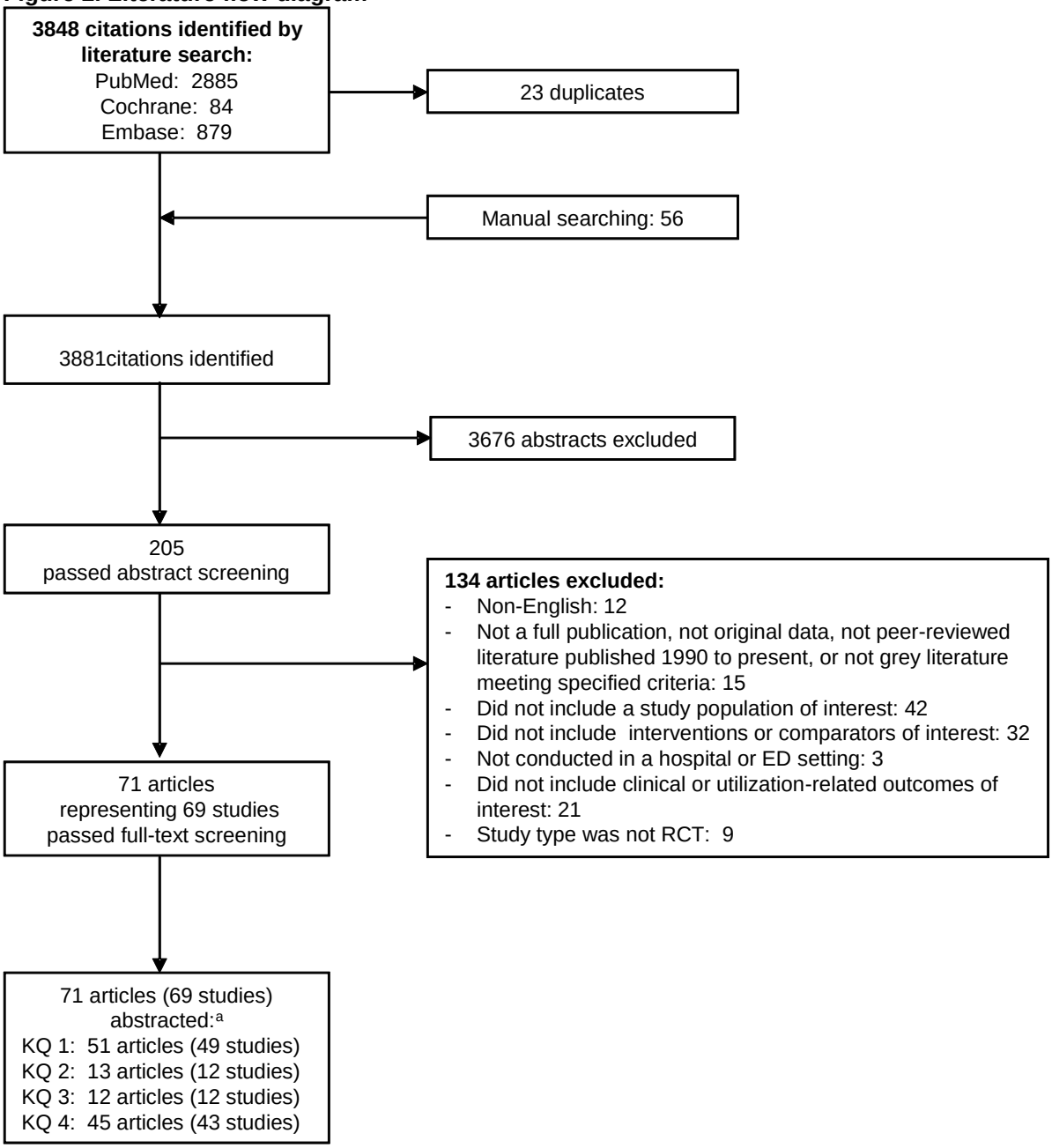
A list of abbreviations and acronyms used in this chapter is provided at the end of the report.

Results of Literature Searches

Figure 2 depicts the flow of articles through the literature search and screening process. Searches of PubMed®, Embase®, and the Cochrane Database of Systematic Reviews yielded 3848 citations, 23 of which were duplicate citations. Manual searching identified 56 additional citations, for a total of 3881 citations. After applying inclusion/exclusion criteria at the title-and-abstract level, 205 full-text articles were retrieved and screened. Of these, 134 were excluded at the full-text screening stage, leaving 71 articles (representing 69 unique studies) for data abstraction. As indicated in Figure 2, many articles/studies were relevant to more than one KQ. The two information request strategies described in the Methods chapter (contacts to device manufacturers and the U.S. Food and Drug Administration) did not result in any additional data for consideration.

Appendix E provides a detailed listing of included articles. Appendix F provides a complete list of articles excluded at the full-text screening stage, with reasons for exclusion.

Figure 2. Literature flow diagram



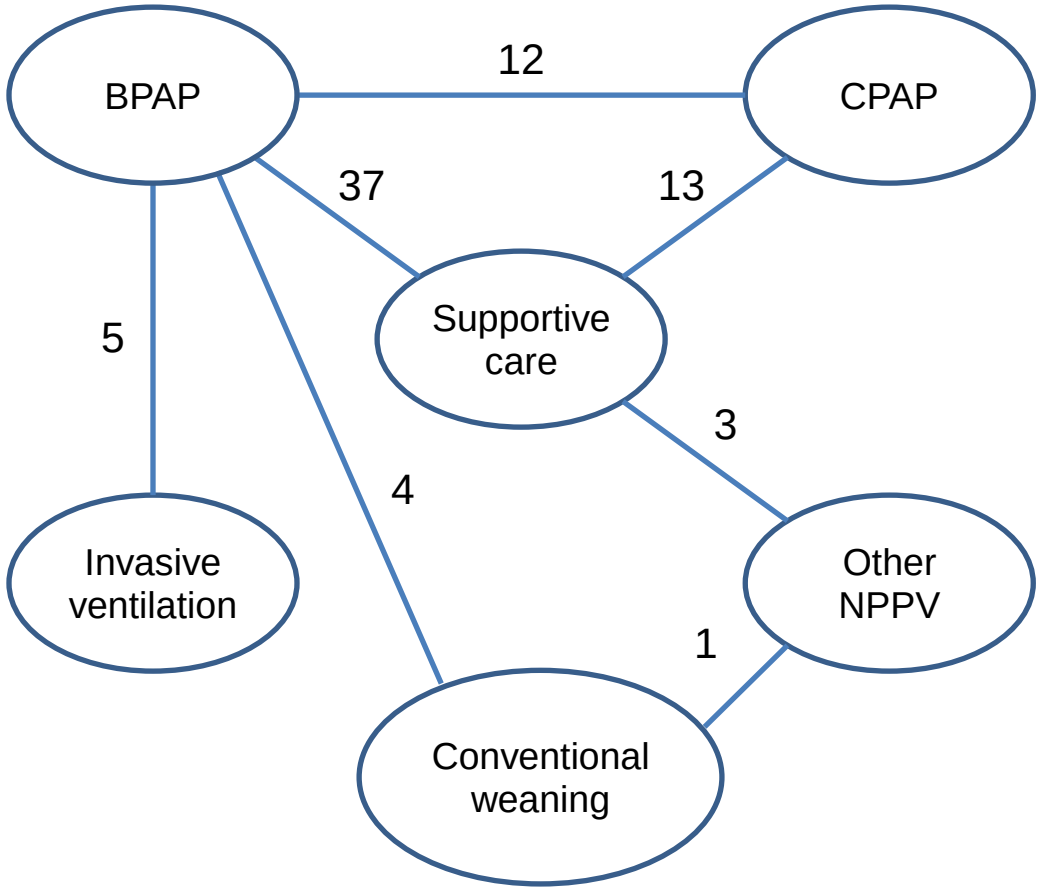
[a]Some studies/articles were included for more than one KQ, so that numbers given in this box total to more than 71 articles/69 studies.
Abbreviations: ED = emergency department; KQ = Key Question; RCT = randomized controlled trial

Description of Included Studies

Overall, we included 69 studies, some of which were relevant to more than one KQ: 49 studies were relevant to KQ 1, 12 to KQ 2, and 12 to KQ 3. Studies were conducted in Europe (61%); Asia (19%); the United States or Canada (12%); and South America, Australia, Africa, or multiple continents (8%). One-third of studies enrolled patients with acute cardiogenic pulmonary edema (ACPE) and another one-third patients with acute respiratory failure due to chronic obstructive pulmonary disease (COPD). Noninvasive positive-pressure ventilation (NPPV) was evaluated infrequently in patients with asthma (5%) and in patients with acute respiratory failure in the postoperative (3%) or post-transplant setting (3%).

Figure 3 maps the direct comparisons between treatments evaluated in this report. The most common comparisons were between bilevel positive airway pressure (BPAP) and supportive care (49% of comparisons), followed by continuous positive airway pressure (CPAP) versus supportive care (17%) and BPAP versus CPAP (16%). Relatively few studies compared any mode of NPPV with invasive ventilation or to conventional weaning (both 7%).

Figure 3. Treatment comparisons evaluated



Abbreviations: Abbreviations: BPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; NPPV = noninvasive positive-pressure ventilation

Of the 69 studies, 30 (43%) were judged to be of good quality, 31 (45%) of fair quality, and 8 (12%) of poor quality. Considering individual components of study design and conduct, strengths were comparable groups at baseline, good followup, and valid outcome measures. However, only about 50 percent of studies reported power or sample size calculations and clear procedures for random assignment and allocation concealment. Outcomes were not assessed by an observer blind to treatment allocation, but for some outcomes (e.g., death), lack of blinding is unlikely to bias results. One-quarter of studies were supported at least in part by industry; in another 50 percent, conflict of interest was not explicitly addressed.

Further details are provided in the relevant KQ results sections, below, and in Appendix G, which reports details of the characteristics of each included study, including geographical location, clinical setting, study population, intervention(s), comparator(s), and quality rating.

As described in the Methods chapter, we searched ClinicalTrials.gov to identify completed but unpublished studies as a mechanism for ascertaining publication bias. Our search yielded 125 citations. A single reviewer identified 34 of these as potentially relevant; 15 of these had been completed at least 1 year prior to our search of the published literature. Of these 15, 12 were not relevant to our KQs, and the remaining 3 were published and are among our included studies. Of the 17 studies not completed at least 1 year prior to our search of the published literature, 11 were relevant to one or more of our KQs. Eight of these 11 are ongoing (4 applicable to KQ 1; 4 applicable to KQ 3), 1 was terminated early due to mortality benefit, 1 was withdrawn prior to enrollment, and 1 has an indeterminate status. In summary, our search of ClinicalTrials.gov did not find evidence for completed but unpublished studies relevant to our KQs.

Key Question 1. NPPV Versus Supportive Care or Invasive Ventilation

KQ 1: Is noninvasive positive-pressure ventilation (NPPV) associated with less morbidity (including from intubation), lower mortality, fewer adverse events, or lower medical utilization when compared with supportive medical therapy or invasive ventilation:

a. In adults with chronic obstructive pulmonary disease (COPD) and acute respiratory failure?
b. In adults with acute cardiogenic pulmonary edema (ACPE)?
c. In adults with acute respiratory failure due to other causes including: pneumonia, asthma, obesity-hypoventilation syndrome, and interstitial lung disease?
d. In adults with acute respiratory failure in selective settings including: postoperative setting and post-transplant setting?

Key Points

- In patients treated for acute respiratory failure, current evidence supports a reduction in mortality when NPPV plus supportive care is used versus supportive care alone. This evidence is strongest for patients with COPD and ACPE, but limited evidence supports an effect in the postoperative and post-transplant settings.

- In patients treated for acute respiratory failure, current evidence supports a reduction in intubation rates when NPPV plus supportive care is used versus supportive care alone. This evidence is strongest for patients with COPD, but also supports an effect in patients with ACPE and in the postoperative and post-transplant settings.
- In patients treated for acute respiratory failure, current evidence supports a reduction in hospital-acquired pneumonia when NPPV plus supportive care is used versus supportive care alone. This evidence is strongest for patients with COPD.
- The evidence does not support an increase in rate of myocardial infarction related to NPPV.
- Evidence for treatment effects of NPPV in acute respiratory failure is sparse in many other etiologic subgroups, including acute respiratory distress syndrome (ARDS) and asthma.
- Effects of NPPV on medical utilization are uncertain.
- Outcomes for psychological response, functional status, or health-related quality of life were not reported. Duration of mechanical ventilation was reported infrequently.

Description of Included Studies

Forty-nine studies involving 4,527 patients met our inclusion criteria.[57-105] Study characteristics are summarized in Table 4. Six studies were conducted in the United States or Canada.[74,77,79,81,84,94] Of the 49 studies, 22 (45%) were of good methodological quality,[57-59,62-65,67,68,71-73,77,79,87,89,92,94,95,100,104,105] 21 (43%) were of fair quality,[61,66,70,74-76,78,80-85,88,90,91,93,96-99] and 6 (12%) were of poor quality.[60,69,86,101-103] Poor-quality studies tended to be older, smaller, single-center studies with limited reported data. In most instances, the funding source was not reported or was unclear.

Regarding the effects of NPPV, 43 studies reported mortality,[57-62,64,65,67-71,73,75-81,83-87,89-105] 39 studies reported intubation rates,[57,59-65,67-71,73,74,77-87,89-91,94,95,99-101,103,104 Wermke, 2011 #3676,105] 7 studies reported myocardial infarction,[62,67,71,81,87,94,100] and 8 studies reported rates of hospital-acquired pneumonia.[57,62,70,73,77,89,94,96] No studies reported effects on health-related quality of life or anxiety associated with NPPV use. Most studies enrolled patients with COPD or ACPE who were older adults, although the range of mean ages was broad (33.3 to 84.0). The proportion of females included ranged from 9–79 percent.

Of the 49 studies, 40 compared NPPV plus supportive medical therapy with supportive medical therapy alone, 5 compared NPPV with invasive ventilation,[58,66,75,76,98] and 4 were 3-arm trials comparing CPAP, BPAP, and supportive care.[67,71,86,99] BPAP was the most common modality used and, when described, was applied with an inspiratory pressure ranging from 6 to 20 cm H2O. CPAP was provided across a range of 2 to 12.5 cm H2O. NPPV was delivered by a helmet interface in one study, through mixed approaches in three, by nasal mask in nine, and by full mask in the remainder of studies. Only three studies[71,72,105] described training or provider experience and these studies reported substantial training or high levels of experience with NPPV among providers, and 12 described the type of provider adjusting NPPV; these providers included generalist and critical care trained physicians, nurses, and respiratory therapists.

Table 4. Study characteristics for comparisons of NPPV versus supportive care or invasive ventilation

Characteristic	NPPV Vs. Supportive Care	NPPV Vs. Invasive Ventilation
Mean age of sample: Median (range)	68.4 (33.3 to 84.0)	67.4 (54.5 to 71.9)
Sex: N (%)		
Male	1837 (45%)	234 (58%)
Female	1715 (42%)	112 (28%)
Not reported	570 (13%)	59 (15%)
Race: N (%)		
African-American	30 (< 1%)	0
White	75 (2%)	0
Other	17 (< 1%)	0
Not reported	4000 (97%)	405 (100%)
Morbidity index: Median (range)		
APACHE II	18.0 (10.7 to 20.5); 15 studies	24.5 (23.5 to 24.5); 3 studies
SAPS	24.3 (12.0 to 43.5); 12 studies	12.4 (NR); 1 study
Not reported	17 studies	0 studies
Setting: No. of studies (N)		
ICU	18 (994)	5 (405)
ED	10 (1616)	0
Postoperative	2 (257)	0
Mixed/Other	14 (1255)	0
NPPV modality: No. of studies (N)		
BPAP	28 (1893)	5 (405)
CPAP	9 (725)	0
Mixed/Other	7 (1504)	0
Diagnoses: No. of studies (N)		
COPD	15 (1228)	3 (277)
ACPE	14 (1926)	0
Asthma	3 (121)	0
Postoperative	2 (257)	0
Post-transplant	3 (178)	0
ARDS	1 (40)	0
Mixed[a]	6 (372)	2 (128)
Geographical region: No. of studies (N)		
U.S.A./Canada	6 (244)	0
Europe	24 (2863)	5 (405)
South America	2 (209)	0
Asia	10 (750)	0
Multiple continents	1 (123)	0
Other/NR	1 (33)	0
Funding source: No. of studies (N)[b]		
Government	8 (1784)	3 (292)
Industry	3 (243)	0
Professional society/Foundation	3 (138)	0
Not reported/Unclear	30 (1957)	2 (113)
Study quality: No. of studies (N)		
Good	21 (2958)	1 (64)
Fair	17 (961)	4 (341)
Poor	6 (203)	0

[a]"Mixed" diagnosis refers to studies where fewer than 70% of patients had a single etiology for acute respiratory failure.
[b]Some studies had multiple funding sources; therefore, totals may not sum to the total number of studies.
Abbreviations: ACPE = acute cardiogenic pulmonary edema; APACHE II = Acute Physiology And Chronic Health Evaluation II; ARDS = acute respiratory distress syndrome; COPD = chronic obstructive pulmonary disease; ED = emergency department; ICU = intensive care unit; N = number of participants; NPPV = non-invasive positive-pressure ventilation; NR = not reported; SAPS = Simplified Acute Physiology Score

Detailed Synthesis

Mortality

Overview

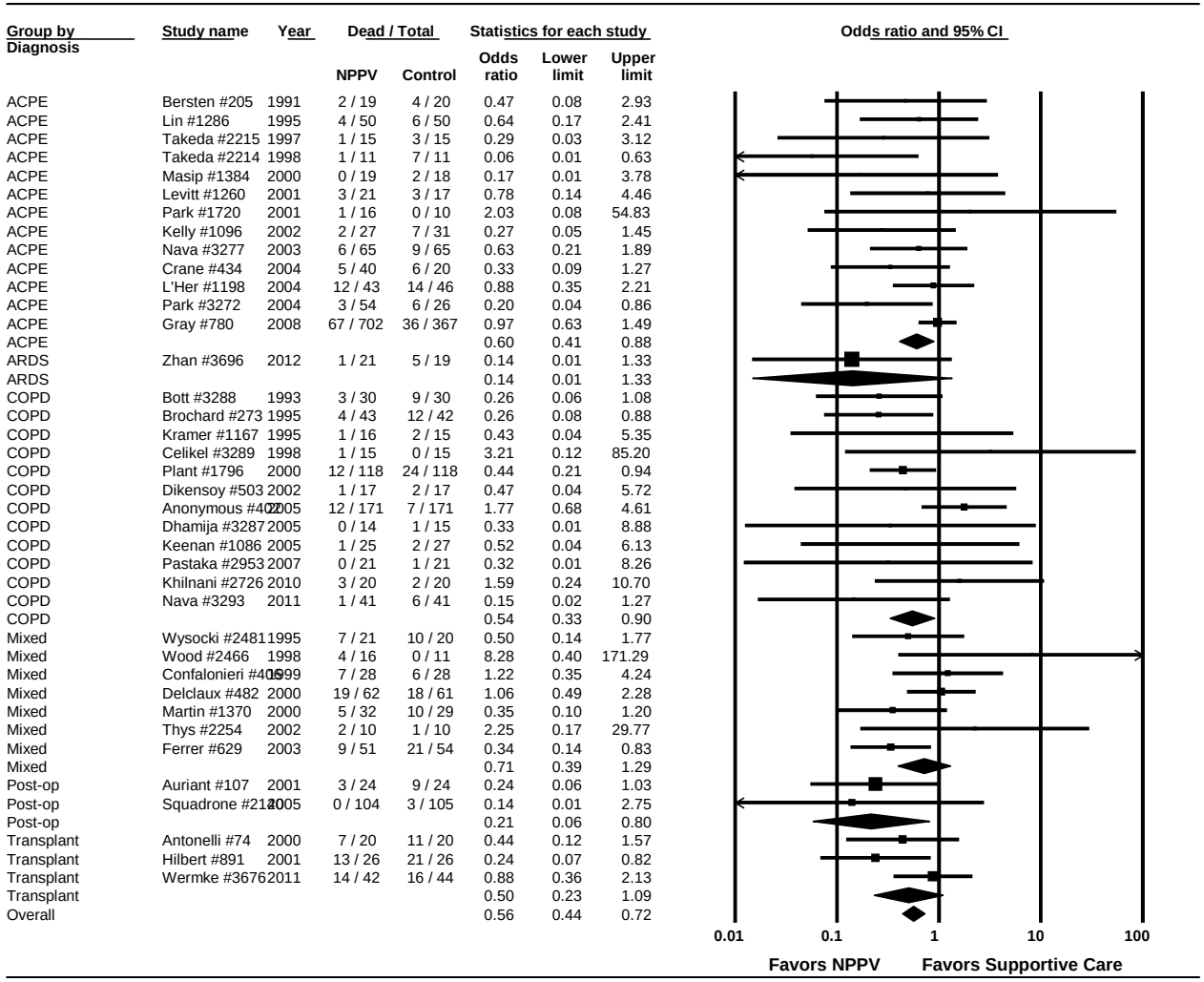
A total of 43 studies reported the effects of NPPV on mortality and were included in our analyses; 39 compared NPPV with usual supportive care,[57,59-62,64,65,67-71,73,77-81,83-87,89-97,99-105] and 4 compared NPPV with invasive ventilation.[58,75,76,98] The majority of studies were relatively small in size, with only 9 having ≥ 100 subjects;[64,68,70,71,76,83,87,89,99,100] one study[71] accounted for almost 25 percent of the total number of patients. Most studies enrolled patients with ACPE or COPD; few studies enrolled patients with asthma, interstitial lung disease, ARDS, or who were post-transplant or postoperative. One study enrolled adults older than age 75 with acute respiratory failure, most of whom had underlying COPD and a "do not intubate" order.[104] Approximately two-thirds of the studies reported a morbidity index (Acute Physiology And Chronic Health Evaluation II [APACHE II] or Simplified Acute Physiology Score [SAPS]) that relies primarily on physiological measures. The median predicted mortality for enrolled patients was approximately 12 to 29 percent depending on the measure used.

NPPV Versus Supportive Care

Mortality rates ranged from 0 to 33 percent for NPPV and 0 to 80 percent for usual supportive care. Overall, there was a lower risk of mortality when NPPV was employed in addition to usual supportive care (Figure 4). Effects were consistent across studies ($Q = 44.1$, $df = 37$, $p = 0.20$, $I^2 = 16\%$); funnel plots and test statistics did not suggest publication bias (Appendix D). Because the study by Gray et al.[71] contributed a large proportion of subjects, we conducted an influence analysis, recomputing the summary OR after removing one study at a time. No single study affected the pooled OR by more than 5 percent. An exploratory mixed-effects subgroup analysis across study quality and diagnosis also suggested a relatively consistent mortality benefit (Table 5). This effect was most pronounced in the postoperative or post-transplant settings, but CIs overlapped ($p = 0.50$ for differences in treatment effect by diagnostic group), and confounding factors (factors other than the subgroups being compared, such as comorbid medical conditions) varied across studies and could have affected these results; therefore, results from the subgroup analyses should be interpreted cautiously. The single good-quality trial examining NPPV in older adults, many with "do not intubate" orders, showed lower mortality rates.[104] We also conducted an exploratory analysis to determine if there were time trends in the effects of NPPV. Using the year of publication as a proxy for when the study was completed, we found a smaller treatment effect for more recent studies ($p = 0.006$).

Effects on longer term mortality were reported at 30–120 days in four studies.[59,65,70,71] NPPV was associated with a nonstatistically significant reduction in mortality (summary OR 0.58; 95% CI, 0.31 to 1.06; $Q = 6.1$, $df = 3$, $p = 0.11$, $I^2 = 51\%$).

Figure 4. Random-effects analysis of data on mortality—NPPV versus supportive care



Note: “Mixed” diagnosis refers to studies where fewer than 70% of patients had a single etiology for acute respiratory failure.
The study by Barbe et al.60 had zero events in each treatment arm and is not displayed in the forest plot.
Abbreviations: ACPE = acute cardiogenic pulmonary edema; ARDS = acute respiratory distress syndrome; CI = confidence interval; COPD = chronic obstructive pulmonary disease; NPPV = noninvasive positive-pressure ventilation

Table 5. Results of meta-analysis of data on mortality for NPPV versus supportive care

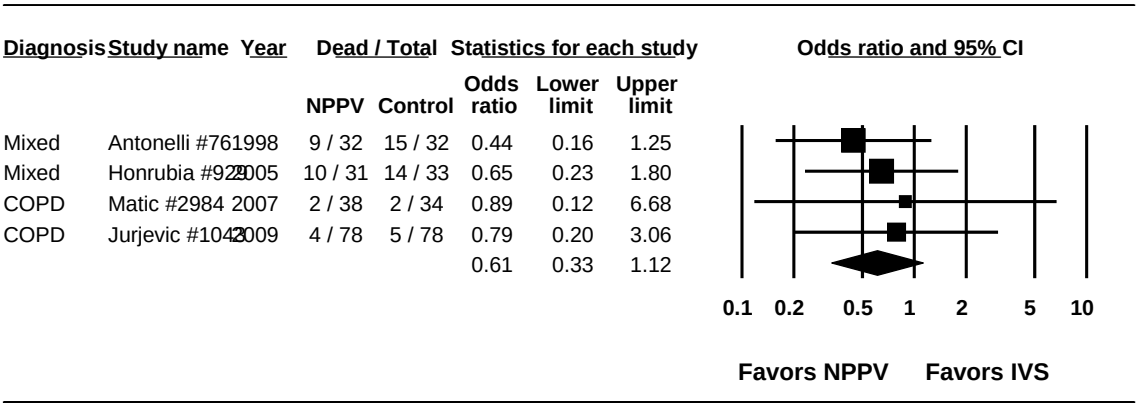
Subgroup Category	Subgroup	No. of Studies (N)	Summary OR (95% CI)	Tests for Heterogeneity
All participants	NA	39 (4111)	0.56 (0.44 to 0.72)	p = 0.20, I^2 = 16%
Study quality[a]	Good	19 (3085)	0.59 (0.42 to 0.85)	p = 0.07, I^2 = 34%
	Fair	14 (827)	0.50 (0.34 to 0.72)	p = 0.54, I^2 = 0%
	Poor	6 (199)	0.46 (0.17 to 1.31)	p = 0.59, I^2 = 0%
Diagnosis[b]	ACPE	13 (1778)	0.60 (0.41 to 0.88)	p = 0.31, I^2 = 14%
	ARDS	1 (40)	0.14 (0.01 to 1.33)	NA
	COPD	13 (1425)	0.54 (0.33 to 0.90)	p = 0.32, I^2 = 12%
	Mixed[c]	7 (433)	0.71 (0.39 to 1.29)	p = 0.16, I^2 = 21%
	Postoperative	2 (257)	0.21 (0.06 to 0.80)	p = 0.75, I^2 = 0%
	Post-transplant	3 (178)	0.50 (0.23 to 1.09)	p = 0.24, I^2 = 31%

ap = 0.77 for differences in treatment effect by study quality.
bp = 0.50 for differences in treatment effect by diagnosis.
c"Mixed" diagnosis refers to studies where fewer than 70% of patients had a single etiology for acute respiratory failure.
Abbreviations: ACPE = acute cardiogenic pulmonary edema; ARDS = acute respiratory distress syndrome; CI = confidence interval; COPD = chronic obstructive pulmonary disease; N = number of participants; NA = not applicable; NPPV = noninvasive positive-pressure ventilation; OR = odds ratio

NPPV Versus Invasive Ventilation

Four studies compared NPPV with invasive ventilation and reported effects on mortality.[58,75,76,98] Etiology of acute respiratory failure was COPD (two studies) and mixed (two studies). One study was of good quality;[58] the others were of fair quality. The mortality rate for invasive ventilation ranged from 6 to 47 percent. Overall, there was no difference in mortality when NPPV was employed versus invasive ventilation (summary OR 0.61; 95% CI, 0.33 to 1.12; Figure 5). Effects were consistent across studies (Q = 0.65, df = 3, p = 0.89, I^2 = 0%). However, the CI for the summary estimate was wide, and the numbers of patients randomized and events (61 deaths) were small. There were insufficient numbers of studies to perform subgroup analyses.

Figure 5. Random-effects analysis of data on mortality—NPPV versus invasive ventilation



Note: "Mixed" diagnosis refers to studies where fewer than 70% of patients had a single etiology for acute respiratory failure.
Abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; IVS = invasive ventilator support; NPPV = noninvasive positive-pressure ventilation

Intubation

Overview

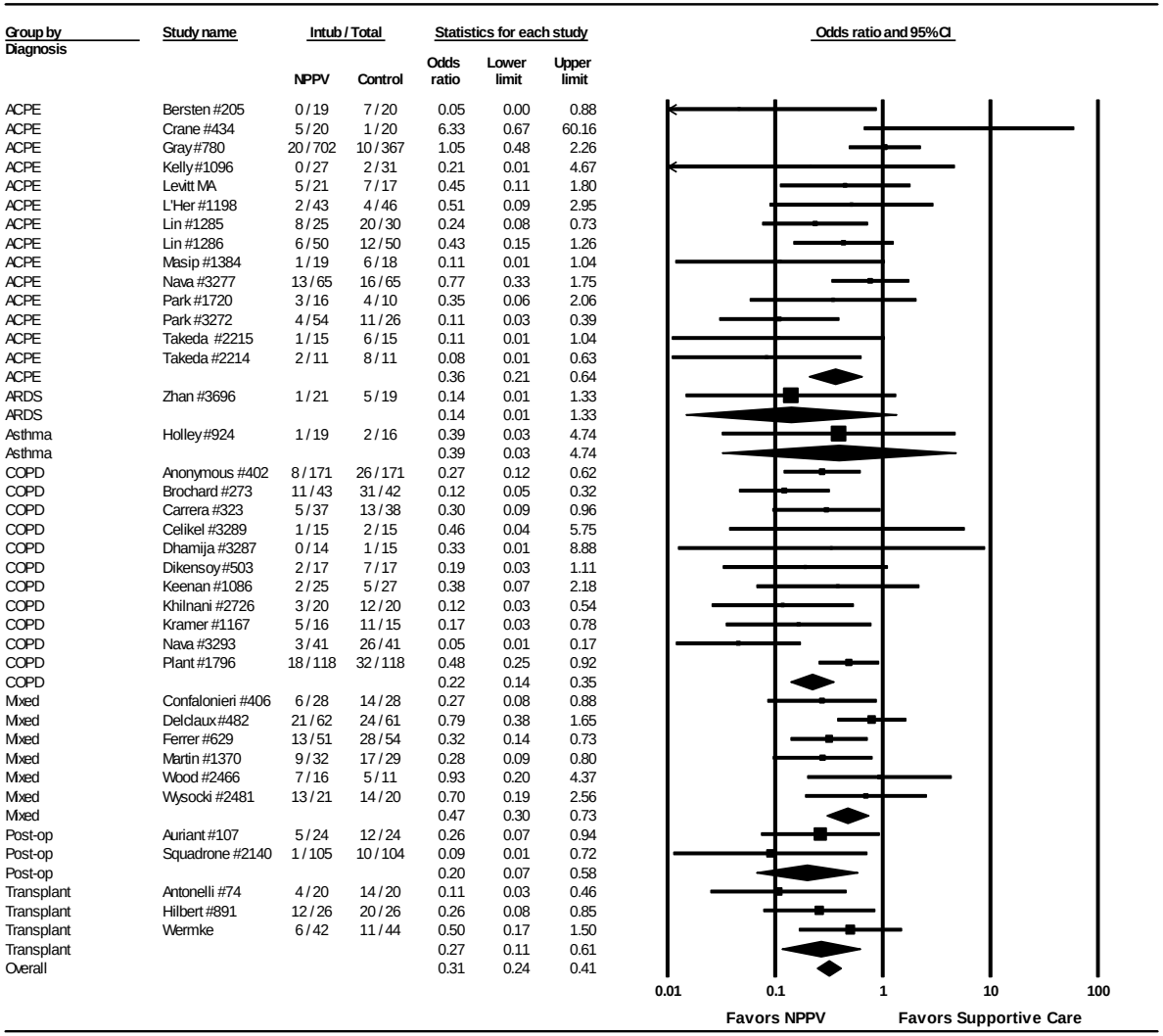
We identified 39 studies reporting on the relative effects of NPPV versus supportive care on intubation rates;[57,59-65,67-71,73,74,77-87,89-91,93-96,99-101,103-105] this outcome was not relevant for studies comparing NPPV with invasive ventilation.

NPPV Versus Supportive Care

Intubation rates ranged from 0 to 62 percent for NPPV and 3–77 percent for supportive care. Overall, there was a lower risk of intubation for patients when NPPV was employed in addition to supportive care (summary OR 0.31; 95% CI, 0.24 to 0.41; Figure 6). Tests for heterogeneity showed moderate variability in treatment effects across studies ($Q = 59.2$, $df = 37$, $p = 0.01$, $I^2 = 37\%$). An exploratory mixed-effects subgroup analysis across study quality and diagnosis showed a relatively stable effect across these subgroups (Table 6), but did not fully explain the

observed heterogeneity. In addition, a funnel plot suggested possible publication bias (Appendix D). However, a significant treatment effect remained after adjusting for publication bias (adjusted OR = 0.45; 95% CI, 0.33 to 0.61). As with the analysis for effects on mortality, we conducted an influence analysis to evaluate the influence of single studies on the summary OR. Removing studies sequentially from the analysis did not have a significant impact on the summary OR.

Figure 6. Random-effects analysis of data on intubation rates—NPPV versus supportive care



Note: "Mixed" diagnosis refers to studies where fewer than 70% of patients had a single etiology for acute respiratory failure.
The study by Barbe et al.60 had zero events in each treatment arm and is not displayed in the forest plot.
Abbreviations: ACPE = acute cardiogenic pulmonary edema; ARDS = acute respiratory distress syndrome; CI = confidence interval; COPD = chronic obstructive pulmonary disease; NPPV = noninvasive positive-pressure ventilation

Table 6. Results of meta-analysis of data on intubation for NPPV versus supportive care

Subgroup Category	Subgroup	No. of Studies (N)	Summary OR (95% CI)	Tests for Heterogeneity
All participants	NA	39 (3792)	0.31 (0.24 to 0.41)	p = 0.01, I^2 = 37%
Study quality[a]	Good	19 (2778)	0.35 (0.23 to 0.53)	p < 0.001, I^2 = 60%
	Fair	15 (875)	0.26 (0.18 to 0.38)	p = 0.75, I^2 = 0%
	Poor	5 (139)	0.29 (0.10 to 0.85)	p = 0.94, I^2 = 0%
Diagnosis[b]	ACPE	14 (1813)	0.36 (0.21 to 0.64)	p = 0.02, I^2 = 50%
	ARDS	1 (40)	0.14 (0.01 to 1.33)	NA
	Asthma	1 (35)	0.39 (0.03 to 4.74)	NA
	COPD	12 (1117)	0.22 (0.14 to 0.35)	p = 0.16, I^2 = 30%
	Mixed[c]	6 (352)	0.47 (0.30 to 0.73)	p = 0.34, I^2 = 12%
	Postoperative	2 (257)	0.20 (0.07 to 0.58)	p = 0.39, I^2 = 0%
	Post-transplant	3 (178)	0.27 (0.11 to 0.61)	p = 0.25, I^2 = 27%

ap = 0.63 for differences in treatment effect by study quality.
bp = 0.32 for differences in treatment effect by diagnosis.
c"Mixed" diagnosis refers to studies where fewer than 70% of patients had a single etiology for acute respiratory failure.
Abbreviations: ACPE = acute cardiogenic pulmonary edema; ARDS = acute respiratory distress syndrome; CI = confidence interval; COPD = chronic obstructive pulmonary disease; N = number of participants; NA = not applicable; NPPV = noninvasive positive-pressure ventilation; OR = odds ratio

Myocardial Infarction

Overview

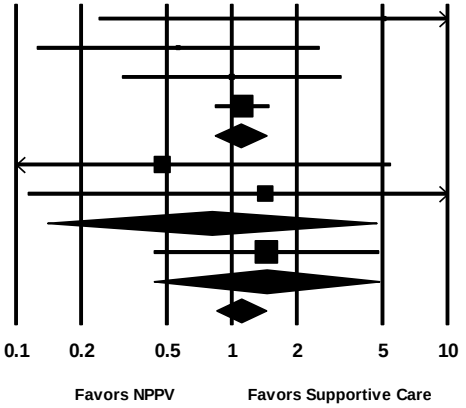
We identified seven studies reporting on the relative effects of NPPV versus supportive care on myocardial infarction rates.[62,67,71,81,87,94,100] Etiologies of acute respiratory failure were ACPE (four studies), COPD (two studies), and mixed etiologies (one study). Six of these were judged to be of good quality. Two studies (one good and one fair quality) reported this outcome for NPPV compared with invasive ventilation.[58,75] Given little variability in study quality, we did not complete subgroup analyses by quality.

NPPV Versus Supportive Care

Rates of myocardial infarction ranged from 2–30 percent for NPPV and from 0 to 30 percent for supportive care. Overall, there was no difference in the rate of myocardial infarction when NPPV was employed in addition to supportive care (Figure 7). There was no significant variability in treatment effects across studies (Q = 2.45, df = 6, p = 0.87, I^2 = 0%). An exploratory mixed-effects subgroup analysis across diagnosis also suggested no difference in the rate of myocardial infarction related to NPPV; there was no significant difference in treatment effects across these subgroups (Q = 0.32, df = 2, p = 0.85; Table 7).

Figure 7. Random-effects analysis of data on myocardial infarction rates—NPPV versus supportive care

Group by Diagnosis	Study name	Year	MI / Total		Statistics for each study		
			NPPV	Control	Odds ratio	Lower limit	Upper limit
ACPE	Plant #1796	2000	2 / 118	0 / 118	5.09	0.24	107.08
ACPE	Levitt #1260	2001	4 / 21	5 / 17	0.56	0.12	2.55
ACPE	Crane #434	2004	12 / 40	6 / 20	1.00	0.31	3.23
ACPE	Gray #780	2008	189 / 702	91 / 367	1.12	0.84	1.49
ACPE					1.10	0.83	1.45
COPD	Brochard #273	1995	1 / 43	2 / 42	0.48	0.04	5.46
COPD	Wood #2466	1998	2 / 16	1 / 11	1.43	0.11	18.00
COPD					0.81	0.14	4.68
Mixed	Nava #3277	2003	7 / 65	5 / 65	1.45	0.43	4.82
Mixed					1.45	0.43	4.82
Overall					1.11	0.85	1.44



Note: "Mixed" diagnosis refers to studies where fewer than 70% of patients had a single etiology for acute respiratory failure.
Abbreviations: ACPE = acute cardiogenic pulmonary edema; CI = confidence interval; COPD = chronic obstructive pulmonary disease; NPPV = noninvasive positive-pressure ventilation

Table 7. Results of meta-analysis of data on myocardial infarction for NPPV versus supportive care

Subgroup Category	Subgroup	No. of Studies	Summary OR (95% CI)	Tests for Heterogeneity
All participants	NA	7	1.11 (0.85 to 1.44)	p = 0.87, I^2 = 0%
Diagnosis[a]	ACPE	4	1.10 (0.83 to 1.45)	p = 0.62, I^2 = 0%
	COPD	2	0.81 (0.14 to 4.68)	p = 0.54, I^2 = 0%
	Mixed[b]	1	1.45 (0.43 to 4.82)	NA

ap = 0.85 for differences in treatment effect by diagnosis.
b"Mixed" diagnosis refers to studies where fewer than 70% of patients had a single etiology for acute respiratory failure.
Abbreviations: ACPE = acute cardiogenic pulmonary edema; CI = confidence interval; COPD = chronic obstructive pulmonary disease; NA = not applicable; NPPV = noninvasive positive-pressure ventilation; OR = odds ratio

NPPV Versus Invasive Ventilation

Only two studies comparing NPPV with invasive ventilation reported rates of myocardial infarction.[58,75] In each study, fewer patients in the NPPV-treated groups (1 of 31 and 2 of 32) had myocardial infarctions compared with invasive ventilation (2 of 33 and 4 of 32).

Hospital-Acquired Pneumonia

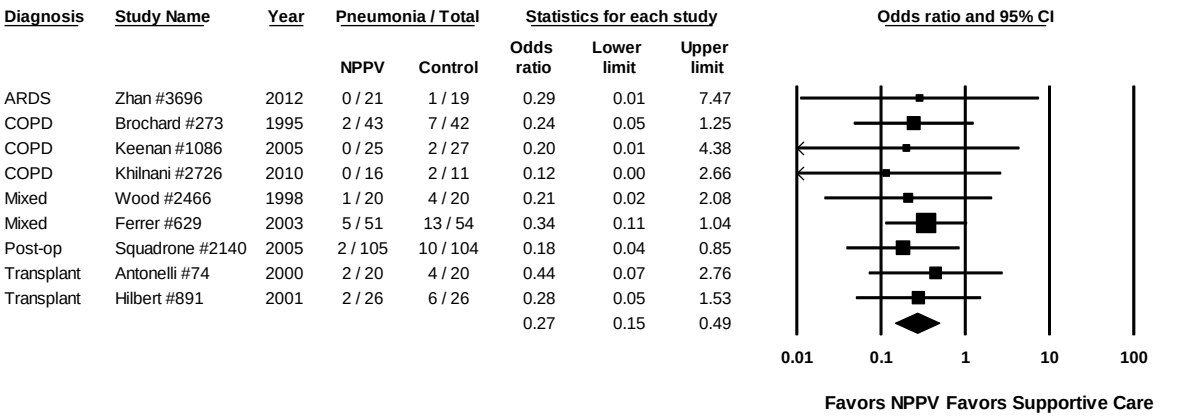
Overview

We identified nine studies reporting on the relative effects of NPPV versus supportive care on hospital-acquired pneumonia.[57,62,70,73,77,89,94,96,105] Seven of these were judged to be of good quality. Four studies compared NPPV with invasive ventilation for this outcome.[58,66,75,76]

NPPV Versus Supportive Care

Rates of hospital-acquired pneumonia ranged from 0–10 percent for NPPV and from 7 to 24 percent for supportive care. Hospital-acquired pneumonia is defined as pneumonia that develops more than 48 hours after hospitalization but that was not incubating at the time of admission. Overall, there was a lower risk of pneumonia when NPPV was employed in addition to usual supportive care (Figure 8). There was no significant variability in treatment effects across studies ($Q = 1.09$, $df = 8$, $p = 0.99$, $I^2 = 0\%$). An exploratory mixed-effects subgroup analysis across study quality and diagnosis showed a consistent effect across these subgroups (Table 8). An influence analysis showed no significant change in the summary odds ratio by omitting any single study.

Figure 8. Random-effects analysis of data on hospital-acquired pneumonia rates—NPPV versus supportive care



Note: "Mixed" diagnosis refers to studies where fewer than 70% of patients had a single etiology for acute respiratory failure.
Abbreviations: ARDS = acute respiratory distress syndrome; CI = confidence interval; COPD = chronic obstructive pulmonary disease; NPPV = noninvasive positive-pressure ventilation.

Table 8. Results of meta-analysis of data on hospital-acquired pneumonia for NPPV versus supportive care

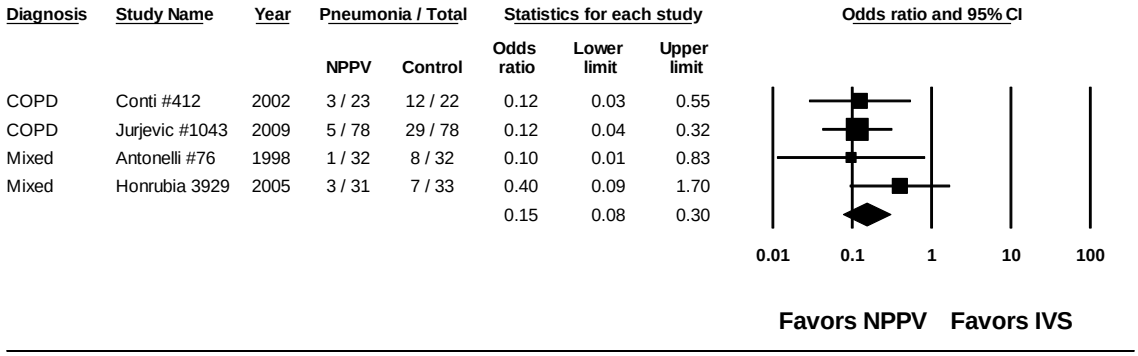
Subgroup Category	Subgroup	No. of Studies	Summary OR (95% CI)	Tests for Heterogeneity
All participants	NA	9	0.27 (0.15 to 0.49)	p = 0.99, I^2 = 0%
Study quality[a]	Good	7	0.25 (0.12 to 0.53)	p = 0.99, I^2 = 0%
	Fair	2	0.30 (0.11 to 0.87)	p = 0.52, I^2 = 0%
Diagnosis[b]	ARDS	1	0.29 (0.01 to 7.47)	NA
	COPD	3	0.21 (0.06 to 0.77)	p = 0.92, I^2 = 0%
	Mixed[c]	2	0.31 (0.11 to 0.85)	p = 0.71, I^2 = 0%
	Postoperative	1	0.18 (0.04 to 0.85)	NA
	Post-transplant	2	0.35 (0.10 to 1.20)	p = 0.71, I^2 = 0%

ap = 0.78 for differences in treatment effect by study quality.
bp = 0.96 for differences in treatment effect by diagnosis.
c"Mixed" diagnosis refers to studies where fewer than 70% of patients had a single etiology for acute respiratory failure.
Abbreviations: ARDS = acute respiratory distress syndrome; CI = confidence interval; COPD = chronic obstructive pulmonary disease; NA = not applicable; NPPV = noninvasive positive-pressure ventilation; OR = odds ratio

NPPV Versus Invasive Ventilation

Four studies reported the relative effects of NPPV versus invasive ventilation on hospital-acquired pneumonia. Overall, there was a markedly lower risk of pneumonia with NPPV (summary OR 0.15; 95% CI, 0.08 to 0.30; Figure 9). There was no significant variability in treatment effects across studies (Q = 2.19, df = 3, p = 0.53, I^2 = 0%).

Figure 9. Random-effects analysis of data on hospital-acquired pneumonia rates—NPPV versus invasive ventilation



Note: "Mixed" diagnosis refers to studies where fewer than 70% of patients had a single etiology for acute respiratory failure.
Abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; IVS = invasive ventilator support; NPPV = noninvasive positive-pressure ventilation

Length of Stay

NPPV Versus Supportive Care

Twenty-nine studies reported effects on hospital length of stay. Of these, we focused our analysis on the 11 studies with larger sample sizes.[63,64,70,71,80,83,87,89,100,102,104] Mean length of stay varied substantially across studies, from 8.5 to 20.7 days for NPPV-treated patients and from 5.1 to 26.8 days for patients receiving supportive care. None of the 11 studies showed a statistically significant difference in length of stay. Two studies reported subgroup analyses on the hospital survivors; neither found a statistically significant effect on length of stay in the survivor and nonsurvivor subgroups.

ICU length of stay was reported in 14 studies. We focused our analyses on the five largest of these.[65,70,72,83,89] Mean ICU length of stay range from 1.4 to 10 days in NPPV-treated patients and from 2.6–24 days in patients receiving supportive care. Of the five studies, two found a statistically significant reduction in length of stay with NPPV versus supportive care.[65,72]

Several issues limit these findings. Length-of-stay data typically have a skewed distribution, making statistical tests that assume normality inappropriate, but such tests were sometimes used in these studies. Second, the results may be biased if NPPV reduces mortality, thus increasing length of stay. Few studies reported subgroup analyses that limited the results to surviving patients. In summary, current evidence does not support shorter hospital length or ICU length of stay with NPPV versus supportive care. However, these results should be interpreted with caution.

NPPV Versus Invasive Ventilation

No study reported effects on hospital length of stay. However, five studies reported effects on ICU length of stay.[58,66,75,76] Mean ICU length of stay range from 5 to 22 days in NPPV-treated patients and from 9.3 to 21 days in patients receiving invasive ventilation. Of the four studies with larger sample sizes, three found a statistically significant reduction in ICU length of stay.

Intolerance and Facial Ulcerations

Ten studies (12 NPPV arms) reported rates of discontinuation due to poor patient tolerability. The median rate of discontinuation was 12.1 percent (range 0–29%). Limiting the analysis to two larger studies, which are more likely to give stable estimates, rates ranged from 3.8–5.2 percent for CPAP[71,89] and 8.4 percent for BPAP.[71] Rates of facial abrasions or ulcerations were reported in 15 studies and varied widely, ranging from 0 to 47 percent. Variability appears related in part to different definitions for facial injury and in part to differing durations of followup. Two larger studies that reported facial ulcerations reported rates of 20 percent[100] and 25.5 percent.[70]

Other Outcomes

Other outcomes were reported infrequently or not at all. No study reported effects on psychological response, functional status, or health-related quality of life for NPPV compared with either supportive care or invasive ventilation. Antonelli et al.[58] was the only study to report rates of sinusitis; 0 of 32 for NPPV versus 2 of 32 with invasive ventilation.

For NPPV compared with supportive care, duration of mechanical ventilation was reported in two studies, showing a statistically significant shorter duration in one study[65] and no effect in the other.[73] Duration of invasive ventilation was reported in two studies comparing NPPV with invasive ventilation, one showing a statistically significant shorter duration,[76] with no effect in the other.[66] One study reported the rate of ventilator dependence at hospital discharge in the NPPV-treated patients (0 of 23) and those treated with invasive ventilation (1 of 26).[66]

Key Question 2. BPAP Versus CPAP

KQ 2. Is NPPV with bilevel positive airway pressure (BPAP), compared with NPPV with continuous positive airway pressure (CPAP), associated with less morbidity, lower mortality, fewer adverse events, or lower medical utilization:

a. In adults with COPD and acute respiratory failure?

b. In adults with ACPE?

c. In adults with acute respiratory failure due to other causes including: pneumonia, asthma, obesity-hypoventilation syndrome, and interstitial lung disease?

d. In adults with acute respiratory failure in selective settings including: postoperative setting and post-transplant setting?

Key Points

- Twelve RCTs of varied quality showed no statistically significant difference between providing NPPV with BPAP compared with CPAP for the outcomes of:
    - Mortality
    - Need for endotracheal intubation
    - Myocardial infarction

- Current evidence is insufficient to determine if BPAP or CPAP have differential treatment effects for hospital or ICU length of stay, hospital-acquired pneumonia, psychological distress, functional status or health-related quality of life, and mortality rates beyond hospitalization.
- All studies but one included only participants with acute cardiogenic pulmonary edema (ACPE), although indirect comparisons included other diagnoses and supported these findings. This limits the applicability of these findings in patients with other causes of acute respiratory failure, such as COPD, as well as those in postoperative and post-transplant settings.

Description of Included Studies

A total of 12 studies, all RCTs, were included in our analyses.[67,71,86,99,106-113] Important study characteristics are summarized in Table 9. Ten studies enrolled patients from emergency departments,[67,71,99,106-109,111-113] one from an unclear setting,[86] and one from a high-dependency unit.[110] Seven studies were performed in Europe,[67,71,106,107,109,110,112] two in Brazil,[86,99] one in Tunisia,[113] one in Canada,[111] and one in Australia.[108] Of these, four were of good quality,[67,71,109,113] six were of fair quality,[99,106-108,110,112] and two were of poor quality.[86,111] The funding source was reported in five studies.[71,108,110,112,113] Studies enrolled patients between 1994 and 2008. The number of patients included in studies ranged from 26[86] to 1156,[71] with a total of 1463 patients. The mean age of study participants ranged from 64–78 years. The proportion of female patients included ranged from 48 to 67 percent. No studies reported the racial demographics of the study participants.

Although we aimed to address a variety of populations, all but one study included only patients with ACPE. Of the 101 participants enrolled in the single exceptional study,[108] only 30 (30%) did not have pulmonary edema as their admission diagnosis; these included patients with COPD (21%), pneumonia (8%), and asthma (1%). Therefore, no studies included in these analyses addressed obesity hypoventilation syndrome, interstitial lung disease, or the postoperative or post-transplant setting. Six studies reported illness severity based on the APACHE II (median 18.1, range 16.0 to 18.3) or SAPS (median 43.8, range 41.6 to 46.0).

Four studies included three treatment arms (BPAP, CPAP, and supportive care with supplemental oxygen);[67,71,86,99] the remainder compared BPAP with CPAP alone. NPPV was delivered by nasal mask in one study,[111] and the remainder of studies described the use of a full face mask. In general, information on NPPV settings and protocols was provided. However, only one study provided information on what general type of provider adjusted NPPV.[67]

Table 9. Study characteristics for direct comparisons of BPAP with CPAP

Characteristic	Values
Mean age of sample: Median (range)	76.5 (63.5–77.6)
Sex: N (%) Male Female Not reported	 561 (38.3%) 721 (49.3%) 181 (12.4%)
Race: N (%) Not reported	 1463 (100%)
Setting: No. of studies (N) ED High-dependency unit Not reported	 10 (1447) 1 (52) 1 (497)
Diagnoses: No. of studies (N) ACPE COPD Pneumonia Asthma	 12 (1966) 1 (21) 1 (8) 1 (1)
Geographical region: No. of studies (N) U.S.A./Canada Europe Brazil Africa Australia/New Zealand	 1 (27) 7 (1553) 2 (106) 1 (200) 1 (101)
Funding source: No. of studies (N) Government Industry Other None or not reported	 3 (1378) 0 0 9 (718)
Study quality: No. of studies (N) Good Fair Poor	 4 (1409) 6 (424) 2 (53)

Abbreviations: ACPE = acute cardiogenic pulmonary edema; BPAP = bilevel positive airway pressure; COPD = chronic obstructive pulmonary disease; CPAP = continuous positive airway pressure; ED = emergency department; N = number of participants

Detailed Synthesis

Overview

Our analyses addressed the comparative effect of BPAP versus CPAP using the primary outcomes of mortality, endotracheal intubation rate, and incidence of myocardial infarction. Summary results are provided in Table 10. Overall, no significant variability in treatment effects across studies was detected. Further, funnel plots did not suggest publication bias (Appendix D).

Table 10. Summary of meta-analysis results for BPAP versus CPAP

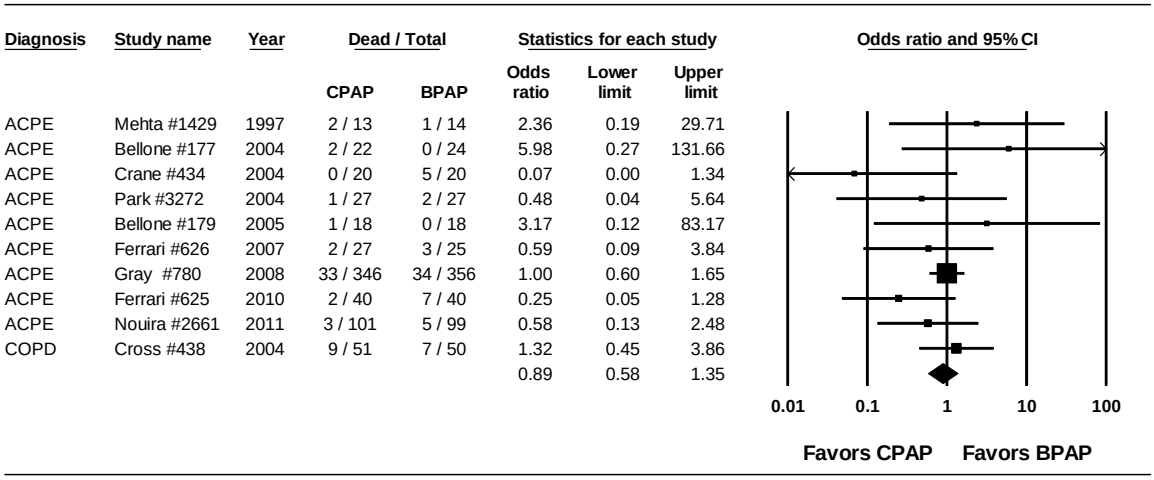
Outcome	No. of Studies (N)	Summary OR (95% CI)	Tests for Heterogeneity
Mortality	10 (1338)	0.89 (0.58 to 1.35)	$p = 0.41$, $I^2 = 3\%$
Intubation	12 (1463)	0.84 (0.51 to 1.38)	$p = 0.65$, $I^2 = 0\%$
Myocardial infarction	7 (1056)	0.69 (0.34 to 1.40)	$p = 0.09$, $I^2 = 46\%$

Abbreviations: BPAP = bilevel positive airway pressure; CI = confidence interval; CPAP = continuous positive airway pressure; N = number of participants; OR = odds ratio

Mortality

In-hospital mortality ranged from 0 to 25 percent for BPAP, 0 to 21 percent for CPAP, and 0 to 30 percent for oxygen alone. Overall, there was no difference in in-hospital mortality between BPAP and CPAP groups in a random-effects model meta-analysis (OR 0.89; 95% CI, 0.58 to 1.35) drawn from a total of 10 studies (Figure 10). Mortality was generally assessed across the duration of hospitalization (9 studies), although one study reported 7-day mortality.[71]

Figure 10. Random-effects analysis of data on mortality—BPAP versus CPAP



Abbreviations: ACPE = acute cardiogenic pulmonary edema; BPAP = bilevel positive airway pressure; CI = confidence interval; CPAP = continuous positive airway pressure

There are caveats and limitations to consider. One study alone accounted for 58 percent of all patients included in these analyses.[71] This study included three treatment arms (BPAP, CPAP, and supplemental oxygen only). Study investigators found that there was no difference in 7-day mortality between oxygen and NPPV (9.8% vs. 9.5%, p = 0.81). Further, in this study there was no significant difference between BPAP and CPAP groups for the combined end point of intubation or death within 7 days (11.1% vs. 11.7%, p = 0.81). Nevertheless, even after removing this study, analyses did not show a clinically or statistically important intervention effect (OR 0.88; 95% CI 0.39 to 1.48). Second, fewer than 2 percent of patients enrolled in these studies carried a primary diagnosis other than ACPE. Based on direct comparisons, no conclusions can be made about the effect of BPAP versus CPAP for those with COPD, pneumonia, asthma, and interstitial lung disease, or for those in postoperative or post-transplant settings. Third, in general, few studies described NPPV protocols in sufficient detail that the interventions could be reproduced. Therefore, both replication of the research and translation of this research into practice are difficult.

We supplemented these analyses with a mixed-treatment effects analysis that included indirect comparisons (e.g., CPAP vs. supportive care). This analysis, which included data from 39 additional studies, found a similar relative mortality for CPAP compared with BPAP (OR 0.96; 95% CI, 0.71 to 1.31) to the analysis of studies including only direct comparisons (0.88; 95% CI, 0.39 to 1.48). Note that the mixed-treatment effects analysis suggests even more

similarity in mortality associated with CPAP and BPAP based on an OR nearer to 1 and narrower confidence limits than the analysis of direct comparisons.

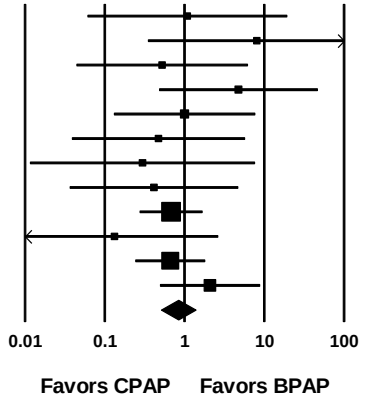
Intubation

Endotracheal intubation rates ranged from 0 to 29 percent for BPAP, 0 to 33 percent for CPAP, and 2.8 to 42 percent for oxygen alone. Based on analysis of 12 studies, there was no difference in the incidence of endotracheal intubation between BPAP and CPAP groups in a random-effects model meta-analysis (OR 0.84; 95% CI, 0.51 to 1.38; Figure 11). No significant variability in treatment effects across studies was detected (Q = 8.73, df = 11, p = 0.65, I^2 = 0%). There was also no evidence of publication bias based on a funnel plot (Appendix D). An influence analysis, performed by removing one study at a time and recomputing the summary OR, suggested that the study by Cross and colleagues[108] had undue influence of the overall summary estimate. Removing this study lowered the point estimate for treatment effect, although this was not statistically significant (OR 0.74; 95% CI, 0.44 to 1.26).

Limitations of these studies have been described above under "Mortality."

Figure 11. Random-effects analysis of data on intubation rates—BPAP versus CPAP

Diagnosis	Study name	Year	Intub / Total		Statistics for each study		
			CPAP	BPAP	Odds ratio	Lower limit	Upper limit
ACPE	Mehta #1429	1997	1 / 13	1 / 14	1.08	0.06	19.31
ACPE	Park #1720	2001	3 / 9	0 / 7	8.08	0.35	187.32
ACPE	Bellone #177	2004	1 / 22	2 / 24	0.52	0.04	6.22
ACPE	Crane #434	2004	4 / 20	1 / 20	4.75	0.48	46.91
ACPE	Park #3272	2004	2 / 27	2 / 27	1.00	0.13	7.67
ACPE	Bellone #179	2005	1 / 18	2 / 18	0.47	0.04	5.71
ACPE	Ferrari #626	2007	0 / 27	1 / 25	0.30	0.01	7.63
ACPE	Moritz #1516	2007	1 / 59	2 / 50	0.41	0.04	4.70
ACPE	Gray #780	2008	8 / 346	12 / 356	0.68	0.27	1.68
ACPE	Ferrari #625	2010	0 / 40	3 / 40	0.13	0.01	2.65
ACPE	Nouira #2661	2011	7 / 101	10 / 99	0.66	0.24	1.82
COPD	Cross #438	2003	6 / 51	3 / 50	2.09	0.49	8.86
					0.84	0.51	1.38



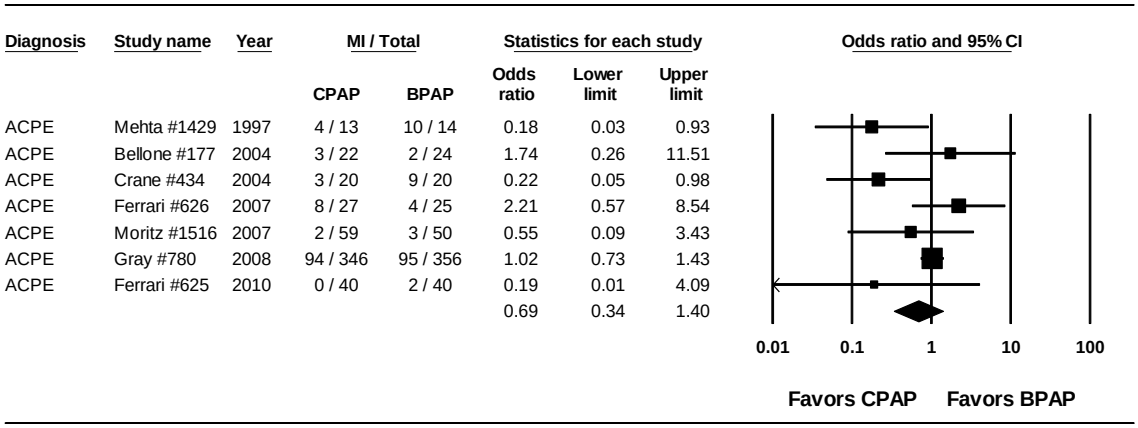
Abbreviations: ACPE = acute cardiogenic pulmonary edema; BPAP = bilevel positive airway pressure; CI = confidence interval; COPD = chronic obstructive pulmonary disease; CPAP = continuous positive airway pressure

Myocardial Infarction

Seven studies included myocardial infarction as a treatment outcome. All studies were conducted in patients with ACPE. Myocardial infarction rates ranged from 0 to 71 percent for BPAP, 7 to 31 percent for CPAP, and 0 to 30 percent for oxygen alone.

A random-effects model meta-analysis demonstrated no significant difference in the rate of myocardial infarction between BPAP and CPAP groups (OR 0.69; 95% CI, 0.34 to 1.40) (Figure 12). There was moderate heterogeneity in treatment effects across studies (Q = 11.1, df = 6, p = 0.09, I^2 = 46%).

Figure 12. Random-effects analysis of data on myocardial infarction rates—BPAP versus CPAP



Length of Stay in Hospital and ICU

Six studies reported hospital length of stay as an outcome.[99,108-112] Mean length of stay varied substantially across studies, from 4 to 13.6 days in CPAP-treated patients and 5 to 11.3 days for BPAP-treated patients. Of the six studies, only three[108,109,112] had a sample size of at least 60 participants (total n = 278), a large enough sample size to show a difference of 1 or more days in length of stay. None showed a statistically significant difference in length of stay by treatment group.

Two studies reported ICU length of stay as an outcome.[108,111] Median length of ICU stay was zero days in both arms of one study,[108] while mean ICU length of stay was 2.3 and 2.7 days in the CPAP and BPAP arms, respectively, in the other.[111] Positive skew in length-of-stay data in both studies suggests that the studies may be more similar than they seem to be. As with the hospital length-of-stay outcome, ICU length of stay was not significantly different between NPPV types in either of the studies. No meta-analysis was undertaken for this outcome.

In summary, current evidence suggests that neither hospital nor ICU length of stay is any different for CPAP versus BPAP.

Intolerance and Facial Ulcerations

Four studies reported the rate of intolerance to NPPV as a treatment outcome.[67,71,109,111] All used full face masks except for one,[111] which used a nasal mask. No intolerance was observed in either CPAP or BPAP in one study[109] while the others reported rates of intolerance ranging from 5.2 to 15 percent. None of the between-treatment differences in the rates of intolerance between CPAP and BPAP was statistically significant. Only one study was large enough to have the statistical power to detect a difference in intolerance rates of more than 5 percent,[71] and in this study the rates were 5.2 percent for CPAP-treated patients compared with 8.4 percent for BPAP-treated patients, a difference of 3.2 percent which did not reach statistical significance (p = 0.09).

A single study reported the incidence of facial ulcerations in both CPAP and BPAP arms.[111] In this study, which used a nasal mask, no facial ulcerations were observed under either treatment; however, because of the relatively small size of this study (n = 26 participants in both

treatment arms), the confidence limits for the difference in rates is wide and cannot exclude a clinically important difference in the rate of facial ulcerations between NPPV modalities.

Other Outcomes

Other outcomes were reported infrequently or not at all. No study reported effects on psychological response, functional status, health-related quality of life, or sinusitis.

The study by Cross et al.[108], a fair-quality study in 101 subjects, was the only study to report the duration of mechanical ventilation. The median duration of mechanical ventilation did not differ significantly between treatment arms (CPAP, median 123 minutes [range 10–338] versus BPAP, median 132 [range 20–550], p = 0.21).

Key Question 3. Early Extubation to NPPV

KQ3. Is early extubation to NPPV, compared with usual care, associated with less morbidity, lower mortality, fewer adverse events, or lower medical utilization:

- In adults with COPD and acute respiratory failure?
- In adults with ACPE?
- In adults with acute respiratory failure due to other causes including: pneumonia, asthma, obesity-hypoventilation syndrome, and interstitial lung disease?
- In adults with acute respiratory failure in selective settings including: postoperative setting and post-transplant setting?

Key Points

- In eligible studies, BPAP was the only NPPV modality evaluated; no studies used CPAP.
- In patients with COPD who are intubated for acute respiratory failure, current evidence supports a reduction in mortality and hospital-acquired pneumonia when NPPV is used to facilitate extubation. These benefits were not observed in studies enrolling patients with mixed etiologies of acute respiratory failure.
- In patients intubated for acute respiratory failure and deemed at high risk for extubation failure, current evidence supports a reduction in reintubation rates and hospital-acquired pneumonia when NPPV is used to prevent extubation failure. A mortality benefit in this group was suggested but was not statistically significant.
- In patients who develop recurrent acute respiratory failure, current evidence does not support a reduction in mortality, reintubation rates, or hospital-acquired pneumonia rates for NPPV use compared with supportive care.
- Few studies had adequate sample sizes to address effects on length of stay. Available evidence does not support a reduction in hospital length of stay with BPAP versus usual care, but suggests a possible decrease in ICU length of stay with early extubation to BPAP. BPAP-assisted weaning was associated with shorter duration of invasive ventilation.

- No studies reported data on myocardial infarction, psychological response, functional status, or health-related quality of life.

Description of Included Studies

Twelve studies, involving 1519 patients met our inclusion criteria.[114-125] One study was conducted in Canada,[121] and one multicenter study included sites in the United States;[115] all others were carried out in Europe or Asia. Of the 12 studies, 6 (50%) were of good methodological quality,[115,117,121-124] 5 (42%) were of fair quality,[114,116,118,119,125] and 1 (8%) was of poor quality.[120] Eleven studies reported effects on reintubation, and 11 reported mortality; no study reported myocardial infarction rates.

General study characteristics are summarized by treatment comparison in Table 11. All studies were conducted in ICU settings and used BPAP as the NPPV mode. In all but one study, the type of interface used was a full face mask, with one study including full face as well as nasal mask. BPAP, when described, was applied with an inspiratory pressure ranging from 10–20 cm H2O, but was variably adjusted to tidal volume or respiratory rate. Experience in using NPPV was not often described. One study[118] reported a 15-year experience, and one[121] described a 1-year experience with the specific intervention device, but none described the specific training or experience of the intervention staff. Composition of the intervention team was described in seven studies and consisted of combinations of critical care trained physicians, respiratory therapists, and nurses.

Study participants were predominately older adults, with more men than women. Ethnicity was not reported in any of the studies. When examining etiologies for respiratory failure, there were several different populations included in these weaning studies. Ten studies included a mixed population of patients with a variety of diagnoses causing respiratory failure. Two studies included only patients with a diagnosis of COPD. Severity of illness was described by the APACHE II score in 9 studies (median 18.2, range 9.0 to 36.5) and the SAPS in 3 studies (median 38.4, range 32.5 to 42.0).

The included studies described three general strategies for using NPPV in the management of ventilator weaning. Five studies investigated the use of NPPV in facilitating early extubation (i.e., comparing "usual" weaning strategy with extubation prior to meeting extubation criteria but with the application of NPPV as a bridge to liberation from invasive mechanical ventilation).[114,116,119,122,124,125] A second category of studies (five studies) described the use of NPPV versus supportive care in preventing extubation failure, primarily in those deemed at higher than average risk for requiring reintubation.[117,118,120,123] Finally, two studies examined the use of NPPV versus supportive care in the treatment of recurrent, postextubation acute respiratory failure.[115,121] We analyzed each of these groups separately.

Table11. Study characteristics by treatment comparison

Characteristic	Weaning: NPPV Vs. "Usual" Strategy	Preventing Respiratory Failure Postextubation: NPPV Vs. Supportive Care	Treating Respiratory Failure Postextubation: NPPV Vs. Supportive Care
Mean age of sample: Median age (range)	68.6 (64.2 to 70.7)	68.5 (54.6 to 72.7)	64.0 (59.5 to 68.5)
Sex: n (%)			
Male	184 (52%)	562 (65%)	127 (42%)
Female	87 (25%)	302 (35%)	94 (31%)
Not reported	83 (23%)	0	81 (27%)
Race: n (%)			
Not reported	354 (100%)	864 (100%)	302 (100%)
Setting: No. of studies (N)			
ICU	5 (354)	5 (864)	2 (302)
High-dependency unit	0	0	0
NPPV modality: No. of studies (N)			
BPAP	5 (354)	5 (864)	2 (302)
CPAP	0	0	0
Diagnoses: No. of studies (N)			
Mixed[a]	3 (214)	5 (864)	2 (302)
COPD	2 (140)	0	0
ACPE	0	0	0
Geographical region: No. of studies (N)			
U.S.A./Canada	0	0	1 (81)
Europe	4 (264)	3 (365)	0
Asia	1 (90)	2 (499)	0
Multiple continents	0	0	1 (221)
Funding source:[b] No. of studies (N)			
Government	1 (138)	2 (512)	2 (302)
Industry	0 (0)	0	1 (81)
Professional society/Foundation	0 (0)	2 (268)	1 (81)
Not reported/Unclear	4 (216)	2 (190)	0
Study quality: No. of studies (N)			
Good	2 (188)	2 (203)	2 (302)
Fair	3 (166)	2 (568)	0
Poor	0	1 (93)	0

[a]"Mixed" diagnosis refers to studies where fewer than 70% of patients had a single etiology for acute respiratory failure.
[b]Some studies had multiple funding sources; therefore totals may not sum to the total number of studies.
Abbreviations: ACPE = acute cardiogenic pulmonary edema; BPAP = bilevel positive airway pressure; COPD = chronic obstructive pulmonary disease; CPAP = continuous positive airways pressure; ICU = intensive care unit; N = number of participants; NPPV = noninvasive positive-pressure ventilation

Detailed Analysis

Weaning from Ventilatory Support by Early Extubation to NPPV

We identified five studies that evaluated the relative effects of NPPV versus "usual" weaning strategies on facilitating extubation for patients with acute respiratory failure.[114,116,119,122,124] All studies used BPAP. Table 12 summarizes the pooled treatment effects. Mortality and hospital-acquired pneumonia were significantly reduced with early extubation to NPPV in the subgroup of patients with COPD. Reintubation was not significantly decreased with NPPV, but the point estimate favored early weaning to NPPV in the single study of patients with COPD. The small

numbers of studies and patients, relatively few events, and increased risk of bias from the three fair-quality studies limit all summary estimates. Because formal statistical techniques for publication bias are not effective with small numbers of studies, we did not conduct analyses for publication bias.

Table 12. Summary of effects for key outcomes—early extubation to NPPV

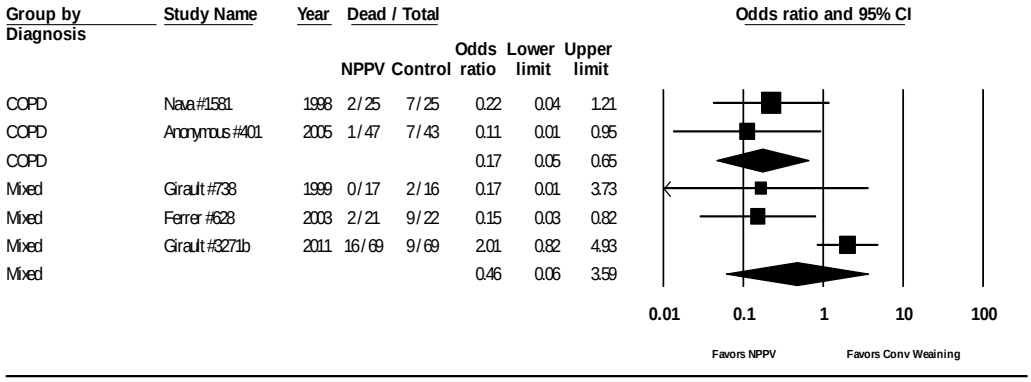
Outcome	No. of Studies (N)	Summary OR (95% CI)	Tests for Heterogeneity
Mortality			
COPD	2 (140)	0.17 (0.05 to 0.65)	$p = 0.62$, $I^2 = 0\%$
Mixed[a] sample	3 (214)	0.46 (0.06 to 3.59)	$p = 0.02$, $I^2 = 76\%$
Reintubation	4 (303)	0.83 (0.48 to 1.44)	$p = 0.44$, $I^2 = 0\%$
Hospital-acquired pneumonia			
COPD	2 (140)	0.14 (0.04 to 0.48)	$p = 0.43$, $I^2 = 0\%$
Mixed[a] sample	3 (214)	0.53 (0.19 to 1.46)	$p = 0.22$, $I^2 = 33\%$
Myocardial infarction	0 (0)	NR	NR

[a] "Mixed" sample refers to studies where fewer than 70% of patients had a single etiology for acute respiratory failure.
Abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; NPPV = noninvasive positive-pressure ventilation; NR = not reported; OR = odds ratio

Mortality

Mortality ranged from 0 to 23 percent for early extubation to NPPV and 13 to 41 percent for conventional weaning in five studies.[114,116,119,122,124] Because treatment effects were highly variable across studies and across diagnostic groups, we give summary estimates by diagnoses only. For the two studies in patients with CODP, NPPV decreased mortality (summary OR 0.17; 95% CI, 0.05 to 0.65; Figure 13). In the three studies conducted in patients with mixed etiologies of acute respiratory failure, NPPV was not associated with a decrease in mortality (summary OR 0.46; 95% CI, 0.06 to 3.59; Figure 13). For this latter group, the number of patients randomized and events (38 deaths) were small, and the results were highly variable across studies ($Q = 8.41$, $df = 2$, $p < 0.001$, $I^2 = 76\%$). There were too few studies to explore other potential reasons for heterogeneity quantitatively. However, qualitative analyses show that Girault 2011,[124] the only study that suggested the potential for increased risk of early extubation to NPPV, enrolled the oldest cohort of patients.

Figure 13. Random-effects analysis of data on mortality—early extubation to NPPV versus conventional weaning



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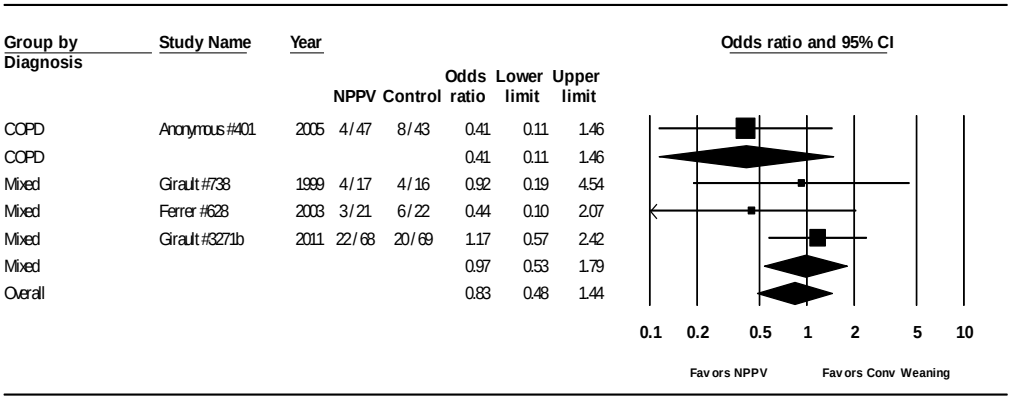
Abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; NPPV = noninvasive positive-pressure ventilation

Reintubation

Four studies[114,116,119,124] reported reintubation rates that ranged from 9–32 percent for NPPV and 19–29 percent for usual care. Overall, there was no difference in reintubation rates between early extubation to NPPV and usual weaning practices (OR 0.83; 95% CI, 0.48 to 1.44; Figure 14). Tests of heterogeneity suggested suggest no significant variability in treatment effects across studies ($Q = 2.72$, $df = 3$, $p = 0.44$, $I^2 = 0\%$). When analyzed by diagnostic subgroups (Figure 14), there is the suggestion that NPPV may be more effective in patients with COPD than samples with mixed etiologies of acute respiratory failure, but these comparisons are based on small numbers of studies and indirect comparisons, and were not statistically significant.

Figure 14. Random-effects analysis of data on reintubation rates—early extubation to NPPV versus conventional weaning



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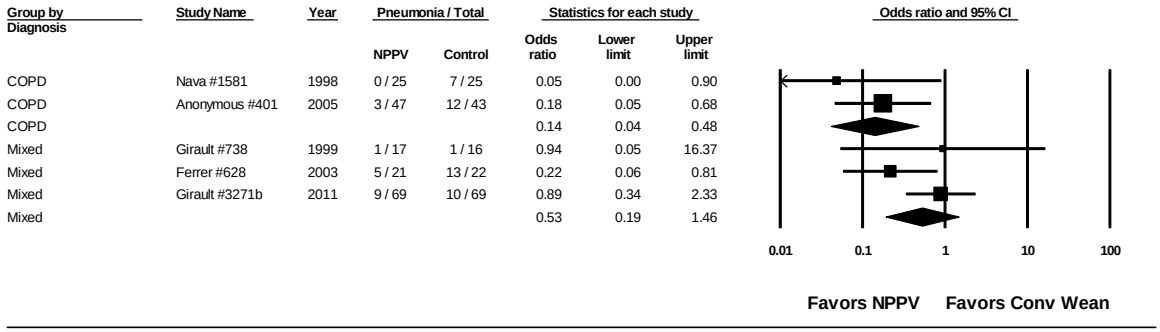
Abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; NPPV = noninvasive positive-pressure ventilation

Hospital-Acquired Pneumonia

Hospital-acquired pneumonia ranged from 0 to 24 percent for NPPV and 6 to 59 percent for usual care. Because treatment effects showed important variability across studies and across diagnostic groups, we give summary estimates by diagnoses. For the two studies in patients with COPD, NPPV decreased rates of hospital-acquired pneumonia (summary OR 0.14; 95% CI, 0.04 to 0.48; Figure 15). In the three studies conducted in patients with mixed etiologies of acute respiratory failure, NPPV was not associated with a decrease in hospital-acquired pneumonia (summary OR 0.53; 95% CI, 0.19 to 1.46; Figure 15) but confidence intervals were broad and the number of patients studied were few.

Figure 15. Random-effects analysis of data on hospital-acquired pneumonia rates—early extubation to NPPV versus conventional weaning



Note: "Mixed" diagnosis refers to studies where fewer than 70% of patients had a single etiology for acute respiratory failure.
Abbreviations: CI = confidence interval; Conv Wean = conventional weaning; COPD = chronic obstructive pulmonary disease; NPPV = noninvasive positive-pressure ventilation

Length of Stay

Four studies reported effects on hospital length of stay.[114,116,119,124] Mean length of stay varied substantially across studies, from 18 to 28 days in NPPV-treated patients and 20 to 41 days with conventional weaning. Of the four studies, two had large enough sample sizes to show a difference of 1 or more days in length of stay; neither study found a statistically significant difference.

ICU length of stay was reported in five studies. Mean ICU length of stay range from 8 to 15 days in NPPV-treated patients and 8 to 25 days with conventional weaning. Of the five studies, three had large enough sample sizes to show a difference of 1 or more days in length of stay; two found a statistically significant reduction in length of stay for early extubation to NPPV. In a good-quality study of 50 patients with mixed etiologies for acute respiratory failure, Nava et al.[122] found a shorter mean (standard deviation [SD]) length of stay of 15.1 (5.4) days with NPPV versus 24.0 (13.7) days with conventional weaning ($p = 0.005$). A fair-quality study[114] in 90 patients with acute respiratory failure due to COPD exacerbations also found shorter mean length of stay (12.0 [SD 8] vs. 16 [11]; $p = 0.047$). The largest study,[124] conducted in patients with mixed etiologies for acute respiratory failure, found no difference in the median length of stay (7.5 vs. 7.5 days; $p = 0.69$).

Several issues limit these findings. Length-of-stay data typically have a skewed distribution, making statistical tests that assume normality inappropriate, but such tests were sometimes used in these studies. Second, the results may be biased if NPPV reduces mortality, thus increasing length of stay. None of the studies reported subgroup analyses that limited the results to surviving patients. In summary, current evidence suggests that ICU length of stay, but not hospital length of stay, may be decreased by early extubation to NPPV. However, these results should be interpreted with caution.

NPPV Versus Supportive Care to Prevent Respiratory Failure Postextubation

We identified five studies that evaluated the relative effects of NPPV versus supportive care in patients with acute respiratory failure or at high risk for acute respiratory failure postextubation.[117,118,120,123,125] All studies used BPAP. Three of the five studies enrolled patients judged to be at high risk for postextubation respiratory failure. Study quality was judged to be good in two studies, fair in two studies, and poor in one study. Table 13 summarizes the pooled treatment effects. Mortality, reintubation rates, and hospital-acquired pneumonia rates were not decreased with NPPV following extubation. However, the point estimate favored NPPV in each case. The small numbers of studies and patients and relatively few events limit all summary estimates. Because formal statistical techniques for publication bias are not effective with small numbers of studies, we did not conduct analyses for publication bias.

Table 13. Summary of effects for key outcomes—NPPV versus supportive care to prevent respiratory failure postextubation

Outcome	Group	No. of Studies (N)	Summary OR (95% CI)	Tests for Heterogeneity
Mortality[a]	All	4 (771)	0.65 (0.38 to 1.10)	p = 0.75, I^2 = 0%
	High risk	3 (365)	0.60 (0.34 to 1.04)	p = 0.87, I^2 = 0%
	Average risk	1 (406)	1.52 (0.25 to 9.21)	p = 0.24, I^2 = NA
Reintubation[b]	All	5 (864)	0.76 (0.38 to 1.53)	p = 0.03, I^2 = 63%
	High risk	3 (365)	0.43 (0.24 to 0.77)	p = 0.73, I^2 = 0%
	Average risk	2 (499)	1.56 (0.89 to 2.76)	p = 0.48, I^2 = 0%
Hospital-acquired pneumonia	All	2 (268)	0.52 (0.28 to 0.97)	p = 0.32, I^2 = 0%
Myocardial infarction	All	0 (0)	NR	NR

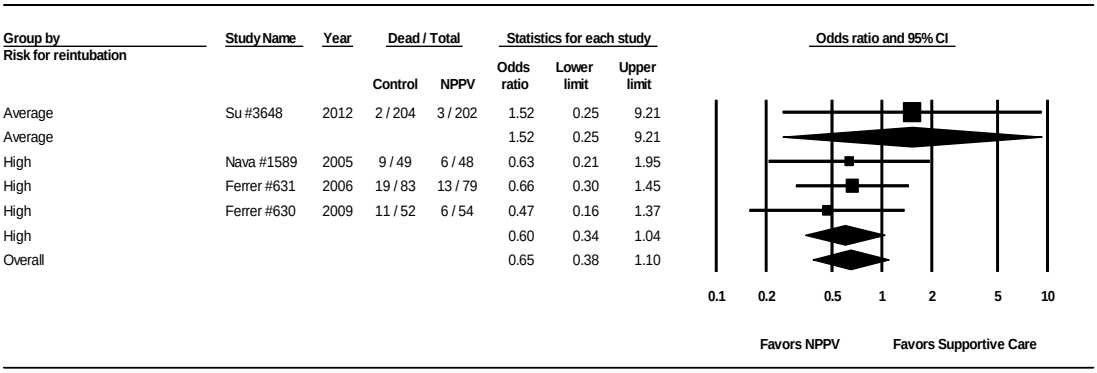
[a]p = 0.33 for differences in treatment effect on mortality by high-risk versus average-risk groups.
[b]p = 0.002 for differences in treatment effect on reintubation by high-risk versus average-risk groups.
Abbreviations: CI = confidence interval; N = number of participants; NA = not applicable; NPPV = noninvasive positive-pressure ventilation; NR = not reported; OR = odds ratio

Mortality

Mortality ranged from 1 to 23 percent for usual care and 1 to 16 percent for NPPV in four studies.[117,118,123,125] Overall, NPPV postextubation did not decrease mortality (OR 0.65; 95% CI, 0.38 to 1.10; Figure 16). Tests for heterogeneity did not suggest important variability in treatment effects across studies (Q = 1.23, df = 3, p = 0.75, I^2 = 0%). Exploratory analysis that grouped studies into those evaluating patients at high versus average risk for recurrent acute

respiratory failure suggested a greater effect in those at high risk, but the difference in effects was not statistically significant (p = 0.33).

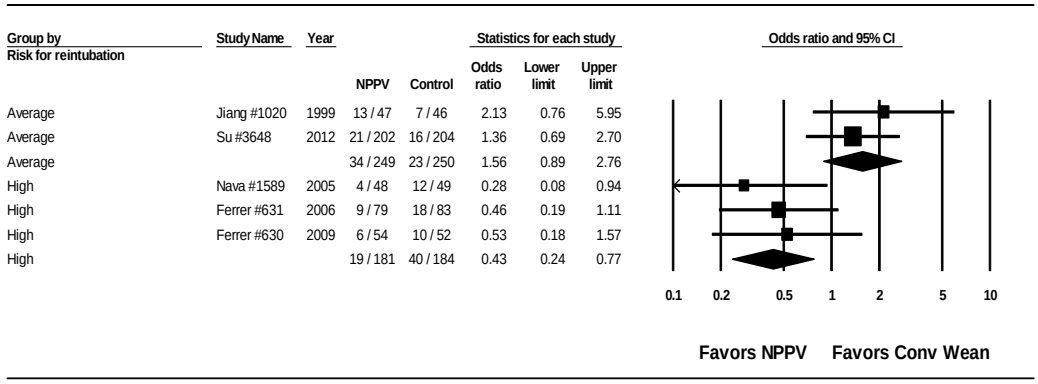
Figure 16. Random-effects analysis of data on mortality—NPPV versus supportive care to prevent respiratory failure postextubation



Reintubation

Five studies reported reintubation rates ranging from 8 to 25 percent for NPPV to 8 to 28 percent for usual care. Overall, NPPV postextubation did not decrease reintubation rates compared with usual supportive care (OR 0.84; 95% CI, 0.56 to 1.27; Figure 17), but tests for heterogeneity suggested significant variability in treatment effects across studies (Q = 10.73, df = 4, p = 0.03, I^2 = 63%). Subgroup analyses by those at high risk for recurrent acute respiratory failure versus those at average risk showed a protective effect only for those at high risk (OR 0.43; 95% CI, 0.24 to 0.77).

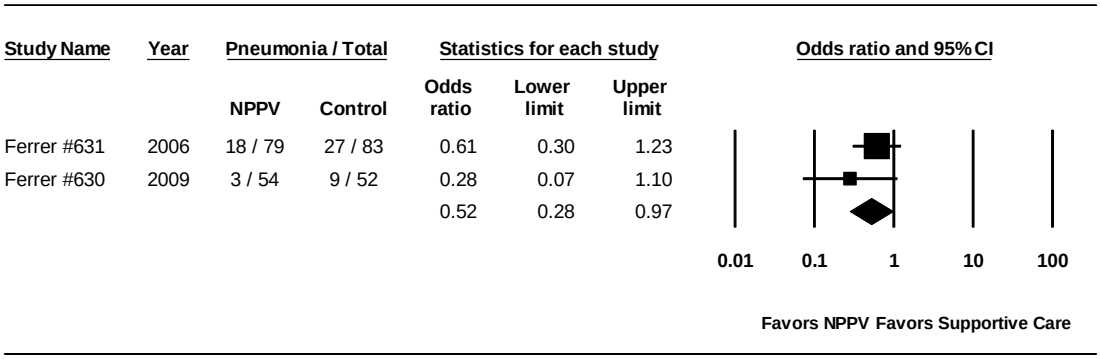
Figure 17. Random-effects analysis of data on reintubation rates—NPPV versus supportive care to prevent respiratory failure postextubation



Hospital-Acquired Pneumonia

Two studies, both in populations at high risk for reintubation, reported rates of hospital-acquired pneumonia, ranging from 6 to 23 percent for NPPV and 17 to 33 percent for usual care. Overall, NPPV postextubation decreased hospital-acquired pneumonia rates compared with usual supportive care (summary OR 0.52; 95% CI, 0.28 to 0.97; Figure 18). Tests for heterogeneity suggested no significant variability in treatment effects (Q = 0.99, df = 1, p = 0.32, I^2 = 0%).

Figure 18. Random-effects analysis of data on hospital-acquired pneumonia rates—NPPV versus supportive care to prevent respiratory failure postextubation



Abbreviations: CI = confidence interval; NPPV = noninvasive positive-pressure ventilation

Length of Stay

Three studies reported effects on hospital length of stay.[117,118,123] Mean length of stay varied from 23 to 30 days in NPPV-treated patients and 24 to 29 days with supportive care. All three had large enough sample sizes to show a difference of 1 or more days in length of stay; none found a statistically significant difference.

ICU length of stay was reported in the same three studies; mean ICU length of stay ranged from 9 to 11 days in NPPV-treated patients and 10 to 13 days with supportive care. Of the three studies, all had large enough sample sizes to show a difference of 1 or more days in length of stay; none found a statistically significant reduction in length of stay for early extubation to NPPV.

Several issues limit these findings. Length-of-stay data typically have a skewed distribution, making statistical tests that assume normality inappropriate, but such tests were sometimes used in these studies. Second, the results may be biased if NPPV reduces mortality, thus increasing length of stay. None of the studies reported subgroup analyses that limited the results to surviving patients. In summary, current evidence suggests that neither hospital nor ICU length of stay is decreased by NPPV postextubation. However, for the reasons described, these results should be interpreted with caution.

NPPV Versus Supportive Care to Treat Respiratory Failure Postextubation

We identified two studies that evaluated the relative treatment effects of NPPV versus supportive care in patients who develop recurrent acute respiratory failure postextubation.[115,121]

Both studies used BPAP and were judged to be good quality. Table 14 summarizes the pooled treatment effects. Mortality, reintubation rates, and hospital-acquired pneumonia rates did not differ for NPPV compared with supportive care. In each case, the point estimate suggested the possibility of worse outcomes for NPPV. The small numbers of studies and patients and relatively few events limit all summary estimates. Because formal statistical techniques for publication bias are not effective with small numbers of studies, we did not conduct analyses for publication bias.

Table 14. Summary of effects for key outcomes—NPPV versus supportive care to treat respiratory failure postextubation

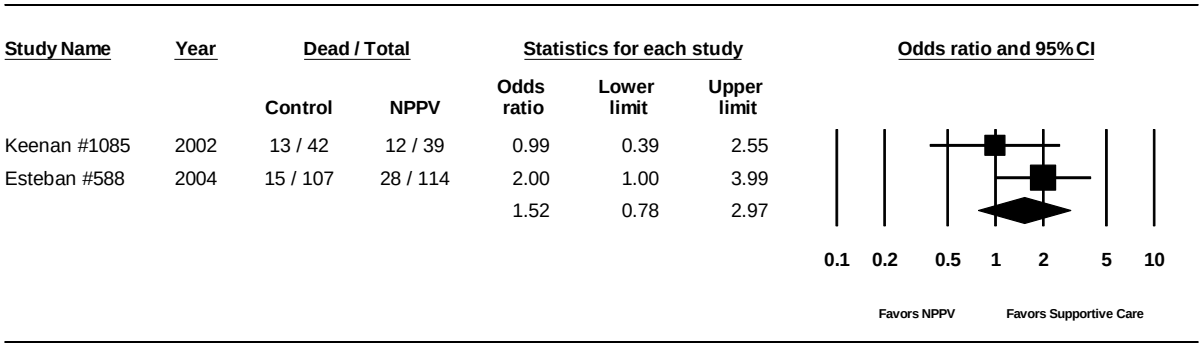
Outcome	Group	No. of Studies (N)	Summary OR (95% CI)	Tests for Heterogeneity
Mortality	All	2 (302)	1.52 (0.78 to 2.97)	p = 0.24, I^2 = 27%
Reintubation	All	2 (302)	1.05 (0.66 to 1.67)	p = 0.85, I^2 = 0%
Hospital-acquired pneumonia	All	1 (81)	1.02 (0.42 to 2.48)	NA
Myocardial infarction	All	0 (0)	NR	NR

Abbreviations: CI = confidence interval; N = number of participants; NA = not applicable; NPPV = noninvasive positive-pressure ventilation; NR = not reported; OR = odds ratio

Mortality

Mortality ranged from 14 to 31 percent for usual care and 25 to 31 percent for NPPV in two studies.[115,121] Overall, NPPV postextubation did not decrease mortality (OR 1.52; 95% CI, 0.78 to 2.97; Figure 19). Tests for heterogeneity did not suggest important variability in treatment effects across studies (Q = 1.38, df = 1, p = 0.24, I^2 = 27%).

Figure 19. Random-effects analysis of data on mortality—NPPV versus supportive care to treat respiratory failure postextubation

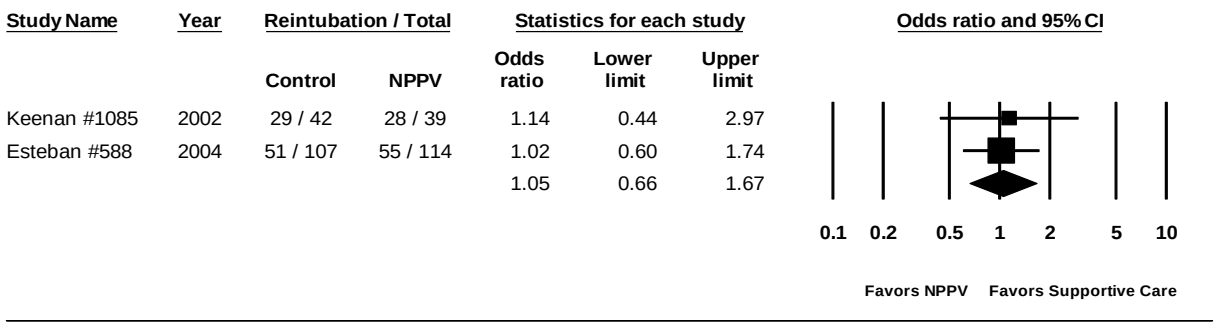


Abbreviations: CI = confidence interval; NPPV = noninvasive positive-pressure ventilation

Reintubation

Two studies reported reintubation rates ranging from 48 to 72 percent for NPPV to 48 to 69 percent for usual care.[115,121] Overall, NPPV postextubation did not decrease reintubation rates compared with usual supportive care (OR 1.05; 95% CI, 0.66 to 1.67; Figure 20). Tests for heterogeneity did not suggest important variability in treatment effects across studies (Q = 0.04, df = 1, p = 0.85, I^2 = 0%).

Figure 20. Random-effects analysis of data on reintubation rates—NPPV versus supportive care to treat respiratory failure postextubation



Abbreviations: CI = confidence interval; NPPV = noninvasive positive-pressure ventilation

Hospital-Acquired Pneumonia

Only one study reported the rate of hospital-acquired pneumonia.[121] In this study the rate of HAP was the same (41%) in both treatment groups.

Length of Stay

Only one study reported effects on hospital length of stay.[121] Mean length of stay did not differ significantly; 32.2 days in NPPV-treated patients and 29.8 days with supportive care. Of the five studies, three had large enough sample sizes to show a difference of 1 or more days in length of stay; none found a statistically significant difference.

ICU length of stay was reported in two studies; median ICU length of stay ranged from 11.9 to 18 days in NPPV-treated patients and 10.8 to 18 days with supportive care. Both studies had large enough sample sizes to show a difference of 1 or more days in length of stay; neither found a statistically significant reduction in length of stay when NPPV was used to treat postextubation respiratory failure.

Several issues limit these findings. Length-of-stay results may be biased if NPPV reduces mortality, thus increasing length of stay. Neither of the studies reported subgroup analyses that limited the results to surviving patients. In summary, current evidence suggests that neither hospital nor ICU length of stay is decreased when NPPV is used to treat respiratory failure postextubation. However, for the reasons described, these results should be interpreted with caution.

Other Outcomes (Weaning and Postextubation Studies)

Intolerance and Facial Ulcerations

Three studies[115,117,121] evaluating NPPV postextubation to prevent recurrent acute respiratory failure reported rates of discontinuation due to poor patient tolerability; median discontinuation was 9.3 percent (range 4.4 to 25.6%). Rates of facial abrasions or ulcerations were reported in four studies[116,118,120,121] and varied widely, ranging from 2.1 to 26 percent. Variability appears related in part to different definitions for facial injury and in part to differing durations of followup.

Other Outcomes

Other outcomes were reported infrequently or not at all. No study reported effects on psychological response, functional status, or health-related quality of life. Giraualt et al,[124] a good-quality study, reported equivalent rates of sinusitis in the NPPV weaning and conventional weaning arms (1 of 69 in each).

The duration of mechanical ventilation was reported in five studies that compared NPPV weaning with conventional weaning. The mean duration of mechanical ventilation ranged from 4.6 to 10.2 days for NPPV weaning and 7.7 to 20.1 days with conventional weaning. All studies showed a statistically significant decrease in invasive ventilation with NPPV weaning. Only one study reported the duration of mechanical ventilation when NPPV was used to treat respiratory distress after extubation.[121] This good-quality study, conducted with 81 patients with ACPE, found a nonstatistically significant decrease in ventilator days with NPPV compared with supportive care (median 6.7 [range 0.5 to 28.6] versus 8.9 [range 2.0 to 146.7, p = 0.12]). One study reported the rate of ventilator dependence at hospital discharge for NPPV weaning (0 of 25) compared with conventional weaning (2 of 25, p-value not reported).[123]

Key Question 4. Variation by Subgroups

KQ 4: For KQs 1–3, do the effectiveness and risks of NPPV vary by setting and associated resources, experience and training of clinicians, and use of protocols or by patient characteristics (e.g., morbid obesity, mental-status changes, overall disease burden)?

Key Points

- The effects of NPPV on intubation rates are stronger when NPPV is initiated in the ICU than when it is initiated in the ED, but these findings are based on indirect comparisons.
- Few studies reported details about clinical setting and associated resources, experience and training of clinicians, or the use of clinical protocols. With the exception of diagnosis at study entry, no studies reported results by patient characteristics.
- The pooled OR associated with NPPV for both mortality and intubation shows a stronger effect for efficacy trials compared with effectiveness trials, but only two effectiveness trials were included in the analysis, and the 95% CIs overlapped.
- The treatment effects for NPPV on mortality and intubation rates are consistent across studies conducted in the United States or Canada versus European countries versus other countries.
- With the exception of the clinical setting in studies that compared NPPV with usual supportive care or invasive ventilator support (KQ 1), too few studies reported sufficient data to evaluate whether effectiveness or risks of NPPV vary by setting or patient characteristics.

Description of Included Studies

Of the 69 eligible studies, 65 (94%) reported information about the clinical setting in which NPPV was initiated, 3 (4%) provided specific information about the experience or training of study clinicians, 2 (3%) reported patients' mean body mass index, 16 (23%) reported data on patients' neurological or mental status, 17 (25%) reported a measure of disease burden, and 46

(67%) reported mean baseline APACHE II, APACHE III, or SAPS scores for predicted ICU mortality.

We conducted subgroup analysis for the clinical setting, the geographical world region, and efficacy-effectiveness category. Of the 49 studies that pertain to KQ 1, NPPV was initiated in the ED setting in 10 studies (20%) and in the ICU setting in 23 studies (47%). In the remaining 16 studies (33%), clinical setting was either not reported, or NPPV was initiated in another setting such as a general medicine ward or ambulance. The majority of studies were conducted in Europe. Most studies were classified as mixed efficacy-effectiveness studies; only two were classified as effectiveness studies. Forty-six studies compared NPPV with supportive care or invasive ventilator support; of these 43 (93%) reported mortality rates and 39 (85%) reported intubation rates and were included in these subgroup analyses.

In addition to the subgroup analyses we conducted, we reviewed each study for subgroup analyses relevant to KQ 4. Nineteen of the 69 eligible studies (28%) reported subgroup analyses. None of these subgroups, however, corresponded to variables that we identified a priori, such as clinical setting, experience of clinicians, use of protocols, or such patient characteristics as obesity, mental status, or overall disease burden. Examples of the subgroups reported in the eligible studies include hypercapnic or acidotic patients, or patients with versus without cardiac disease. Among all the eligible studies (including those that did not report subgroup analyses), too few studies reported resources used, the experience and training of clinicians, the use of protocols, or patient characteristics to justify a qualitative or quantitative summary of the findings by these subgroups for KQs 1–3. Mortality and intubation rates were reported in a sufficient number of studies to justify subgroup analyses for these outcomes by clinical setting for KQ 1. Data were insufficient to justify subgroup analyses for KQ 2 or KQ 3 for these outcomes or for other outcomes considered for KQ 1. There were sufficient data, however, to explore whether estimates of effect of NPPV vary by whether studies were efficacy trials versus effectiveness trials for the outcomes of mortality and intubation, and whether estimates of effect of NPPV vary by the geographical region from which patients were recruited.

Detailed Synthesis

Variations by Clinical Setting

We conducted subgroup analyses to explore whether the effectiveness and risks of NPPV varied by clinical setting. We constrained these analyses to studies that compared NPPV with usual supportive care or invasive ventilation (KQ 1), which together includes the largest set of conceptually similar studies included in our report. These analyses should be considered to be exploratory because they consist of indirect comparisons, and studies may have differed in important ways on characteristics other than the ones we examined. The summary OR for mortality associated with NPPV with usual supportive care as the referent was 0.72 (95% CI, 0.49 to 1.05) in studies in which NPPV was initiated in the ED and 0.48 (95% CI, 0.35 to 0.66) in studies in which NPPV was initiated in the ICU (Table 15). Among studies in which NPPV was initiated in other settings or for which the setting was not reported, the OR for mortality was 0.65 (95% CI, 0.43 to 0.98). The difference in pooled ORs across the three settings (ED, ICU, other) was not statistically significant ($Q = 2.92$, $df = 2$, $p = 0.23$). An analysis that examined risk of intubation showed differences in treatment effect that approached statistical significance: the ORs for intubation were 0.50 (95% CI, 0.26 to 0.95), 0.23 (0.15 to 0.34), and 0.36 (0.25 to 0.51) for NPPV initiated in the ED, ICU, or mixed/unreported, respectively ($Q = 5.10$, $df = 2$, $p =$

0.08). These differences could be related to the treatment setting or other factors (such as severity of illness) not considered in this analysis. Too few studies reported patient characteristics hypothesized to be associated with treatment effects (e.g., experience and training of clinicians or patient characteristics) to conduct subgroup analyses for these variables.

Table 15. Risk of mortality or intubation by clinical setting, NPPV versus usual supportive care or invasive ventilation[a]

Clinical Setting	Mortality[b] (n = 43) Odds Ratio (95% CI)	Intubation[c] (n = 39) Odds Ratio (95% CI)
Emergency department	0.72 (0.49 to 1.05)	0.50 (0.26 to 0.95)
ICU	0.48 (0.35 to 0.66)	0.23 (0.15 to 0.34)
Mixed, other, or not reported	0.65 (0.43 to 0.98)	0.36 (0.25 to 0.51)

[a]Studies that compared NPPV with usual supportive care or invasive ventilator support (KQ 1) are included, but studies that compared different NPPV approaches (KQ 2) or were weaning studies (KQ 3) are not included.
[b]Includes in-hospital mortality when reported and ICU mortality when in-hospital mortality not reported; p = 0.23 for differences in treatment effect by clinical setting.
[c]Does not include studies that compared NPPV with invasive ventilation; p = 0.08 for differences in treatment effect by clinical setting.
Abbreviations: CI = confidence interval; ICU = intensive care unit; KQ = Key Question; NPPV = noninvasive positive-pressure ventilation

Variations by Effectiveness Rating

We performed meta-analyses of the studies that pertain to KQ 1 to explore whether effectiveness of NPPV, as measured by mortality or intubation rates, varies by study type. We used the effectiveness rating scale proposed by Gartlehner et al.50 and assigned a scale score of 0–7 to each study, as described above in the Methods chapter. We defined studies with a score of 0–2 as efficacy trials and studies with a score of 6 to 7 as effectiveness trials. Studies with scores of 3–5 were defined as "mixed."

The median effectiveness score for the 47 studies that pertain to Key Question 1 is 3.5 (range, 0.5–6). Of the 43 studies that compared NPPV with usual supportive care or invasive ventilation and reported mortality rates, 11 (26%) were efficacy trials, 2 (4%) were effectiveness trials, and 30 (70%) were mixed efficacy-effectiveness trials. The pooled ORs for mortality were 0.56 (95% CI, 0.31 to 1.02) and 0.99 (0.66 to 1.49) for efficacy and effectiveness trials, respectively; for mixed efficacy-effectiveness trials, the pooled OR was 0.52 (95% CI, 0.41, 0.66; Table 16). An analysis that examined risk of intubation yielded similar results: for intubation, the pooled ORs for efficacy (n = 10), effectiveness (n = 2), and mixed efficacy-effectiveness trials (n = 25) were, respectively, 0.29 (95% CI, 0.19 to 0.46), 0.58 (0.16 to 2.13), and 0.29 (0.21 to 0.41; Table 16). The difference in pooled ORs across the three categories of effectiveness was statistically significant for mortality (Q = 7.96, p = 0.02) but not for intubation (Q = 0.98, p = 0.61). For both mortality and intubation, there were only two effectiveness trials, thereby potentially rendering the pooled OR an unreliable estimate. The 95% CIs associated with the efficacy and effectiveness studies overlapped for both mortality and intubation.

Table 16. Risk of mortality or intubation by effectiveness rating, NPPV versus usual supportive care or invasive ventilation[a]

Effectiveness Rating	Mortality[b] (n = 43) Odds Ratio (95% CI)	Intubation[c] (n = 39) Odds Ratio (95% CI)
Efficacy trial	0.56 (0.31 to 1.02)	0.29 (0.19 to 0.46)
Mixed efficacy-effectiveness trial	0.52 (0.41 to 0.66)	0.29 (0.21 to 0.41)
Effectiveness trial	0.99 (0.66 to 1.49)	0.58 (0.16 to 2.13)

[a]Studies that compared NPPV with usual supportive care or invasive ventilator support (KQ 1) are included, but studies that compared different NPPV approaches (KQ 2) or were weaning studies (KQ 3) are not included.
[b]Includes in-hospital mortality when reported and ICU mortality when in-hospital mortality not reported; p = 0.02 for differences in treatment effect by effectiveness rating.
[c]Does not include studies that compared NPPV with invasive ventilation; p = 0.61 for differences in treatment effect by effectiveness rating.
Abbreviations: CI = confidence interval; NPPV = noninvasive positive-pressure ventilation

Variations by Geographical Region

There is evidence to suggest that several European countries have more extensive experience with NPPV than the United States, Canada, or other countries. We explored the hypothesis that studies conducted in Europe demonstrate greater effectiveness associated with NPPV compared with studies conducted in the U.S. or Canada. We conducted meta-analyses of the 43 studies that pertain to KQ 1 that reported mortality and the 39 studies that pertain to KQ 1 that reported intubation rates using three subgroups: (1) studies that included primarily patients recruited in Europe; (2) studies that included primarily patients recruited in the U.S. or Canada; and (3) studies that included primarily patients recruited in other countries. Results of these meta-analyses are summarized in Table 17. The pooled OR for mortality for the 25 studies conducted in Europe is 0.58 (95% CI, 0.46 to 0.73), compared with 0.58 (95% CI, 0.25 to 1.33) for the 5 studies conducted in the U.S. or Canada, and 0.64 (95% CI, 0.36 to 1.13) for the 13 studies conducted in other countries. The difference in pooled ORs for mortality across the three categories of countries was not statistically significant (Q = 0.11, df = 2, p = 0.95). For the 39 studies that pertain to KQ 1 and reported intubation rates, the pooled OR was 0.33 (95% CI, 0.22 to 0.48) for the 19 studies conducted in Europe, 0.36 (0.20 to 0.66) for the 6 studies conducted in the U.S. or Canada, and 0.25 (95% CI, 0.14 to 0.43) for the 14 studies conducted in other countries. The difference in pooled odds ratios for intubation across the three categories of countries was not statistically significant (Q = 0.73, p = 0.70).

Table 17. Risk of mortality or intubation by geographical location, NPPV versus usual supportive care or invasive ventilation[a]

Geographical Location	Mortality[b] (n = 43) Odds Ratio (95% CI)	Intubation[c] (n = 39) Odds Ratio (95% CI)
Europe	0.58 (0.46 to 0.73)	0.33 (0.22 to 0.48)
U.S. or Canada	0.58 (0.25 to 1.13)	0.36 (0.20 to 0.66)
Other countries	0.64 (0.36 to 1.13)	0.25 (0.14 to 0.43)

[a]Studies that compared NPPV with usual supportive care or invasive ventilator support (KQ 1) are included, but studies that compared different NPPV approaches (KQ 2) or were weaning studies (KQ 3) are not included.
[b]Includes in-hospital mortality when reported and ICU mortality when in-hospital mortality not reported; p = 0.95 for differences in treatment effect by geographical location'
[c]Does not include studies that compared NPPV with invasive ventilation; p = 0.70 for differences in treatment effect by geographical location.
Abbreviations: CI = confidence interval; NPPV = noninvasive positive-pressure ventilation

Summary

The results of our meta-analyses suggest that NPPV initiated in the ICU is effective in reducing mortality (OR 0.48; 95% CI, 0.35 to 0.66) and intubation rates (OR 0.23; 95% CI, 0.15 to 0.34). The 95% CIs for the pooled OR for mortality (0.72) included 1.0 among studies that initiated NPPV in the ED. These analyses should be considered exploratory because they consist of indirect comparisons, and studies may have differed in important ways on characteristics other than the ones we examined. There were too few studies that pertain to KQ 1 that reported patient characteristics, too few studies that pertain to either KQ 2 or KQ 3 that reported setting or patient characteristics, and too few studies that pertain to any of the KQs that reported adverse events to further explore whether effectiveness or risks of NPPV vary by setting or patient characteristics.

The pooled ORs associated with NPPV for both mortality and intubation were lower for efficacy trials compared with effectiveness trials, but only two effectiveness trials were included in the analysis, and the 95% CIs overlapped. Treatment effects for NPPV on mortality and intubation rates were similar between European countries, the U.S. or Canada, and other countries.

Discussion

Key Findings and Strength of Evidence

Acute respiratory failure is a common life-threatening disorder and is the most frequent condition managed in intensive care units (ICUs) around the world. Noninvasive positive-pressure ventilation (NPPV), most commonly delivered as continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BPAP), is a form of mechanical ventilatory support that improves gas exchange and decreases a patient's work of breathing.

In this review, we included 69 trials that that compared NPPV with other common treatment strategies. Most studies compared NPPV with supportive care for the treatment of acute respiratory failure. A smaller group compared NPPV with conventional mechanical ventilation, compared different types of NPPV with one another (CPAP vs. BPAP), or considered NPPV to facilitate extubation or prevent or treat recurrent respiratory failure postextubation. We included common outcomes of interest such as mortality and adverse events, but also examined more difficult to measure issues such as resource utilization and efforts to shorten the duration of mechanical ventilation (by facilitating weaning from invasive ventilation, preventing extubation failure, and treating recurrent respiratory failure).

Results for these outcomes and comparisons, along with ratings for the strength of evidence (SOE)[54,55] are summarized in Tables 18 and 19. Key findings with a high strength of evidence were decreased mortality and intubation rates for NPPV versus supportive care. This effect was established most strongly for patients with acute cardiogenic pulmonary edema (ACPE), or severe exacerbations of chronic obstructive pulmonary disease (COPD). Few studies enrolled patients with asthma, acute respiratory distress syndrome (ARDS), postoperative acute respiratory failure, or acute respiratory failure in post-transplant patients. We found moderate strength of evidence for a lack of treatment effect on myocardial infarction rates and reduced hospital-acquired pneumonia. Evidence was also moderately strong for comparable effects of CPAP and BPAP, but direct comparisons of these modalities come almost exclusively from studies of patients with ACPE. For NPPV versus supportive care, we found low SOE of no effect on length of hospitalization. We found insufficient evidence for other effects on utilization of medical resources due to inconsistent effects across studies, indirectness of the outcomes reported (length of stay) and imprecise results. Few studies reported effects beyond the duration of hospitalization, and no studies reported effects on functional status or quality of life.

NPPV was compared with invasive ventilation in only 405 subjects. Compared with invasive ventilation, NPPV lowered hospital-acquired pneumonia (SOE = high) but did not reduce mortality or length of stay (SOE = low).

Table 18. Summary of the strength of evidence for KQ 1—NPPV versus supportive care

Number of Studies (Subjects)	Domains Pertaining to SOE				Strength of Evidence
	Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	Effect Estimate (95% CI)
Hospital mortality					**High**
39 (4111)	RCT/Good	Consistent	Direct	Precise	OR = 0.56 (0.44 to 0.72) RD = 64 fewer per 1000 (40 to 83)
Intubation rate					**High**
39 (3792)	RCT/Good	Inconsistent	Direct	Precise	OR = 0.31 (0.24 to 0.41) RD = 217 fewer per 1000 (177 to 247)
Myocardial infarction					**Moderate**
7 (1517)	RCT/Good	Consistent	Direct	Imprecise	OR = 1.11 (0.85 to 1.44) RD = not applicable
Medical utilization: Hospital length of stay (LOS)					**Low**
11 (2499)[a]	RCT/Good	Consistent	Indirect	Imprecise	No study found a statistically significant difference in LOS
Medical utilization: ICU length of stay (LOS)					**Insufficient**
5 (523)[a]	RCT/Good	Inconsistent	Indirect	Imprecise	Not estimable; 2 of 5 studies found a statistically significant decrease in LOS
Hospital-acquired pneumonia					**Moderate**
9 (650)	RCT/Good	Consistent	Direct	Imprecise	OR = 0.27 (0.15 to 0.49) RD = 121 fewer per 1000 (81 to 144)

[a]Data are for larger studies with sufficient power to test for a 1-day difference in LOS.
Abbreviations: CI = confidence interval; ICU = intensive care unit; LOS = length of stay; NA = not applicable; OR = odds ratio; RCT = randomized controlled trial; RD = risk difference; SOE = strength of evidence

Table 19. Summary of the strength of evidence for KQ 2—CPAP versus BPAP

Number of Studies (Subjects)	Domains Pertaining to SOE				Strength of Evidence
	Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	Effect Estimate (95% CI)
Hospital mortality					**Moderate**
10 (1338)	RCT/Good	Consistent	Direct	Imprecise	OR = 0.89 (0.58 to 1.35) RD = NA
Intubation rate					**Moderate**
12 (1463)	RCT/Good	Consistent	Direct	Imprecise	OR = 0.84 (0.51 to 1.38) RD = NA
Myocardial infarction					**Low**
7 (1056)	RCT/Good	Inconsistent	Indirect	Imprecise	OR = 0.69 (0.34 to 1.40) RD = NA
Medical utilization: hospital length of stay (LOS)					**Insufficient**
3 (278)[a]	RCT/Good	Consistent	Indirect	Imprecise	Not estimable; No study found a statistically significant difference in LOS
Medical utilization: ICU length of stay (LOS)					**Insufficient**
0 (0)	NA	NA	NA	NA	Not estimable
Hospital-acquired pneumonia					**Insufficient**
0 (0)	NA	NA	NA	NA	Not estimable

[a]Data are for larger studies with sufficient power to test for a 1-day difference in LOS.
Abbreviations: CI = confidence interval; ICU = intensive care unit; LOS = length of stay; NA = not applicable; OR = odds ratio; RCT = randomized controlled trial; RD = risk difference; SOE = strength of evidence

Compared with studies evaluating NPPV for initial treatment of acute respiratory failure, fewer studies examined the effects of NPPV to assist in weaning from invasive ventilation or to prevent or treat recurrent acute respiratory failure postextubation. Results for these comparisons, along with ratings for the SOE are summarized in Tables 20–22. When compared with conventional weaning, we found low SOE for lower mortality in patients with COPD and a nonstatistically significant reduction in mortality in studies enrolling patient with mixed etiologies of acute respiratory failure. Results were similar for hospital-acquired pneumonia rates. NPPV did not affect reintubation rates, an effect that was consistent across diagnostic subgroups. Evidence was insufficient to estimate effects for other outcomes. When used to prevent acute respiratory failure postextubation, NPPV decreased mortality and reintubation (low SOE) only for patients at high-risk of recurrent acute respiratory failure (Table 21). Only two studies evaluated NPPV to treat recurrent acute respiratory failure postextubation. These studies did not show a benefit for NPPV on any outcome (Table 22).

Table 20. Summary of the strength of evidence for KQ 3—NPPV-assisted ventilator weaning versus conventional weaning

Number of Studies (Subjects)	Domains Pertaining to SOE				Strength of Evidence
	Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	Effect Estimate (95% CI)
Hospital mortality—COPD					**Low**
2 (140)	RCT/Fair	Consistent	Direct	Imprecise	OR = 0.17 (0.05 to 0.65) RD = 129 fewer per 1000 (50 to 151)
Hospital mortality—mixed etiologies					**Insufficient**
3 (214)	RCT/Fair	Inconsistent	Direct	Imprecise	OR = 0.46 (0.06 to 3.59) RD = NA
Reintubation rate					**Low**
4 (303)	RCT/Good	Consistent	Direct	Imprecise	OR = 0.83 (0.48 to 1.44) RD = NA
Myocardial infarction					**Insufficient**
0 (none)	NA	NA	NA	NA	OR = not estimated
Medical utilization: hospital length of stay (LOS)					**Insufficient**
2 (229)	RCT/	Consistent	Indirect	Imprecise	Not estimable; No study found a statistically significant difference in LOS
Medical utilization: ICU length of stay (LOS)					**Insufficient**
3 (279)[a]	RCT/Good	Consistent	Indirect	Imprecise	Not estimable; 2 of 3 studies found a statistically significant decrease in LOS
Hospital acquired pneumonia—COPD					**Low**
2 (140)	RCT/Fair	Consistent	Direct	Imprecise	OR = 0.14 (0.04 to 0.48) RD = 167 fewer per 1,000 (33 to 233)
Hospital-acquired pneumonia—mixed etiologies					**Low**
3 (214)	RCT/Fair	Inconsistent	Direct	Imprecise	OR = 0.53 (0.19 to 1.46) RD = NA

[a]Data are for larger studies with sufficient power to test for a 1-day difference in LOS.
Abbreviations: CI = confidence interval; LOS = length of stay; NA = Not applicable; OR = odds ratio; RCT = randomized controlled trial; RD = risk difference; SOE = strength of evidence

Table 21. Summary of the strength of evidence for KQ 3—NPPV versus supportive care to prevent respiratory failure postextubation

Number of Studies (Subjects)	Domains Pertaining to SOE				Strength of Evidence
	Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	Effect Estimate (95% CI)
Hospital mortality—high-risk group					**Low**
3 (365)	RCT/Good	Consistent	Direct	Imprecise	OR = 0.60 (0.34 to 1.04) RD = NA
Hospital mortality—average-risk group					**Insufficient**
1 (406)	RCT/Fair	NA	Direct	Imprecise	OR = 1.52 (0.25 to 9.21) RD = NA
Reintubation rate—high-risk group					**Low**
3 (365)	RCT/Good	Consistent	Direct	Imprecise	0.43 (0.24 to 0.77)
Reintubation rate—average-risk group					**Low**
2 (499)	RCT/Fair	Consistent	Direct	Imprecise	OR = 1.56 (0.89 to 2.76) RD = NA
Myocardial infarction					**Insufficient**
0 (none)	NA	NA	NA	NA	OR = not estimated
Medical utilization: hospital length of stay (LOS)					**Insufficient**
3 (365)	RCT/Good	Consistent	Indirect	Imprecise	Not estimable; No study found a statistically significant difference in LOS
Medical utilization: ICU length of stay (LOS)					**Insufficient**
3 (365)[a]	RCT/Good	Consistent	Indirect	Imprecise	Not estimable; No study found a statistically significant difference in LOS
Hospital acquired pneumonia					**Low**
2 (268)[a]	RCT/Fair	Consistent	Direct	Imprecise	OR = 0.52 (0.28 to 0.97) RD = 102 fewer per 1,000 (6 to 164)

[a]Data are for larger studies with sufficient power to test for a 1-day difference in LOS.

Abbreviations: CI = confidence interval; LOS = length of stay; OR = odds ratio; RCT = randomized controlled trial; RD = risk difference; SOE = strength of evidence

Table 22. Summary of the strength of evidence for KQ 3—NPPV versus supportive care to treat respiratory failure postextubation

Number of Studies (Subjects)	Domains Pertaining to SOE				Strength of Evidence
	Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	Effect Estimate (95% CI)
Hospital mortality					**Low**
2 (302)	RCT/Good	Consistent	Direct	Imprecise	OR = 1.52 (0.78 to 2.97) RD = NA
Reintubation rate					**Low**
2 (302)	RCT/Good	Consistent	Direct	Imprecise	OR = 1.05 (0.66 to 1.67) RD = NA
Myocardial infarction					**Insufficient**
0 (none)	NA	NA	NA	NA	OR = not estimated
Medical utilization: hospital length of stay (LOS)					**Insufficient**
1 (81) [a]	RCT/Good	NA	Indirect	Imprecise	Not estimable
Medical utilization: ICU length of stay (LOS)					**Insufficient**
2 (302)[a]	RCT/Good	Consistent	Indirect	Imprecise	Not estimable; No study found a statistically significant difference in LOS
Hospital-acquired pneumonia					**Insufficient**
1 (81)	RCT/Good	NA	Direct	Imprecise	OR = 1.02 (0.42 to 2.48)

[a]Data are for larger studies with sufficient power to test for a 1-day difference in LOS.
Abbreviations: CI = confidence interval; LOS = length of stay; OR = odds ratio; RCT = randomized controlled trial; RD = risk difference; SOE = strength of evidence

We also sought to determine whether the effects of NPPV varied by clinical setting, the experience and composition of the treating clinicians, by patient characteristics and by whether each individual study was primarily an efficacy trial, an effectiveness trial, or mixed efficacy-effectiveness (Table 23). Too few studies reported clinician experience, treating team composition, or patient characteristics such as body mass index, mental status or overall disease burden to evaluate for differential effects. We used global geographical region as a proxy for experience with NPPV and found no significant difference in treatment effects across different regions. Most studies were classified as mixed efficacy-effectiveness studies; only two were classified as predominately effectiveness studies. Effects on mortality were lower for effectiveness studies but did not differ for intubation rates. These analyses were limited by the paucity of effectiveness trials. NPPV was initiated in intensive care unit, emergency departments (EDs), and mixed or other settings. In an exploratory analysis, treatment effects for death or intubation did not differ significantly by clinical setting.

Table 3. Summary of the strength of evidence for KQ 4—variability in treatment effect by study characteristics

Number of Studies (Subjects)	Domains Pertaining to SOE				Strength of Evidence
	Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	Summary of Effect
Different treatment effects by study effectiveness characteristics					**Low**
43 (4467)[a]	Observational	Inconsistent	Direct	Imprecise	OR (95% CI) for mortality: Efficacy trial: 0.56 (0.31 to 1.02) Mixed trial: 0.52 (0.41 to 0.66) Effectiveness trial: 0.99 (0.66 to 1.49) OR (95% CI) for intubation: Efficacy trial: 0.29 (0.19 to 0.46) Mixed trial: 0.29 (0.21 to 0.41) Effectiveness trial: 0.58 (0.16 to 2.13)
Different treatment effects across clinical settings					**Low**
43 (4467)[a]	Observational	Consistent	Direct	Imprecise	OR (95% CI) for mortality: ED: 0.72 (0.49 to 1.05) ICU: 0.48 (0.35 to 0.66) OR (95% CI) for intubation: ED: 0.50 (0.26 to 0.95) ICU: 0.23 (0.15 to 0.34)
Different treatment effects across geographical regions[b]					**Low**
43 (4467)[a]	Observational	Consistent	Direct	Imprecise	OR (95% CI) for mortality: Europe: 0.58 (0.46 to 0.73) U.S./Canada: 0.58 (0.25 to 1.33) OR (95% CI) for intubation: Europe: 0.33 (0.22 to 0.48) U.S./Canada: 0.36 (0.20 to 0.66)

[a]39 studies and 3792 patients for analyses of intubation rates.
[b]Geographical regions used were: U.S./Canada, Europe, and other
Abbreviations: KQ = Key Question; OR = odds ratio; SOE = strength of evidence; ED = emergency department; ICU = intensive care unit

Findings in Relation to What Is Already Known

Our results are generally consistent with previous systematic reviews[45,47,48] and clinical guidelines.[26,41,126] Previous reviews have found similar benefits on mortality and intubation rates in patients with respiratory failure due to ACPE[36,39,42,47,48] and severe exacerbations of COPD.[45,46] Our review spanned multiple conditions, finding consistent treatment effects across conditions, whereas prior reviews tend to be focused on a single cause of acute respiratory failure. Like others, we found few studies addressing acute respiratory failure in patients who are postoperative, post-transplant, or who have acute respiratory failure in the context of obesity-hypoventilation syndrome, asthma, or interstitial lung disease. As in other reviews, we found comparable effects for CPAP and BPAP, but we were able to strengthen this conclusion by incorporating indirect comparisons. Also of note, our review is the first to classify trials by efficacy and effectiveness characteristics, an analysis that highlights the paucity of effectiveness studies.

There are several other considerations that warrant further discussion. Regarding NPPV for ACPE, our positive findings are in contrast to the Three Interventions in Cardiogenic Pulmonary Oedema (3CPO) trial, the largest published trial, comprising about one-quarter of our overall sample. Investigators in that trial concluded that NPPV does not reduce early mortality.[71,127] The lack of treatment effect in the 3CPO study was likely related to the relatively short duration of the NPPV intervention, a patient sample that was less severely ill than in many other studies, and the large number of patients assigned to supportive care who crossed over to the NPPV treatment arms. It should also be considered that standard medical therapy for ACPE has likely improved over the past 20 years. The 3CPO study is a relatively recent study and improved supportive treatments could diminish the differential treatment effects. In fact, our analysis of time trends showed smaller treatment effects in more recent studies.

A systematic review and meta-analysis by Burns et al.[34] demonstrated a consistent positive effect of NPPV weaning on mortality and ventilator-associated pneumonia, which is in contrast to our findings of significant effects that vary by population. However, the Burns review and the trials included had important limitations. Most studies in their review were restricted to patients with predominately or exclusively COPD. There was also evidence for publication bias, imprecision due to a relatively small number of study participants (n = 530) and events (102 deaths), and the review included studies from countries with health systems that are less applicable to care in the United States. Our review also has limitations when evaluating this question. We too identified a relatively small number of trials that were analyzed in three subgroups depending on the specific clinical application of NPPV. For each clinical scenario, we conducted exploratory analysis by diagnostic group or risk of recurrent acute respiratory failure, indirect comparisons that are subject to confounding.

Applicability

The positive effects of interventions do not always translate well to usual practice, where clinician training, clinical setting, system resources and patients characteristics may vary importantly from trial conditions. In our review, relatively few studies were conducted in the United States or Canada (n = 8), with most studies (57%) conducted in Europe. There is a longer clinical experience with NPPV in Europe compared with the United States, leading us to hypothesize that outcomes may be better in European countries. However, our analyses showed treatment effects for NPPV that were consistent across studies conducted in the U.S. or Canada compared with European or other countries. Treatment effects associated with NPPV were also fairly consistent across clinical settings. Summary odds ratios (ORs) for NPPV initiated in the ICU showed greater, although not statistically significant, differences compared with usual supportive care or invasive ventilator support. Our analysis of differential treatment effects by design characteristics showed inconsistent results for those with more effectiveness characteristics (more real-world application) than those designed as efficacy trials. Effectiveness studies showed significantly less effect on mortality but not on intubation. Collectively, these results do not show strong differential effects related to experience in using NPPV, but our analyses were limited by few studies in some categories and proxies for experience. Given these limitations, current evidence is insufficient to estimate the effect of clinician experience, setting, system resources, and patient characteristics on treatment effects.

Other study reporting issues also affect applicability. The study interventions were not well-described in the majority of the studies, a limitation that could impede dissemination. Twelve of the 69 studies poorly described the patient population, and 9 reported only outcomes that

occurred 72 hours or less after initiating NPPV or a control intervention. More consistent reporting of patient characteristics, including overall medical comorbidity, race and body mass index, would facilitate evaluations of differential effects in these important subgroups.

Implications for Clinical and Policy Decisionmaking

Our review updates and strengthens the evidence for the benefits of NPPV, particularly in patients with acute respiratory failure due to severe exacerbations of COPD or congestive heart failure (CHF). The Canadian Critical Care Society recently made strong recommendations to use NPPV in these two populations.[41] Guidelines groups from the United States have made weaker recommendations to use NPPV in patients with CHF[128] or have not addressed the use of NPPV.[129] The Canadian guideline panel made weaker recommendations suggesting that centers with expertise in NPPV use this treatment for early liberation from mechanical ventilation and in patients at high risk for respiratory failure postextubation.

Consistent with other systematic reviews, our review highlights the limited data for patient with acute respiratory failure not due to COPD or CHF. Although additional studies are needed to strengthen the evidence, current studies support the use of NPPV for patients with acute respiratory failure postoperatively or who are post-transplant and immunocompromised. The data for other indications are insufficient to draw any conclusions. The Canadian guideline panel made a weak recommendation to use NPPV for these indications but limited their recommendation to postoperative use after abdominal or lung-resection surgery.

We found that factors potentially related to treatment effects, such as the experience of the treating clinicians, resources such as staffing ratios, and patient characteristics were poorly reported. Understanding whether treatment effects vary by patient characteristics can help to target treatment to patients most likely to benefit. Understanding whether treatment effects in real-world practice are similar to those found in carefully controlled trials can inform needed improvements in patient selection and clinician training. This is particularly important because the misuse of NPPV, which may occur by persons insufficiently trained in its application, could in fact be associated with patient harm. A survey of respiratory care directors in two northeastern states showed relatively low use of NPPV (20% of ventilator starts) and high variability in estimated use across hospitals (none to greater than 50%).[14] The top two reasons given for lower utilization rates were a lack of physician knowledge and inadequate equipment. A more recent study in Veterans Affairs hospitals found a wide range in training and experience with NPPV, underutilization and low rates of perceived efficacy.[24] Respiratory therapists had greater training and experience with NPPV than physicians and more recently trained physicians had greater training than their older peers. Surveys of EDs in the United States and United Kingdom report higher rates of use.[130,131] Reassuringly, use is most common for patients where the evidence is strongest, in those with acute respiratory failure due to COPD or ACPE. Nevertheless, the gap between the evidence for strong effects in specific patient populations and routine clinical use suggests the need for better dissemination of clinical guidelines and efforts to implement NPPV more uniformly. A review that uses Rogers Diffusions of Innovations as a model outlines potential steps for improving uptake into clinical practice.[131]

Limitations of the Comparative Effectiveness Review Process

Our findings have limitations related to the literature and our approach. Important limitations of the literature include few studies in certain populations of high interest, incomplete reporting of outcomes related to resource utilization, and descriptions of the interventions that were often inadequate to permit replication. In addition, the limited reporting of adverse effects and myocardial infarction suggest the possibility of selective outcomes reporting. Limitations in reporting precluded any analyses of variability in treatment effects by patient characteristics. A patient level meta-analysis was not possible in the current study, but would be a useful approach to examine this issue.

Our review methods also had limitations. Our study was limited to English-language publications which may have contributed to different conclusions about the effects of NPPV on ventilator weaning compared with Burns et al.34 Some outcomes, such as hospital-acquired pneumonia, were not defined explicitly in many of the primary studies, and depending on the definition and method of ascertainment, could be biased when outcome assessors were not blind to treatment allocation. Although we attempted to evaluate the impact of effectiveness versus efficacy studies, our approach consisted of indirect comparisons without adjustment for potential confounders. The approach was further limited by a simple rules based approach to classifying certain items in the efficacy-effectiveness scale (e.g., university affiliation = highly trained) and few effectiveness studies. Finally, some would argue that summary estimates across different etiologies of acute respiratory failure are not indicated. Although the underlying pathophysiology of acute respiratory failure differs by etiology, the studies were conceptually similar in design, intervention, and outcomes. In most instances, there was small to moderate variability in effects, even across diagnostic groups, and thus we computed summary estimates of effect for most outcomes.

Research Gaps

We used the framework recommended by Robinson et al.[132] to identify gaps in evidence and classify why these gaps exist. This approach considers PICOTS (population, intervention, comparator, outcomes, timing, and setting) to identify gaps and classifies gaps as due to (a) insufficient or imprecise information, (b) biased information; (c) inconsistency or unknown consistency, and (d) not the right information. In addition, we considered studies in progress identified from ClinicalTrials.gov when making recommendations for future research. Gaps and recommendations are presented in Table 24. Although we recommend multicenter RCTs to address some evidence gaps, we are aware that there are some particular challenges to conducting these RCTs. It is difficult to blind patients or treating clinicians to the treatment group. While lack of blinding is unlikely to bias ascertainment of mortality outcomes, it could introduce bias in the assessment of more subjective outcomes and a subtle bias into patient care. Therefore it is critical that supportive treatments be specified carefully and that outcomes be assessed by individuals who are blind to treatment assignment. Blinded outcome assessment and carefully defined endpoints are particularly important for outcomes that include subjectivity such as the need for intubation. Some studies included in our review reported effects on length of stay for the sample overall and the subgroup of survivors. Since NPPV has a mortality advantage, length-of-stay analyses could be biased if analyses use all patients randomized. Studies should report length of stay for the sample overall and for the subgroup of survivors. Additionally, the

application of NPPV among patients at the end of life needs further study. Many providers do not conceptualize NPPV as a form of life support, and this constitutes a potential threat to the patient-centeredness of care among those with do not attempt resuscitation orders. Finally, we recommend that authors provide more careful descriptions of the patient population, details of randomization and allocation concealment, and detailed intervention protocols to facilitate dissemination of effective treatments.

Table 24. Evidence gaps and future research

Evidence Gap	Reason	Type of Studies To Consider
Patients		
Effects versus supportive care in patients with asthma, interstitial lung disease, pneumonia, acute decompensated, obesity-hypoventilation syndrome and those who are postoperative or post-transplant	Insufficient or imprecise information	Multicenter RCTs
Uncertain benefit of NPPV to assist weaning	Imprecise information	Multicenter RCTs
Uncertain benefit of NPPV to prevent recurrent acute respiratory failure postextubation	Imprecise information	Multicenter RCTs
Whether NPPV treatment effects vary by patient characteristics	Insufficient information	Patient level meta-analyses Subgroup analyses from large, multicenter RCTs Improved reporting in trial publications
Outcomes		
Effects on resource utilization NPPV compared with supportive care for acute respiratory failure	Insufficient information; not the right information	Analyze effects on resource utilization from large trials Model effects on resource utilization
Effects on psychological response, functional status, or health-related quality of life	Insufficient information	Multicenter RCTs
Settings		
Effectiveness of NPPV as implemented in usual care (outside of RCTs)	Insufficient information	Observational studies
Uncertainty about the effects of training, staffing composition/ratios and use of algorithms on NPPV effectiveness	Insufficient information	Observational studies

Abbreviations: NPPV = noninvasive positive-pressure ventilation; RCT = randomized controlled trial

Conclusions

In summary, for patients with acute respiratory failure due to severe exacerbations of COPD or congestive heart failure, NPPV plus supportive care shows important reductions in mortality and intubation rates compared with supportive care alone. BPAP has been studied more rigorously, but direct comparisons of CPAP and BPAP in patients with ACPE show similar efficacy. Current evidence suggests potential benefit for patients with acute respiratory failure who are postoperative or post-transplant and as a method to facilitate weaning from invasive ventilation or prevent recurrent postextubation respiratory failure in those at high risk. However, the evidence for these indications is much weaker. Limited evidence shows similar treatment effects across different settings and the possibility of less benefit in trials designed to replicate usual clinical practice. There is a clear need for further studies in patient populations where NPPV has not been rigorously studied and to understand the role of training and effectiveness when used as part of routine clinical care.

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Abbreviations and Acronyms

3CPO	Three Interventions in Cardiogenic Pulmonary Oedema (3CPO)
ACPE	acute cardiogenic pulmonary edema
AHRQ	Agency for Healthcare Research and Quality
APACHE	Acute Physiology And Chronic Health Evaluation
ARDS	acute respiratory distress syndrome
BPAP	bilevel positive airway pressure
CER	comparative effectiveness review
CHF	congestive heart failure
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
ED	emergency department
ICU	intensive care unit
KQ	Key Question
MeSH	medical subject headings
NPPV	noninvasive positive-pressure ventilation
OR	odds ratio
PaCO2	partial pressure of carbon dioxide in blood
PaO2	partial pressure of oxygen in arterial blood
PICOTS	Population, Intervention, Comparator, Outcome, Timing, Setting
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomized controlled trial
SAPS	Simplified Acute Physiology Score
SD	standard deviation
TEP	Technical Expert Panel
TOO	Task Order Officer

Appendix A. Exact Search Strings

PubMed®:

Original search date: April 7, 2011

Strategy:
((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals[mh] NOT humans[mh])) AND (positive airway pressure respiration OR continuous positive airway pressure OR bilevel positive airway pressure OR bi-level positive airway pressure OR NPPV OR NIPPV OR BIPAP OR CPAP OR ippv OR ippb OR niv OR niav OR pav OR "proportional assist ventilation" OR "respiratory assist devices" OR ((noninvasive[tiab] OR non-invasive[tiab]) AND (ventilat*[tiab] OR respirat*[tiab])) OR (ventilat* AND helmet[tiab]) OR ((facial[tiab] OR nasal[tiab] OR face[tiab]) AND mask*[tiab]))

Limits: English, All Adult: 19+ years, Publication Date from 1990/01/01

Final search date: January 31, 2012

Strategy:
((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals[mh] NOT humans[mh])) AND (positive airway pressure respiration OR continuous positive airway pressure OR bilevel positive airway pressure OR bi-level positive airway pressure OR NPPV OR NIPPV OR BIPAP OR CPAP OR ippv OR ippb OR niv OR niav OR pav OR "proportional assist ventilation" OR "respiratory assist devices" OR ((noninvasive[tiab] OR non-invasive[tiab]) AND (ventilat*[tiab] OR respirat*[tiab])) OR (ventilat* AND helmet[tiab]) OR ((facial[tiab] OR nasal[tiab] OR face[tiab]) AND mask*[tiab]))

Limits: English, Entry Date from 2011/03/07 to present

Note: The 'All Adult: 19+ years' limit was removed when updating the PubMed® search to avoid exclusion of in-process citations.

Total number of unique results: 2885

Embase®:

Final search date: January 31, 2012

Total number of results: 879

Strategy:
'positive end expiratory pressure'/exp OR 'positive end expiratory pressure' OR 'pressure support ventilation'/exp OR 'pressure support ventilation' OR 'positive airway pressure respiration' OR 'continuous positive airway pressure' OR 'bilevel positive airway pressure' OR 'bi-level positive airway pressure' OR nppv OR nippv OR bipap OR cpap OR ippv OR ippb OR niv OR niav OR pav OR 'proportional assist ventilation' OR 'respiratory assist devices' OR (noninvasive:ti OR 'non invasive':ti AND (ventilat*:ti OR respirat*:ti)) OR (noninvasive:ab OR 'non invasive':ab AND (ventilat*:ab OR respirat*:ab)) OR (ventilat*:ti AND helmet:ti) OR (ventilat*:ab AND helmet:ab) OR (facial:ti OR nasal:ti OR face:ti AND mask*:ti) OR (facial:ab OR nasal:ab OR face:ab AND mask*:ab) AND (random* OR factorial* OR crossover* OR 'cross over' OR 'cross overs' OR placebo* OR doubl* NEAR/1 blind* OR singl* NEAR/1 blind* OR assign* OR allocat* OR volunteer* OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'randomized controlled trial'/exp OR 'single blind procedure'/exp) AND [humans]/lim AND [english]/lim AND [embase]/lim NOT [medline]/lim AND [1990-2012]/py

Cochrane Database of Systematic Reviews:

Final search date: January 31, 2012

Total number of results: 84

Strategy:
#1 (positive airway pressure respiration OR continuous positive airway pressure OR bilevel positive airway pressure OR bi-level positive airway pressure OR NPPV OR NIPPV OR BIPAP OR CPAP OR ippv OR ippb OR niv OR niav OR pav OR "proportional assist ventilation" OR "respiratory assist devices"):ti,ab,kw
#2 (ventilat* AND helmet):ti,ab,kw
#3 (noninvasive OR non invasive):ti,ab,kw and (respirat* OR ventilat*):ti,ab,kw
#4 (facial OR nasal OR face):ti,ab,kw and (mask):ti,ab,kw
#5 (#1 OR #2 OR #3 OR #4)
#6 (#1 OR #2 OR #3 OR #4), from 1990 to 2012

ClinicalTrials.gov:

Final search date: January 27, 2012

Total number of results: 125

Strategy:
(noninvasive OR positive pressure ventilation OR positive airway pressure AND respiration OR continuous positive airway pressure OR bilevel positive airway pressure OR bi-level positive airway pressure OR proportional AND assist ventilation OR respiratory assist AND device) [ALL-FIELDS] AND "Interventional" [STUDY-TYPES] AND respiratory failure [DISEASE] AND ("Adult" OR "Senior") [AGE-GROUP]

Appendix B. Efficacy-Effectiveness Rating Form

Directions: For each article, rate the study along the seven dimensions listed. For each dimension, consider whether, on balance, the study is most consistent with the definition of efficacy or effectiveness. Make your best judgment, but if the article does not give adequate information to make a determination, choose "unclear."

Dimension	Efficacy	Effectiveness
1. Setting [ ] Unclear	Highly specialized setting for administering NPPV (e.g., specialized NPPV unit) or Tertiary care setting (referral population or Academic medical Center) or restricted to highly trained practitioners	Community Hospitals without specialized NPPV units or specifies that practitioners do not have any special training
2. Eligibility criteria [ ] Unclear	Convenience sample or sample selection criteria that excludes typical comorbidities (e.g., mild hemodynamic instability, chronic medical conditions, dysrhythmias, recent surgery) or those less likely to adhere to treatment	Consecutive patients; allows usual comorbidities and those less likely to be adherent
3. Health Outcomes [ ] Unclear	Does not include mortality or health related quality of life	In the methods section, specifies mortality (in hospital or longer) or Health related quality of life outcomes
4. Study Duration/clinically relevant NPPV [ ] Unclear	NPPV administration is fixed (e.g., given for pre-specified, inflexible duration), OR specific respirator settings not based on clinical response, OR outcomes are short-term only (e.g. ICU stay or shorter)	Intervention given to clinical endpoints rather than pre-specified duration. NPPV administration is flexible and responds to clinical status. Outcomes are measured for full hospitalization or longer
5. Assessment of adverse events [ ] Unclear	Report fewer than 2 of the following: discontinuation of NPPV due to intolerance, rates of infection, facial ulcerations	Reports at least 2 of the following: discontinuation of NPPV due to intolerance, rates of infection, facial ulcerations
6. Adequate sample size for health outcomes [ ] Unclear	Sample size not given for mortality or HRQOL	Sample size calculation given for mortality or minimum clinically important difference for HRQOL
7. ITT analysis [ ] Unclear	Completers analysis or excludes those with protocol deviations.	Follows intent-to-treat principle for analysis (includes all patients regardless of compliance, eligibility)

Appendix C. Data Abstraction Elements

I. Study Characteristics

- Additional articles used in this abstraction
    - If an additional article is used to supplement this abstraction, provide the article(s)' full citation(s).
- Study dates
    - Year enrollment started
    - Year enrollment ended
- Study sites
    - Single center
        - Geographic location: Enter City and State (if U.S.) and Country (if outside the U.S.).
    - Multicenter
        - Enter number of sites
        - Select all applicable geographical regions from the following options: US, Canada, UK, Europe, South America, Central America, Asia, Africa, Australia/New Zealand, Not reported/Unclear, Other (specify)
    - Not reported/Unclear
- Funding source (check all that apply): Government, Private foundation, Industry, Not reported, Other (specify)
- Setting (check all that apply): ICUs, Emergency departments, Critical care units, Postoperative settings, General medical units, Not reported/unclear, Other (specify)
- Enrollment approach (check all that apply): Consecutive patients, Convenience sample (not explicitly consecutive), Not reported/Unclear, Other (specify)
- Study inclusion and exclusion criteria
    - Copy/paste criteria as reported in the article
    - Were any of the following exclusion reasons applied?
        - Need for emergent intubation (includes respiratory arrest, severe hemodynamic instability [e.g., SBP < 90, severe bradycardia, severe arrhythmia], other indications)
        - Unable to cooperate with NPPV (includes decreased level of consciousness, encephalopathy, agitation)
        - Acute respiratory failure requiring a specific treatment (e.g. pulmonary embolus, pneumothorax, acute myocardial infarction)
        - Conditions that preclude NPPV face mask or nasal prong application (e.g., tracheostomy; facial deformities; recent oral, esophageal, or gastric surgery)
- Study enrollment and completion
    - Number of subjects assessed for eligibility
    - Number eligible
    - Number randomized
    - Number that completed follow-up
- Comments (if needed)

II. Ventilation Procedures

- Does the study address weaning? (Yes, No)
- Are there significant baseline imbalances between the patient groups? (Yes, No)
- For each treatment arm, indicate type of treatment and answer questions specific to that treatment:
    - Treatment type: NPPV, Supportive care, or Invasive Ventilatory Support
        - If NPPV
            - Interface used: Full face, Nasal prongs, Nasal mask, Not reported, Other (specify)
            - Type of NPPV
                - Bilevel positive airway pressure with supportive care
                    - Bilevel upper/inspiratory pressure
                    - Bilevel lower/expiratory pressure
                - Continuous positive airway pressure (CPAP) with supportive care
                    - Planned CPAP pressure:
                        - Fixed pressure
                        - Acceptable pressure range
                            - Min pressure
                            - Max pressure
                    - Mean CPAP pressure delivered
                - Other
                - Not reported
            - Other Details:
                - Autotitrating: Yes, No, Not reported/ Not available
                - Duration of ventilation, per protocol (mean hours per day, or if not given, mean and intended duration for Day 1)
                - Protocolized (presence of a structured algorithm for adjusting the non-invasive ventilation): Yes, No, Not reported
        - If Supportive care
            - Is planned supportive care identical for the intervention arm(s) and the comparator arm?
            - Describe supportive care
        - If Invasive Ventilatory Support
            - Autotitrating: Yes, No, Not reported/ Not available
            - Duration of ventilation, per protocol (mean hours per day, or if not given, mean and intended duration for Day 1)
- Staffing/training experience
- Staffing composition (check all that apply): Respiratory therapist, Nurse practitioner, Physician's assistant, Physician (general), Physician (other subspecialty), Physician (critical care trained), Nurse, Not reported
- Adjunctive treatments
    - High flow oxygen: Yes, No, Not reported/Unclear
    - Helium gas mixture: Yes, No, Not reported/Unclear
    - Sedatives and anxiolytics: Yes, No, Not reported/Unclear
        - If yes, was Precedex (dexametomidine) used?

- Comments (if needed)

III. Applicability of Key Questions

- Indicate populations included in the study (check all that apply):
    - Adults with chronic obstructive pulmonary disease (COPD) and acute respiratory failure
    - Adults with acute cardiogenic pulmonary edema (ACPE)
    - Adults with acute respiratory failure due to other causes including pneumonia, asthma, obesity-hypoventilation syndrome, and interstitial lung disease
    - Adults with acute respiratory failure in selective settings including perioperative setting and post-transplant setting
- Indicate applicable Key Questions
    - Key Question 1: Is noninvasive positive-pressure ventilation (NPPV) associated with less morbidity (including from intubation), lower mortality, lower adverse events, or lower medical utilization when compared to supportive medical therapy or invasive ventilation:
        - In adults with chronic obstructive pulmonary disease (COPD) and acute respiratory failure?
        - In adults with acute cardiogenic pulmonary edema (ACPE)?
        - In adults with acute respiratory failure due to other causes including: pneumonia, asthma, obesity-hypoventilation syndrome, and interstitial lung disease?
        - In adults with acute respiratory failure in selective settings including: perioperative setting and post-transplant setting?
    - Key Question 2: Is NPPV with bilevel positive airway pressure (BiPAP^{TM}), compared to NPPV with continuous positive airway pressure (CPAP), associated with less morbidity, lower mortality, lower adverse events, or lower medical utilization:
        - In adults with chronic obstructive pulmonary disease (COPD) and acute respiratory failure?
        - In adults with acute cardiogenic pulmonary edema (ACPE)?
        - In adults with acute respiratory failure due to other causes including: pneumonia, asthma, obseity-hypoventilation syndrome, and interstitial lung disease?
        - In adults with acute respiratory failure in selective settings including: perioperative setting and post-transplant setting?
    - Key Question 3: Is early extubation to NPPV, compared to usual care, associated with less morbidity, lower mortality, lower adverse events, or lower medical utilization:
        - In adults with chronic obstructive pulmonary disease (COPD) and acute respiratory failure?
        - In adults with acute cardiogenic pulmonary edema (ACPE)?
        - In adults with acute respiratory failure due to other causes including: pneumonia, asthma, obesity-hypoventilation syndrome, and interstitial lung disease?
        - In adults with acute respiratory failure in selective settings including: perioperative setting and post-transplant setting?
    - Key Question 4: Did this study report a subgroup analysis?
- Comments (if needed)

IV. Baseline Characteristics

- Number of subjects: For the total population and each treatment arm, indicate the following:
    - Treatment type: CPAP, Bilevel, Weaning without NPPV, Weaning with NPPV, Endotracheal intubation, Supportive care
    - N: Total, Female, Male
    - Percentage: Female, Male
- Total population age in years: For the total population and each treatment arm, indicate the following:
    - Treatment type: CPAP, Bilevel, Weaning without NPPV, Weaning with NPPV, Endotracheal intubation, Supportive care
    - Mean
    - Standard deviation
    - Median
    - Interquartile range
- Severity of illness score: Apache II score, Apache III score, Simplified acute physiological score, Other (specify), Not reported
    - For the total population and each treatment arm, indicate the following:
        - Treatment type: CPAP, Bilevel, Weaning without NPPV, Weaning with NPPV, Endotracheal intubation, Supportive care
        - Mean
        - Standard deviation
        - Median
        - Interquartile range
- Ethnicity (indicate total N and percentage of total population)
    - Hispanic or Latino
    - Not Hispanic or Latino
- Race (indicate total N and percentage of total population)
    - Black/African American
    - American Indian or Alaska Native
    - Asian
    - Native Hawaiian or other Pacific Islander
    - White
    - Multiracial
    - Other
- Baseline characteristics: For the total population and each treatment arm, indicate the following:
    - N or Percentage of patients
    - Heart rate: Not reported, or Mean and Standard deviation
    - Respiratory rate: Not reported, or Mean and Standard deviation
    - Systolic blood pressure: Not reported, or Mean and Standard deviation Arterial pH: Not reported, or Mean and Standard deviation
    - PaCO2 : Not reported, or Mean and Standard deviation
    - PaO2: Not reported, or Mean and Standard deviation
    - Ratio of PaO2 to Fraction of inspired O2: Not reported, or Mean and Standard deviation
    - Impaired mental status (Define) : Not reported, or Mean and Standard deviation

    - Mental status changes (Define) : Not reported, or Mean and Standard deviation
    - BMI: Not reported, or Mean and Standard deviation
    - Obesity (e.g. BMI>30) (Define): Not reported, or Mean and Standard deviation
    - Other (Specify): Not reported, or Mean and Standard deviation
- Causes of acute respiratory failure: For the total population and each treatment arm, indicate the following:
    - N or Percentage of patients
    - Chronic obstructive pulmonary disease (COPD): N, Percent
    - Pneumonia: N, Percent
    - Asthma: N, Percent
    - Obesity-hypoventilation syndrome: N, Percent
    - Interstitial lung disease: N, Percent
    - Acute cardiogenic pulmonary edema (ACPE) : N, Percent
    - Acute respiratory failure following a solid organ or bone marrow transplant: N, Percent
    - Acute respiratory failure following surgery requiring general anesthesia other than solid organ or bone marrow transplant: N, Percent
    - Other: N, Percent
- Comments (if needed)

V. Outcomes (repeatable per outcome of interest)

- Select outcome reported:
    - Intermediate Outcome/Respiratory Rate
    - Intermediate Outcome/Heart Rate
    - Intermediate Outcome/Partial Pressure of Oxygen in Arterial Blood (PaO2)
    - Intermediate Outcome/Partial Pressure of Carbon Dioxide in Arterial Blood (PaCO2)
    - Intermediate Outcome/Improved PaO2 to Fraction of inspired oxygen
    - Intermediate Outcome/Intubation Rate (NA for weaning studies)
    - Intermediate Outcome/Reintubation Rate (Post-op: weaning)
    - Intermediate Outcome/Duration of Mechanical Ventilation
    - Intermediate Outcome/Time to Reintubation (Post-op: weaning)
    - Intermediate Outcome/Rates of Discontinuing NPPV secondary to treatment intolerance
    - Intermediate Outcome/Successful Extubation
    - Intermediate Outcome/Myocardial Infarctions
    - Intermediate Outcome/Psychological Distress/Anxiety Validated Measure
    - Intermediate Outcome/AE: Discontinued NPPV-unable to tolerate
    - Final Outcome/Functional Status measured by SF36 or equivalent
    - Final Outcome/Health-related Quality of Life (HRQoL)
    - Final Outcome/Disease-specific functional status measure
    - Final Outcome/Mortality rates
    - Outcome/Ventilator dependent days
    - Days Final Outcome/Rate of Ventilator Dependence at Hospital Discharge
    - Final Outcome/Length of Hospital Stay
    - Final Outcome/Length of Intensive Care Stay
    - Final Outcome/Total Hospital Costs

    - Adverse Event/Aspiration
    - Adverse Event/Secondary Infections
    - Adverse Event/Facial Ulcerations
    - Adverse Event/Other (specify)
    - Other (specify)
- Provide the following data for the indicated outcome
    - Timing of the outcome data: 2 hours, 6 hours, 24 hours, At discharge, 30 days, In hospital, Other (Specify)
    - For each treatment arm, record the following:
        - N or Percentage of patients
        - Result, recorded as one of the following:
            - Mean
            - Median
            - Number of points with outcome
            - Percentage of points with outcome
            - Events per denominator
            - Other (specify)
        - Variability, recorded as one of the following:
            - Standard error
            - Standard deviation
            - Range
            - Interquartile range
            - Other (specify)
        - Comparative result, recorded as one of the following:
            - Relative risk
            - Relative hazard
            - Odds ratio
            - Risk difference
            - Other (specify)
            - Comparator: Treatment arm 1, Treatment arm 2, Treatment arm 3
        - Confidence interval (CI) or interquartile range (IQR)
            - Indicate measure (select one): 95% CI, Other percent CI (specify), IQR
            - Lower level (25% if IQR)
            - Upper level (75% if IQR)
- Comments (if needed)

VI. Subgroup Analyses (if applicable)

- Indicate the factor being considered: Setting, Experience and training of clinicians, Use of protocols, Morbid obesity, Mental status changes, Overall disease burden, Other patient characteristic (specify)
- Define the categories considered in this subgroup analysis.
- For each category described, provide data by outcome. Clearly indicate units (number of patients, %, hazard ratio, etc.). Include values for confidence intervals, p values, standard error, standard deviation, etc. when available.
    - Outcomes (provide data for all that apply):
        - Intermediate Outcome/Respiratory Rate

        - Intermediate Outcome/Heart Rate
        - Intermediate Outcome/Partial Pressure of Oxygen in Arterial Blood (PaO2)
        - Intermediate Outcome/Partial Pressure of Carbon Dioxide in Arterial Blood (PaCO2)
        - Intermediate Outcome/Improved PaO2 to Fraction of inspired oxygen
        - Intermediate Outcome/Intubation Rate (NA for weaning studies)
        - Intermediate Outcome/Reintubation Rate (Post-op: weaning)
        - Intermediate Outcome/Duration of Mechanical Ventilation
        - Intermediate Outcome/Time to Reintubation (Post-op: weaning)
        - Intermediate Outcome/Rates of Discontinuing NPPV secondary to treatment intolerance
        - Intermediate Outcome/Successful Extubation
        - Intermediate Outcome/Myocardial Infarctions
        - Intermediate Outcome/Psychological Distress/Anxiety Validated Measure
        - Intermediate Outcome/AE: Discontinued NPPV-unable to tolerate
        - Final Outcome/Functional Status measured by SF36 or equivalent
        - Final Outcome/Health-related Quality of Life (HRQoL)
        - Final Outcome/Disease-specific functional status measure
        - Final Outcome/Mortality rates
        - Outcome/Ventilator dependent days
        - Days Final Outcome/Rate of Ventilator Dependence at Hospital Discharge
        - Final Outcome/Length of Hospital Stay
        - Final Outcome/Length of Intensive Care Stay
        - Final Outcome/Total Hospital Costs
        - Adverse Event/Aspiration
        - Adverse Event/Secondary Infections
        - Adverse Event/Facial Ulcerations
        - Adverse Event/Other (specify)
        - Other (specify)
- Comments (if needed)

VII. Quality Assessment

- Rate each individual risk of bias item as Yes, No, or Unclear
    - Randomization and allocation concealment:
        - Was the allocation sequence adequately generated?*
        - Was the allocation adequately concealed?*
    - Study performance
        - Did variation from the study protocol compromise the conclusion of the study?
    - Outcomes
        - Were outcome assessors blind to treatment assigned for “hard outcomes” such as mortality?*
        - Were outcome assessors blind to treatment assignments for “soft outcomes” such as symptoms?*
        - Were the measures used reliable and valid? If so, choose “Yes,” indicating no important measurement bias.

- Data analysis
  - Are reports of the study free of suggestion of selective outcome reporting (systematic differences between planned and reported findings)?*
  - Was incomplete outcome data adequately addressed?*
    - Yes (no systematic differences between groups in withdrawals from a study and no high overall loss to follow-up; all eligible patients that were randomized are included in analysis ("intention-to-treat" [ITT] analysis; note – mixed models and survival analyses are in general ITT)
    - No
    - Unclear
  - Was there adequate power for main effects?
- Results
  - Were systematic differences observed in baseline characteristics and prognostic factors across the groups compared?
  - Were comparable groups maintained? Consider issues of crossover (e.g., from one intervention to another), adherence (major differences in adherence to the interventions being compared), contamination (e.g., some members of control group get intervention), or other systematic differences in care that was provided.*
- Conflict of interest
  - Was there the absence of potential important conflict of interest? The focus is financial conflict of interest. If no financial conflict of interest (e.g., if funded by government or foundation and authors do not have financial relationships with drug/device manufacturer), then answer "Yes."

*Items contained in the Cochrane Risk of Bias Tool (Chapter 8 in the *Cochrane Handbook,* www.cochrane-handbook.org/)

- Overall study rating: Good, Fair, Poor
  - Assign each study an overall quality rating based on the following definitions:
    - Good. A "Good" study has the least bias, and results are considered valid. A good study has a clear description of the population, setting, interventions, and comparison groups; uses a valid approach to allocate patients to alternative treatments; has a low dropout rate; and uses appropriate means to prevent bias, measure outcomes, and analyze and report results.
    - Fair. A "Fair" study is susceptible to some bias but probably not enough to invalidate the results. The study may be missing information, making it difficult to assess limitations and potential problems. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses. The results of some fair-quality studies are possibly valid, while others are probably valid.
    - Poor. A "Poor" rating indicates significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; have large amounts of missing information; or have discrepancies in reporting. The results of a poor-quality study are at least as likely to reflect flaws in the study design as to indicate true differences between the compared interventions.
  - If the study is rated as "Fair" or "Poor," provide rationale for decision.

- Comments (if needed)

VIII. Applicability

- Use the PICOTS format to identify specific issues that may limit the applicability of the study. Indicate the most important limitations affecting applicability, if any, from the list below.
    - Population (P)
        - Study population poorly specified
        - Overly narrow definition of acute respiratory failure
    - Intervention (I)
        - Intervention not well described
        - Highly selected intervention team or level of training/proficiency not widely available
    - Comparator (C)
        - Inadequate comparison therapy
        - Comparator(s) not well described
    - Outcomes (O)
        - Composite outcomes that mix outcomes of different significance
    - Timing (T)
        - No outcomes at 72 hours or greater
    - Setting (S)
        - Conducted outside of the US and practices not well described or widely divergent relative to US practices
        - Not widely accessible technology
- Comments (if needed)

Appendix D. Analyses of Potential Publication Bias

Testing for publication bias is difficult at best. In effect, one is testing for the number of studies that have not been reported based on the results of those that have been reported. For comparisons with at least 10 studies, we used three tools to look for bias: (1) the funnel plot, which looks for an uneven number of studies falling to the left or right of the funnel; (2) Begg and Mazumdar's test[1] based on the rank correlation between the observed effect sizes and observed standard errors; and (3) Egger's regression intercept, which is similar to Begg and Mazumdar's but uses actual values instead of ranks. For Begg and Egger's test statistics, we report two-sided p-values. When the funnel plot or test statistics suggested publication bias, we used Duval and Tweedie's trim-and-fill method to estimate an effect, corrected for publication bias.[2]

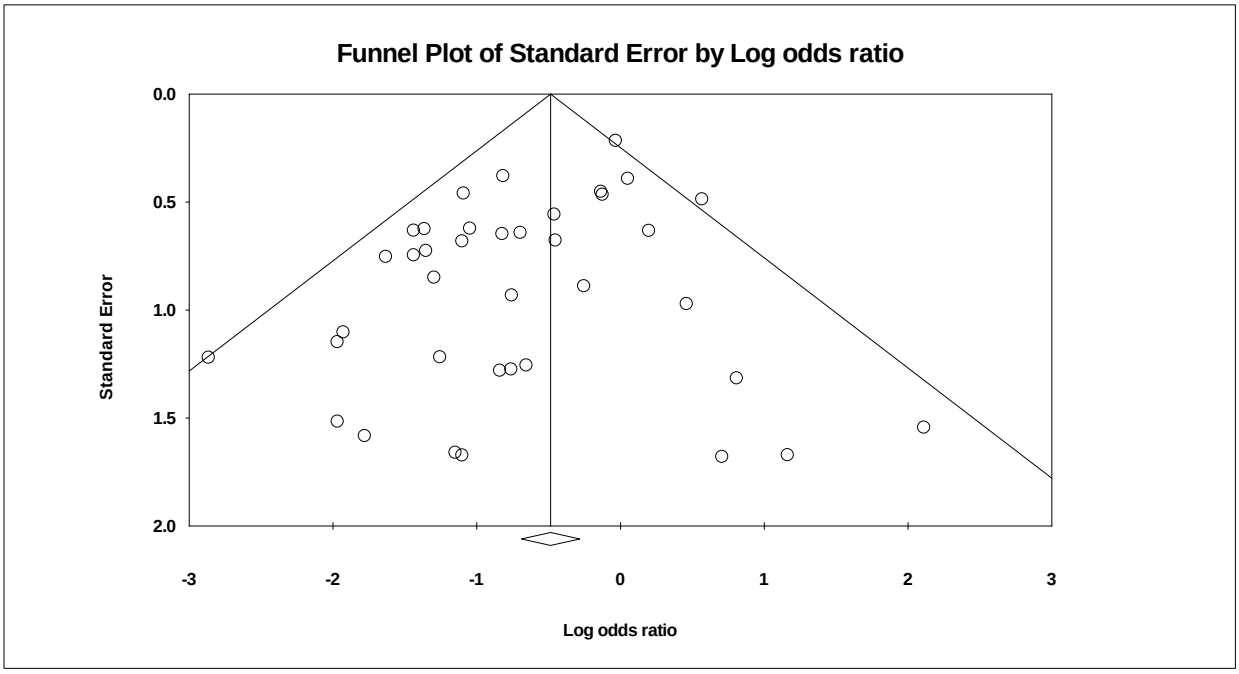
We used Comprehensive Meta-Analysis (Version 2; Biotstat, Englewood, NJ) to test for potential publication bias for the outcomes described below.

Key Question 1

Mortality Outcomes

We used Comprehensive Meta-Analysis to examine any potential publication bias in the studies of mortality outcomes. The resulting funnel plot is shown in Figure D-1.

Figure D-1. Funnel plot for studies of mortality outcomes

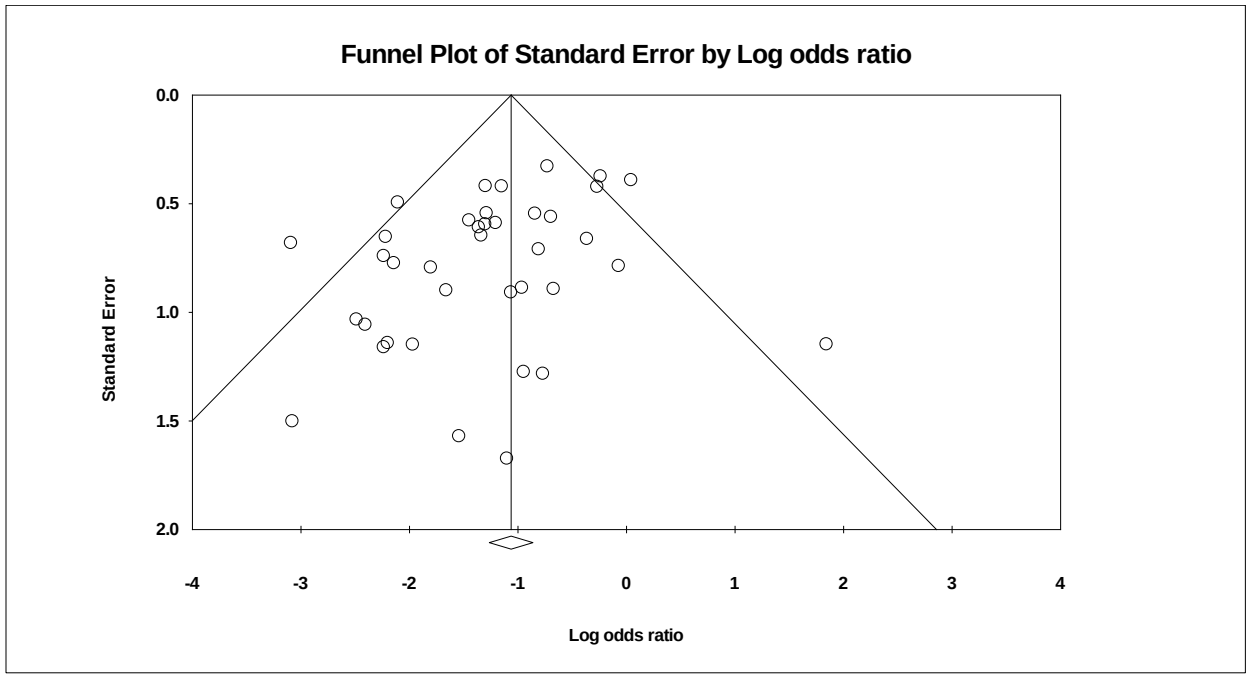


The funnel plot does not suggest significant publication bias: Begg's test statistic, p = 0.80; Eggers test statistic, p = 0.03.

Intubation Rate Outcomes

We used Comprehensive Meta-Analysis to examine any potential publication bias in the studies of intubation rate outcomes. The resulting funnel plot is shown in Figure D-2.

Figure D-2. Funnel plot for studies of intubation rate outcomes



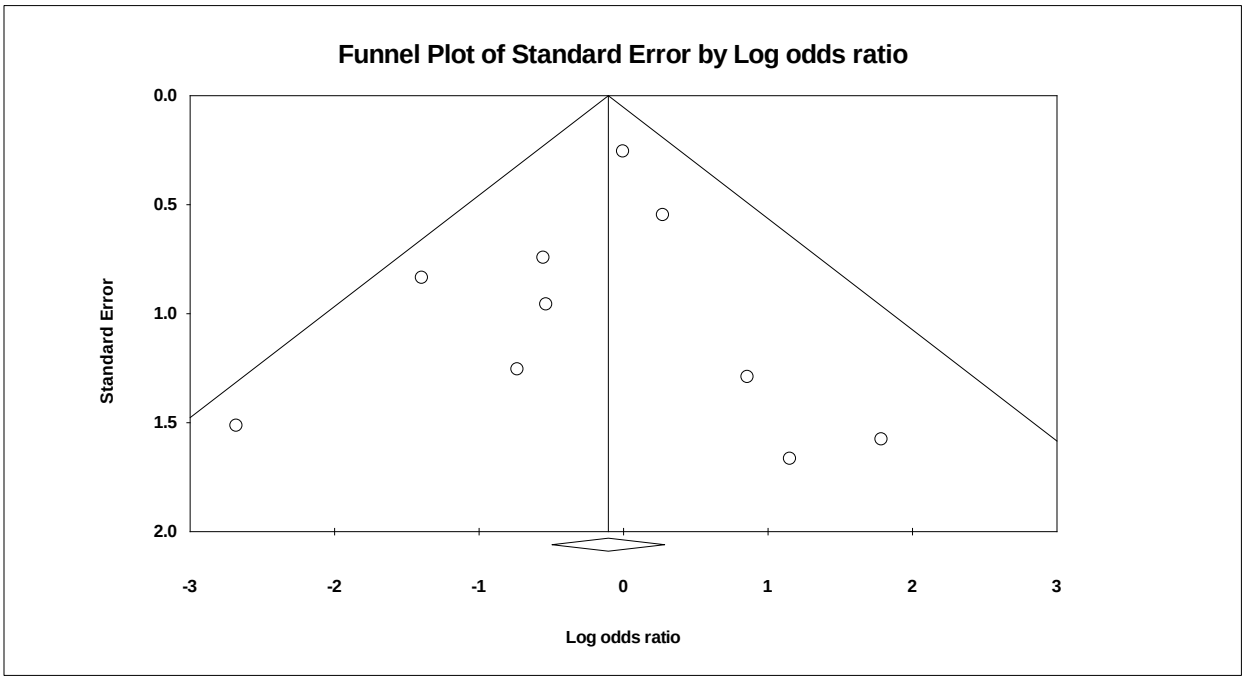
The funnel plots suggest possible publication bias, with expected studies missing to the right of the summary effect. Funnel plot assymetry may have other causes, including true heterogeneity and chance. Begg's test statistic, p = 0.16; Egger's test statistic, p = 0.02. Trim-and-fill adjusted estimate OR = 0.45 (95% CI, 0.33 to 0.61).

Key Question 2

Mortality Outcomes

We used Comprehensive Meta-Analysis to examine any potential publication bias in the studies of mortality outcomes. The resulting funnel plot is shown in Figure D-3.

Figure D-3. Funnel plot for studies of mortality outcomes

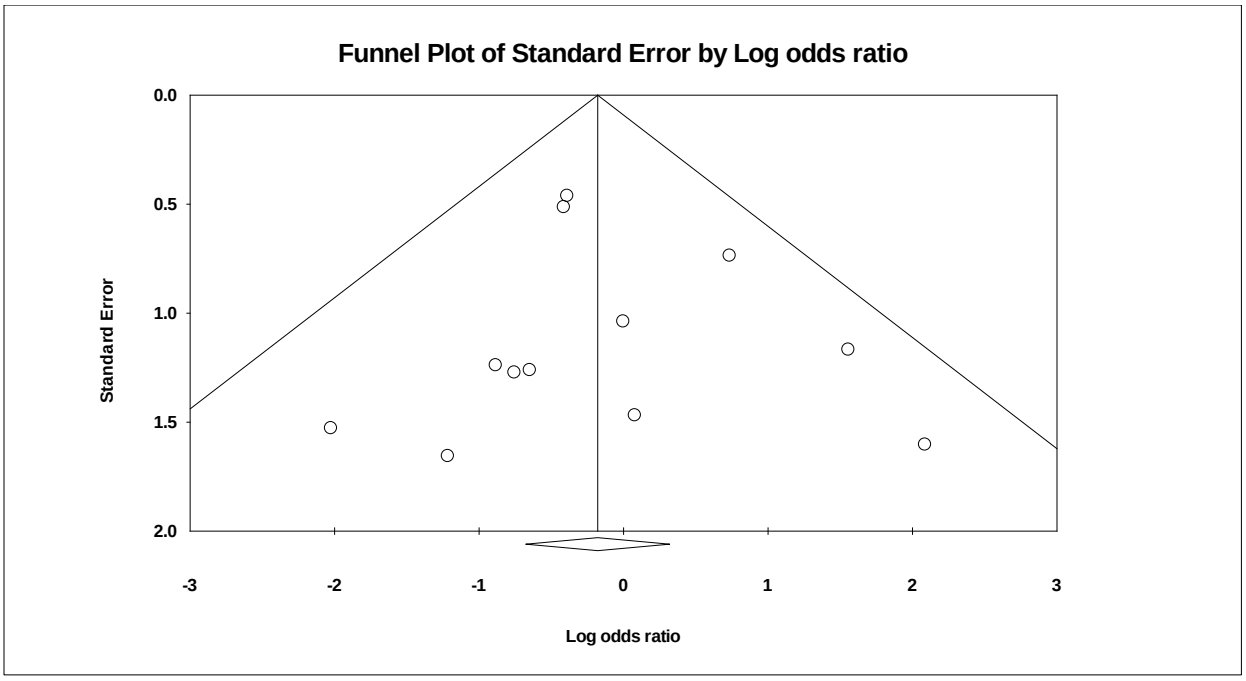


The funnel plot does not suggest publication bias: Begg's test statistic, p = 0.42; Egger's test statistic, p = 0.64.

Intubation Rate Outcomes

We used Comprehensive Meta-Analysis to examine any potential publication bias in the studies of intubation rate outcomes. The resulting funnel plot is shown in Figure D-4.

Figure D-4. Funnel plot for studies of intubation rate outcomes



The funnel plot does not suggest publication bias: Begg's test statistic, p = 0.84; Egger's test statistic, p = 0.80.

Key Question 3

No funnel plots or test statistics were performed because no set of comparisons had at least 10 studies.

References

1. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50(4):1088-101. PMID: 7786990.

2. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000;56(2):455-63. PMID: 10877304.

Appendix E. Included Studies

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Appendix F. Excluded Studies

All studies listed below were reviewed in their full-text version and excluded. Following each reference, in italics, is the reason for exclusion. Reasons for exclusion signify only the usefulness of the articles for this study and are not intended as criticisms of the articles.

Agmy G, Metwally M. Noninvasive ventilation in the weaning of patients with acute-on-chronic respiratory failure due to COPD. Chest. 2011;140(4):1032A. *Exclude: Does not include intervention/comparators of interest.*

Aguilo R, Togores B, Pons S, et al. Noninvasive ventilatory support after lung resectional surgery. Chest. 1997;112(1):117-21. PMID: 9228366. *Exclude: Does not include intervention/comparators of interest.*

Agusti AG, Carrera M, Barbe F, et al. Oxygen therapy during exacerbations of chronic obstructive pulmonary disease. Eur Respir J. 1999;14(4):934-9. PMID: 10573245. *Exclude: Does not include intervention/comparators of interest.*

Allan PF, Thomas KV, Ward MR, et al. Feasibility study of noninvasive ventilation with helium-oxygen gas flow for chronic obstructive pulmonary disease during exercise. Respir Care. 2009;54(9):1175-82. PMID: 19712493. *Exclude: Does not include clinical or utilization-related outcomes of interest.*

Ambrogio C, Lowman X, Kuo M, et al. Sleep and non-invasive ventilation in patients with chronic respiratory insufficiency. Intensive Care Med. 2009;35(2):306-13. PMID: 18795255. *Exclude: Does not include a study population of interest.*

Ambrosino N, Nava S, Bertone P, et al. Physiologic evaluation of pressure support ventilation by nasal mask in patients with stable COPD. Chest. 1992;101(2):385-91. PMID: 1735260. *Exclude: Does not include clinical or utilization-related outcomes of interest.*

Ambrosino N, Vitacca M, Polese G, et al. Short-term effects of nasal proportional assist ventilation in patients with chronic hypercapnic respiratory insufficiency. Eur Respir J. 1997;10(12):2829-34. PMID: 9493669. *Exclude: Does not include clinical or utilization-related outcomes of interest.*

Anderson J, Groth M. Usefulness of noninvasive positive-pressure ventilation in postextubation respiratory distress. Clinical Pulmonary Medicine. 2003;10(2):123-4. *Exclude: Not a full publication (abstract only), not original data, not peer-reviewed literature published 1990 to present, or not grey lit meeting specified criteria.*

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Anonymous. Non-invasive ventilation in acute respiratory failure. Thorax. 2002;57(3):192-211. PMID: 11867822. *Exclude: Study type is not RCT.*

Anton A, Tarrega J, Giner J, et al. Acute physiologic effects of nasal and full-face masks during noninvasive positive-pressure ventilation in patients with acute exacerbations of chronic obstructive pulmonary disease. Respir Care. 2003;48(10):922-5. PMID: 14525628. *Exclude: Does not include intervention/comparators of interest.*

Antonaglia V, Ferluga M, Molino R, et al. Comparison of noninvasive ventilation by sequential use of mask and helmet versus mask in acute exacerbation of chronic obstructive pulmonary disease: a preliminary study. Respiration. 2011;82(2):148-54. PMID: 21447934. *Exclude: Does not include intervention/comparators of interest.*

Antonelli M, Conti G, Pelosi P, et al. New treatment of acute hypoxemic respiratory failure: noninvasive pressure support ventilation delivered by helmet—a pilot controlled trial. Crit Care Med. 2002;30(3):602-8. PMID: 11990923. *Exclude: Study type is not RCT.*

Arzt M, Floras JS, Logan AG, et al. Suppression of central sleep apnea by continuous positive airway pressure and transplant-free survival in heart failure: a post hoc analysis of the Canadian Continuous Positive Airway Pressure for Patients with Central

Sleep Apnea and Heart Failure Trial (CANPAP). Circulation. 2007;115(25):3173-80. PMID: 17562959. *Exclude: Does not include a study population of interest.*

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Baser S, Kiter G, Kavas M, et al. Binasal cannula versus face mask for oxygen therapy in patients with chronic pulmonary disease. Adv Ther. 2006;23(6):1068-74. PMID: 17276974. *Exclude: Does not include intervention/comparators of interest.*

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Bell D, Riordan JF, McNicol MW, et al. Non-invasive mechanical ventilation for acute respiratory failure. BMJ. 1990;300(6729):944. PMID: 2337729. *Exclude: Not a full publication (abstract only), not original data, not peer-reviewed literature published 1990 to present, or not grey lit meeting specified criteria.*

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Bourke SC, Tomlinson M, Williams TL, et al. Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomised controlled trial. Lancet Neurol. 2006;5(2):140-7. PMID: 16426990. *Exclude: Does not include a study population of interest.*

Brandao DC, Lima VM, Filho VG, et al. Reversal of bronchial obstruction with bi-level positive airway pressure and nebulization in patients with acute asthma. J Asthma. 2009;46(4):356-61. PMID: 19484669. *Exclude: Does not include clinical or utilization-related outcomes of interest.*

Cammarota G, Olivieri C, Costa R, et al. Noninvasive ventilation through a helmet in postextubation hypoxemic patients: physiologic comparison between neurally adjusted ventilatory assist and pressure support ventilation. Intensive Care Med. 2011;37(12):1943-50. PMID: 22005826. *Exclude: Does not include intervention/comparators of interest.*

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Delay JM, Sebbane M, Jung B, et al. The effectiveness of noninvasive positive pressure ventilation to enhance preoxygenation in morbidly obese patients: a randomized controlled study. Anesth Analg. 2008;107(5):1707-13. PMID: 18931236. *Exclude: Does not include a study population of interest.*

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Appendix G. Characteristics of Included Studies

Table G-1. Characteristics of included studies (ordered first by KQ, then alphabetically by first author)

Study	KQ Applicability	Location; Setting; Total N	ARF Etiology[a]	Demographics	Disease Severity	Type of NPPV	Comparator	Quality Assessment Rating
Anonymous 2005[1]	KQ 1 KQ 4	Asia GMU 342	COPD	Mean age: 69.5 % Male: 38.0	APACHE II score: 10.9	BPAP	Supportive	Good
Antonelli 1998[2]	KQ 1 KQ 4	Italy ICUs 64	Mixed	Mean age: 54.5 % Male: 59.4	SAPS: 12.5	BPAP	IVS	Good
Antonelli 2000[3]	KQ 1 KQ 4	Italy ICUs 40	Transplant	Mean age: 44.5 % Male: 37.5	SAPS: 13	BPAP	Supportive	Good
Auriant 2001[4]	KQ 1 KQ 4	France ICUs 48	Post-op	Mean age: 61.0 % Male: NR	SAPS: 16.25	BPAP	Supportive	Good
Barbe 1996[5]	KQ 1 KQ 4	Spain Respiratory ward 24	COPD	Mean age: 68.0 % Male: NR	NR	BPAP	Supportive	Poor
Bersten 1991[6]	KQ 1 KQ 4	Australia ED 39	ACPE	Mean age: 75.5 % Male: 33.3	APACHE II score: 20.51	CPAP	Supportive	Fair
Bott 1993[7]	KQ 1 KQ 4	UK NR 60	COPD	Mean age: NR % Male: NR	NR	BPAP	Supportive	Poor
Brochard 1995[8]	KQ 1 KQ 4	Europe ICUs 85	COPD	Mean age: 70.0 % Male: NR	SAPS: 12.49	BPAP	Supportive	Good
Carrera 2009[9]	KQ 1	Europe Respiratory ward 75	COPD	Mean age: 70.5 % Male: NR	NR	BPAP	Supportive	Good

Study	KQ Applicability	Location; Setting; Total N	ARF Etiology[a]	Demographics	Disease Severity	Type of NPPV	Comparator	Quality Assessment Rating
Celikel 1998[10]	KQ 1 KQ 4	Turkey ICUs 30	COPD (≥ 70%)	Mean age: NR % Male: NR	NR	BPAP	Supportive	Poor
Confalonieri 1999[11]	KQ 1 KQ 4	Europe ICUs 56	Mixed	Mean age: 63.5 % Male: 71.4	APACHE II score: 19	Other	Supportive	Good
Conti 2002[12]	KQ 1	Italy ICUs 49	COPD	Mean age: 71.9 % Male: NR	SAPS: 38.22	Other	IVS	Fair
Delclaux 2000[13]	KQ 1 KQ 4	Europe; Africa ICUs 123	Mixed	Mean age: NR % Male: 63.4	NR	CPAP	Supportive	Good
Dhamija 2005[14]	KQ 1 KQ 4	India NR 29	COPD	Mean age: NR % Male: NR	NR	BPAP	Supportive	Poor
Dikensoy 2002[15]	KQ 1 KQ 4	Turkey ED 34	COPD	Mean age: 64.7 % Male: 58.8	NR	BPAP	Supportive	Poor
Ferrer 2003[16]	KQ 1 KQ 4	Europe ICUs 105	Mixed	Mean age: 61.5 % Male: 55.2	SAPS: 33.49	BPAP	Supportive	Fair
Gupta 2010[17]	KQ 1	India ICUs 53	Asthma	Mean age: 43.8 % Male: 20.8	NR	BPAP	Supportive	Good
Hilbert 2001[18]	KQ 1 KQ 4	France ICUs 52	Transplant	Mean age: 49.0 % Male: 71.2	SAPS: 43.5	BPAP	Supportive	Good
Holley 2001[19]	KQ 1	Jacksonville, FL ED 35	Asthma	Mean age: 36.8 % Male: 28.6	NR	BPAP	Supportive	Fair
Honrubia 2005[20]	KQ 1 KQ 4	Europe ICUs 64	Mixed	Mean age: 67.4 % Male: 70.3	APACHE II score: 24.48	BPAP	IVS	Fair

Study	KQ Applicability	Location; Setting; Total N	ARF Etiology[a]	Demographics	Disease Severity	Type of NPPV	Comparator	Quality Assessment Rating
Jurjevic 2009[21]	KQ 1 KQ 4	Croatia ICUs 156	COPD	Mean age: NR % Male: 66.0	NR	BPAP	IVS	Fair
Keenan 2005[22]	KQ 1 KQ 4	Canada Respiratory ward 52	COPD	Mean age: 70.0 % Male: 46.2	APACHE II score: 18.04	BPAP	Supportive	Good
Kelly 2002[23]	KQ 1 KQ 4	NR ED; stepdown unit 58	ACPE	Mean age: 77.5 % Male: 44.8	NR	CPAP	Supportive	Fair
Khilnani 2010[24]	KQ 1 KQ 4	India ICUs 40	COPD	Mean age: 57.5 % Male: 77.5	APACHE II score: 16.44	BPAP	Supportive	Fair
Kramer 1995[25]	KQ 1 KQ 4	U.S. ICUs; GMU; stepdown unit 30	COPD(≥ 70%)	Mean age: 68.5 % Male: 60.0	APACHE II score: 18.48	BPAP	Supportive	Good
Levitt 2001[26]	KQ 1 KQ 4	Oakland, California ED 38	ACPE	Mean age: 67.9 % Male: 34.2	NR	BPAP	Supportive	Fair
L'Her 2004[27]	KQ 1 KQ 4	Europe ED 89	ACPE	Mean age: 84.0 % Male: 41.6	NR	CPAP	Supportive	Fair
Lin 1991[28]	KQ 1	Taiwan ICUs 55	ACPE	Mean age: 73.8 % Male: 90.9	NR	CPAP	Supportive	Fair
Lin 1995[29]	KQ 1 KQ 4	Asia ED; ICU 100	ACPE	Mean age: 72.5 % Male: 90.0	NR	CPAP	Supportive	Fair
Martin 2000[30]	KQ 1 KQ 4	Pittsburg, PA ICU 61	Mixed	Mean age: 61.1 % Male: 47.5	APACHE III score: 61.33	BPAP	Supportive	Fair

Study	KQ Applicability	Location; Setting; Total N	ARF Etiology[a]	Demographics	Disease Severity	Type of NPPV	Comparator	Quality Assessment Rating
Masip 2000[31]	KQ 1 KQ 4	Europe ICUs 142	ACPE	Mean age: 76.9 % Male: 13.4	APACHE II score: 16	BPAP	Supportive	Fair
Matic 2007[32]	KQ 1 KQ 4	Croatia ICUs 72	COPD	Mean age: NR % Male: 66.7	NR	BPAP	IVS	Fair
Nava 2003[33]	KQ 1 KQ 4	ER ED 130	ACPE	Mean age: 72.6 % Male: 77.7	SAPS: 21.1	BPAP	Supportive	Good
Nava 2011[34]	KQ 1 KQ 4	Europe ICU 82	COPD	Mean age: 81.3 % Male: 65.9	SAPS: 33.5	Other	Supportive	Good
Pastaka 2007[35]	KQ 1 KQ 4	Greece Respiratory ward 42	COPD	Mean age: 68.4 % Male: 78.6	NR	BPAP	Supportive	Fair
Plant 2000;[36] Plant 2001[37]	KQ 1 KQ 4	UK GMU; Respiratory ward 236	COPD	Mean age: 69.0 % Male: 49.6	NR	BPAP	Supportive	Good
Soroksky 2003[38]	KQ 1	Tel Aviv, Israel ED 30	Asthma	Mean age: 33.3 % Male: 50.0	NR	BPAP	Supportive	Fair
Squadrone 2005[39]	KQ 1 KQ 4	Europe Postoperative 209	Post-op	Mean age: 65.5 % Male: 64.6	SAPS: 27.5	CPAP	Supportive	Good
Takeda 1997[40]	KQ 1 KQ 4	Japan ICU 30	ACPE	Mean age: 66.5 % Male: 73.3	APACHE II score: 14.65	CPAP	Supportive	Fair
Takeda 1998[41]	KQ 1 KQ 4	Tokyo, Japan ICU 22	ACPE	Mean age: 74.5 % Male: 77.3	APACHE II score: 10.65	CPAP	Supportive	Fair
Thys 2002[42]	KQ 1 KQ 4	Belgium ED 20	Mixed	Mean age: 73.5 % Male: 55.0	NR	BPAP	Supportive	Good

Study	KQ Applicability	Location; Setting; Total N	ARF Etiology[a]	Demographics	Disease Severity	Type of NPPV	Comparator	Quality Assessment Rating
Wermke 2011[43]	KQ 1 KQ 4	Dresden, Germany Oncology unit 86	Transplant	Mean age: NR % Male: NR	NR	BPAP	Supportive	Fair
Wood 1998[44]	KQ 1 KQ 4	St. Louis, MO ED 27	Mixed	Mean age: 58.7 % Male: 59.3	APACHE II score: 17.08	BPAP	Supportive	Good
Wysocki 1995[45]	KQ 1 KQ 4	France ICUs 41	Mixed	Mean age: 63.0 % Male: 58.5	SAPS: 12	Other	Supportive	Good
Zhan 2012[46]	KQ 1 KQ 4	Asia ICUs 40	ARDS	Mean age: 46.3 % Male: 60.0	SAPS: 12.6	BPAP	Supportive	Good
Crane 2004[47]	KQ 1 KQ 2 KQ 4	UK ED 60	ACPE	Mean age: 75.2 % Male: 38.3	NR	CPAP BPAP	Supportive	Good
Gray 2008;[48] Gray 2009[49]	KQ 1 KQ 2 KQ 4	UK ED 1069	ACPE	Mean age: 78.0 % Male: 43.3	NR	CPAP BPAP	Supportive	Good
Park 2001[50]	KQ 1 KQ 2 KQ 4	Sao Paulo, Brazil NR 26	ACPE	Mean age: NR % Male: 38.5	NR	CPAP BPAP	Supportive	Poor
Park 2004[51]	KQ 1 KQ 2 KQ 4	Brazil ED 80	ACPE	Mean age: 64.0 % Male: 42.5	APACHE II score: 19.34	CPAP	BPAP	Fair
Bellone 2004[52]	KQ 2	Italy ED 46	ACPE	Mean age: 77.1 % Male: 50.0	APACHE II score: 18.26	CPAP	BPAP	Fair
Bellone 2005[53]	KQ 2	Italy ED 36	ACPE	Mean age: 76.8 % Male: 33.3	APACHE II score: 18.15	CPAP	BPAP	Fair
Cross 2003[54]	KQ 2	Australia/N.Z. ED 101	COPD (≥ 70%)	Mean age: 72.5 % Male: NR	NR	CPAP	BPAP	Fair

Study	KQ Applicability	Location; Setting; Total N	ARF Etiology[a]	Demographics	Disease Severity	Type of NPPV	Comparator	Quality Assessment Rating
Ferrari 2007[55]	KQ 2	Turin, Italy High dependency unit 52	ACPE	Mean age: 75.5 % Male: 44.2	SAPS: 45.97	CPAP	BPAP	Fair
Ferrari 2010[56]	KQ 2	Europe ED 80	ACPE	Mean age: 77.0 % Male: NR	SAPS: 41.6	CPAP	BPAP	Good
Mehta 1997[57]	KQ 2	Providence, RI ED 27	ACPE	Mean age: 76.5 % Male: 40.7	APACHE II score: 17.93	BPAP	CPAP	Poor
Moritz 2007[58]	KQ 2	Europe ED 109	ACPE	Mean age: 77.6 % Male: 52.3	NR	CPAP	BPAP	Fair
Nouira 2011[59]	KQ 2	Africa ED 200	ACPE	Mean age: 69.0 % Male: 43.5	APACHE II score: 16	CPAP	BPAP	Good
Anonymous 2005[60]	KQ 3	Asia ICUs 90	COPD	Mean age: 68.6 % Male: 66.7	APACHE II score: 9	BPAP	IVS	Fair
Esteban 2004[61]	KQ 3	U.S., Canada, Europe, S. America, Middle East ICUs 221	Mixed	Mean age: 59.5 % Male: 57.5	APACHE II score: 36.52	BPAP	Supportive	Good
Ferrer 2003[62]	KQ 3	Europe ICUs 43	Mixed	Mean age: 70.7 % Male: 69.8	APACHE II score: 18.16	BPAP	IVS	Fair
Ferrer 2006[63]	KQ 3	Spain ICUs 162	Mixed	Mean age: 71.0 % Male: 71.0	APACHE II score: 13.49	BPAP	Supportive	Fair
Ferrer 2009[64]	KQ 3	Europe ICUs 106	Mixed	Mean age: 68.5 % Male: 75.5	APACHE II score: 11	BPAP	Supportive	Good

Study	KQ Applicability	Location; Setting; Total N	ARF Etiology[a]	Demographics	Disease Severity	Type of NPPV	Comparator	Quality Assessment Rating
Girault 1999[65]	KQ 3	Rouen, France ICUs 33	Mixed	Mean age: 64.2 % Male: NR	SAPS: 38.42	BPAP	IVS	Fair
Girault 2011[66]	KQ 3	Europe ICUs 208	Mixed	Mean age: NR % Male: 71.6	NR	Other	Supportive IVS	Good
Jiang 1999[67]	KQ 3	Taiwan ICUs 93	Mixed	Mean age: 72.8 % Male: 63.4	APACHE II score: 16.8	BPAP	Supportive	Poor
Keenan 2002[68]	KQ 3	Canada ICUs 81	Mixed	Mean age: 68.5 % Male: NR	APACHE II score: 23.28	BPAP	Supportive	Good
Nava 1998[69]	KQ 3	Europe ICUs 50	COPD	Mean age: 67.9 % Male: NR	APACHE II score: 23.7	BPAP	IVS	Good
Nava 2005[70]	KQ 3	Europe ICUs 97	Mixed	Mean age: 54.6 % Male: 62.9	SAPS: 32.45	BPAP	Supportive	Good
Su 2012[71]	KQ3	Asia ICUs 406	Mixed	Mean age: 63.9 % Male: 60.8	SAPS: 18.2	BPAP	Supportive	Fair

[a]In instances where a single ARF etiology made up 70% or more of the population, that etiology has been listed, along with the notation "(≥ 70%)." ARF etiology has been listed as "Mixed" if no single etiology made up at least 70% of the population.

Abbreviations: ACPE = acute cardiogenic pulmonary edema; APACHE II = Acute Physiology And Chronic Health Evaluation II; ARF = acute respiratory failure; BPAP = bilevel positive airway pressure; COPD = chronic obstructive pulmonary disease; CPAP = continuous positive airway pressure; GMU = general medical unit; ICU = intensive care unit; IVS = invasive ventilatory support; KQ = key question; N = number of participants; NPPV = noninvasive positive-pressure ventilation; NR = not reported; SAPS = Simplified Acute Physiology Score

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