Comparative Effectiveness Review

Number xx

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 http://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 (http://www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail 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 e-mail 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. 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 to supportive care or invasive ventilation, compared bilevel positive airway pressure (BPAP) to continuous positive airway pressure (CPAP), or evaluated NPPV as a method to wean from invasive ventilation or to prevent or treat acute respiratory failure postextubation.

Review Methods: Two investigators per study screened abstracts and full-text articles 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-seven studies compared NPPV to supportive care, 5 compared NPPV to invasive ventilation, 12 compared BPAP to CPAP, and 11 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 COPD. BPAP was the most common NPPV modality.

Compared to supportive care, NPPV reduced hospital mortality (odds ratio [OR] 0.56; 95 percent confidence interval [CI], 0.43 to 0.72), intubation rates (OR 0.31; 95 percent CI, 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 nonstatistically significant reduction in hospital mortality (OR 0.32; 95 percent CI, 0.08 to 1.33) and a decrease in hospital-acquired pneumonia (OR 0.33; 95 percent CI, 0.13 to 0.84). When used to prevent or treat acute respiratory failure postextubation, NPPV did not improve outcomes.

Subgroup analyses showed that 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 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 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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Effective Health Care

Noninvasive Positive Pressure Ventilation (NPPV) for Acute Respiratory Failure

Executive Summary

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders including consumers.

The full report and this summary are available at www.effectivehealthcare.ahrq.gov/reports/final.cfm

Background

Acute respiratory failure is a life-threatening condition that is 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 is comprised of 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. 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 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.[11,15] 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 ACPE.

Objectives

The literature supporting the use of NPPV in the acute-care setting for respiratory failure 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. Various professional societies have addressed NPPV in clinical practice guidelines; most of these address only the use of NPPV in COPD.[24,25] 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 from the trials. 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 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, lower adverse events, or lower medical utilization when compared to 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 to NPPV with continuous positive airway pressure (CPAP), associated with less morbidity, lower mortality, lower 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 to usual care, associated with less morbidity, lower mortality, lower adverse events, or lower medical utilization:

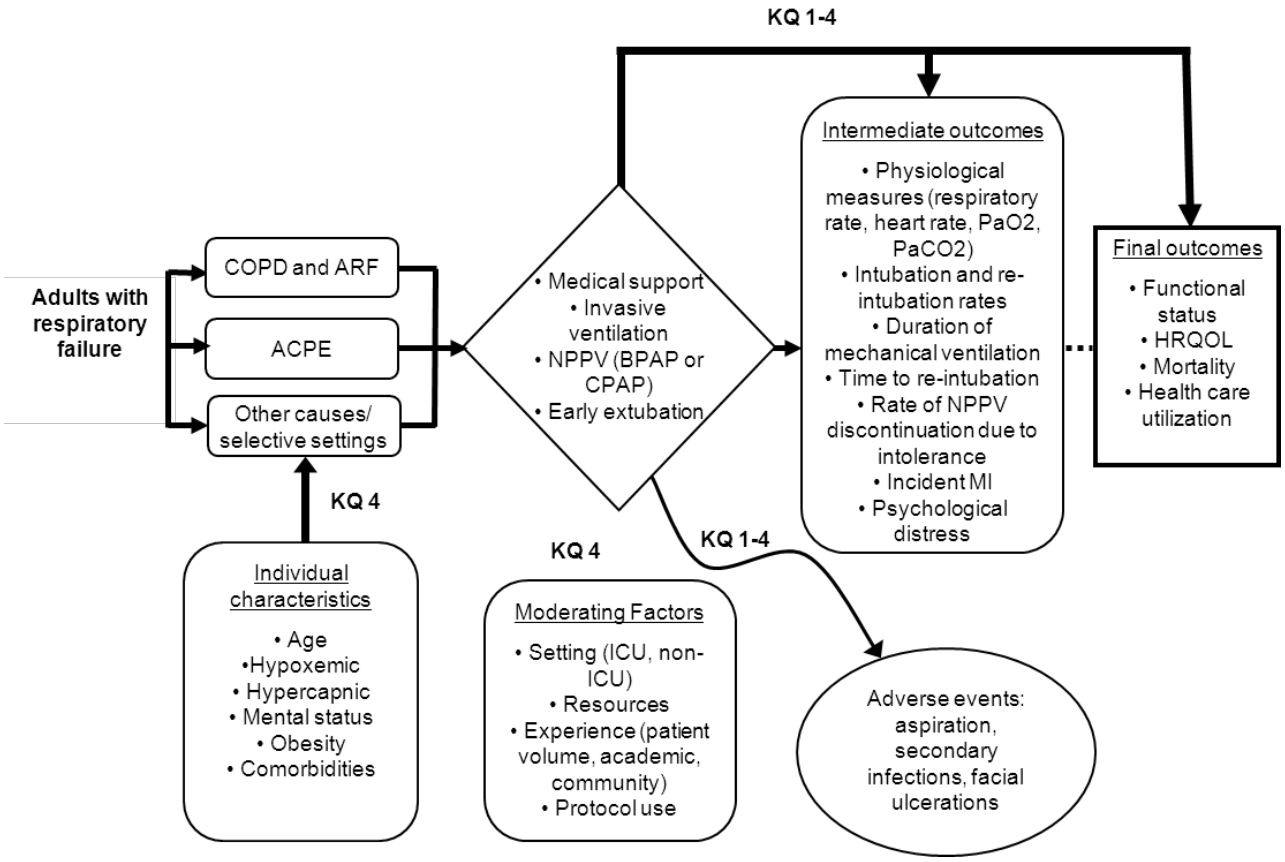
a) In adults with COPD and acute respiratory failure?
b) In adults with ACPE?
c) In adults with acute respiratory failure due to other causes including: pneumonia, asthma, obesity-hypoventilation syndrome, and interstitial lung disease?
d) In adults with acute respiratory failure in selective settings 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 ES-1 shows the analytic framework for this project.

Figure ES-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.

In general, the figure shows that this CER compares morbidity, mortality, adverse events, and health care utilization for patients receiving NPPV versus supportive medical therapy or invasive ventilation (KQ 1), patients receiving NPPV with BPAP versus NPPV with CPAP (KQ 2), and patients receiving early extubation to NPPV versus 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

1. Input from Stakeholders. 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*).[26] 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.[27]

2. Data Sources and Selection. We searched PubMed®, Embase®, and the Cochrane Database of Systematic Reviews (CDSR) 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[28]). We included studies conducted in adults and published in English from 1990 on. We limited studies to 1990 forwards 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.[23,29-41] 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. While the draft report is under peer review, we will update all of the above-descried searches and include any eligible studies in the final report.

We used two approaches to identifying relevant gray 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 (FDA) for any unpublished RCT data available for devices used to provide noninvasive positive pressure ventilation.

Using the criteria described in Table ES-1, 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 ES-1. 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
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	• 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)

Study Characteristic	Inclusion Criteria	Exclusion Criteria
	• 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	
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
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 gray 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), we excluded non-English articles. It is the opinion of the investigators that the resources required for translation of non-English articles would not be justified by the low potential likelihood of identifying relevant data unavailable from English-language sources.

[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

3. Data Extraction and Quality Assessment. The review team created forms for abstracting the data elements for the key questions. 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 over-read the article and the accompanying abstraction form 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[42] 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 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 *General Methods Guide*,[26] 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*[26] 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 over-read 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*.[26,43] 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 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 (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.[44] 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.

4. 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 were often highly skewed for this outcome and were thought not to be amenable to quantitative synthesis. 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.

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; Biotstat, 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.[45]

If these analyses suggested significant publication bias, we computed an adjusted summary estimate using Duval's trim-and-fill method.[46]

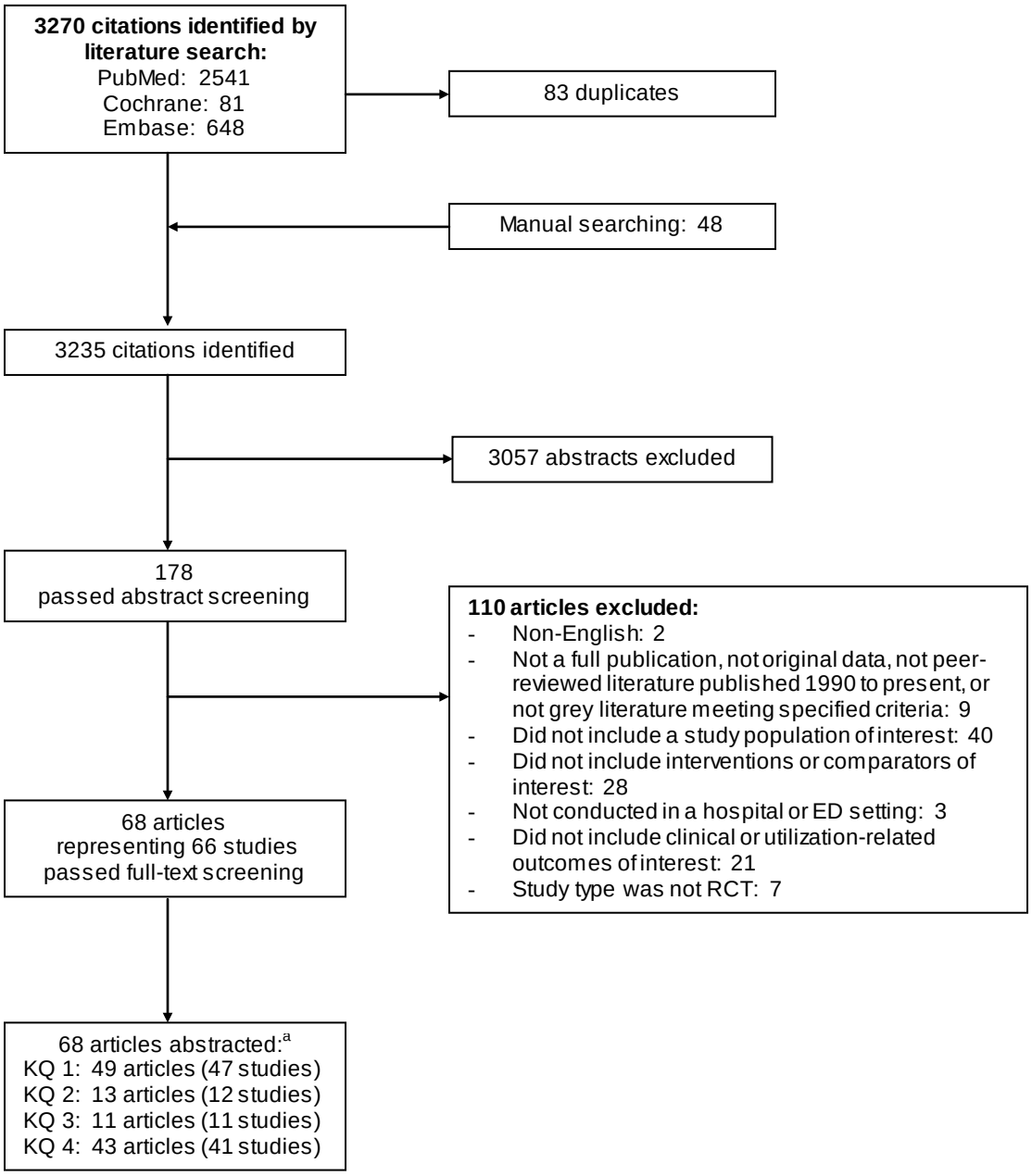
We hypothesized that the methodological quality of individual studies, efficacy-effectiveness score, the characteristics of the comparator, and patients' etiology of acute respiratory failure would be associated with the intervention effects. When there were sufficient studies, we performed subgroup analyses and/or meta-regression 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).

We conducted a secondary, mixed-treatment meta-analysis to address the effects of CPAP, BPAP, and invasive ventilation compared to 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. We used a random-effects analysis, a model that is the same as that used for fixed-effect analysis, except that it includes a coefficient times an error term. This 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[47] describes the application of this methodology to meta-regression problems.

Results

Figure ES-2 depicts the flow of articles through the literature search and screening process. Searches of PubMed, Embase, and the CDSR yielded 3270 citations, 83 of which were duplicate citations. Manual searching identified 48 additional citations, for a total of 3235 citations. After applying inclusion/exclusion criteria at the title-and-abstract level, 178 full-text articles were retrieved and screened. Of these, 110 were excluded at the full-text screening stage, leaving 68 articles (representing 66 unique studies) for data abstraction. As indicated in Figure ES-2, 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 ES-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 68 articles/66 studies.

Abbreviations: KQ = key question; RCT = randomized controlled trial

Key Question 1. NPPV Versus Supportive Care or Invasive Ventilation

Forty seven (47) studies involving 4401 patients met our inclusion criteria. Of the 47 studies, 38 compared NPPV plus supportive medical therapy to supportive medical therapy alone, 5 compared NPPV to invasive ventilation, and 4 were 3-arm trials comparing CPAP, BPAP, and supportive care. Forty-one studies reported mortality, 37 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 percent) were conducted in Europe; six studies (13 percent) were conducted in the United States or Canada. Of the 47 studies, 21 (45 percent) were of good methodological quality, 20 (43 percent) were of fair quality, and 6 (13 percent) were of poor quality.

As measured by morbidity indices that rely primarily on physiological measures, the median predicted mortality for enrolled patients was approximately 25 percent. Table ES-2 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. 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 to 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 to invasive ventilation in only 405 subjects. Compared with invasive ventilation, NPPV lowered hospital-acquired pneumonia (summary OR 0.15; 95 percent CI, 0.08 to 0.30; SOE = high) but did not reduce mortality or length of stay (SOE = low).

Table ES-2. Summary of the strength of evidence for KQ 1—NPPV versus supportive care

Number of Studies (Subjects)	Domains Pertaining to SOE				Strength of Evidence (SOE)
	Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	Effect Estimate (95% CI)
Hospital mortality					**High SOE**
37 (3985)	RCT/Good	Consistent	Direct	Precise	OR = 0.56 (0.43 to 0.72) RD = 64 fewer per 1000 (40 to 85) with NPPV
Intubation rate					**High SOE**
37 (3666)	RCT/Good	Inconsistent	Direct	Precise	OR = 0.31 (0.23 to 0.41) RD = 227 fewer per 1000 (184 to 265) with NPPV
Myocardial infarction					**Moderate SOE**
7 (1645)	RCT/Good	Consistent	Direct	Imprecise	OR = 1.11 (0.85 to 1.44) RD = not applicable
Medical utilization: hospital length of stay (LOS)					**Low SOE**
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 SOE**

Number of Studies (Subjects)	Domains Pertaining to SOE				Strength of Evidence (SOE)
	Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	Effect Estimate (95% CI)
8 (610)	RCT/Good	Consistent	Direct	Imprecise	OR = 0.27 (0.15 to 0.50) RD = 131 fewer per 1000 (86 to 158) with NPPV

[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

Key Question 2. BPAP Versus CPAP

A total of 12 RCTs were included in our analyses. Nine studies enrolled patients from emergency departments, two from unclear settings, and one from a high-dependency unit. The number of patients included in studies ranged from 26 to 1156, with a total of 1996 patients. Four studies included three treatment arms (BPAP, CPAP, and supportive care with supplemental oxygen), while the remainder compared BPAP to 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 ES-3 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 noninvasive positive airway pressure ventilation (NPPV) with bilevel positive airway pressure (BPAP) compared with continuous positive airway pressure (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 of 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. This limits the applicability of these findings to those with COPD and other causes of acute respiratory failure.

Table ES-3. Summary of the strength of evidence for KQ 2—CPAP versus BPAP

Number of Studies (Subjects)	Domains Pertaining to SOE				Strength of Evidence (SOE)
	Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	Effect Estimate (95% CI)
Hospital mortality					**Moderate SOE**
10 (1338)	RCT/Good	Consistent	Direct	Imprecise	OR = 0.89 (0.58 to 1.35) RD = NA
Intubation rate					**Moderate SOE**
12 (1463)	RCT/Good	Consistent	Direct	Imprecise	OR = 0.84 (0.51 to 1.38) RD = NA
Myocardial infarction					**Low SOE**
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**

Number of Studies (Subjects)	Domains Pertaining to SOE				Strength of Evidence (SOE)
	Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	Effect Estimate (95% CI)
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; LOS = length of stay; NA = not applicable; OR = odds ratio; RCT = randomized controlled trial; RD = risk difference; SOE = strength of evidence

Key Question 3. Early Extubation to NPPV

Eleven (11) studies, involving 1114 patients met our inclusion criteria. All studies were conducted in ICU settings and used BPAP as the NPPV mode. Seven 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, and a third study had greater than 70 percent of patients with COPD. One study included patients with a diagnosis of ACPE. 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 versus extubation prior to meeting extubation criteria but with the application of NPPV as a bridge to liberation from invasive mechanical ventilation); four studies described the use of NPPV versus supportive care in preventing extubation failure in those deemed at higher than average risk for requiring reintubation; and two studies examined the use of NPPV versus supportive care in the treatment of recurrent, postextubation acute respiratory failure. All studies reported effects on reintubation, and 10 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 11 studies, 6 were of good methodological quality, 4 were of fair quality, and 1 was of poor quality.

Tables ES-4 and ES-5 summarize the findings and strength of evidence for each major outcome. 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 (pre-symptomatic) BPAP postextubation compared to 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.

Table ES-4. 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 (SOE)
	Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	Effect Estimate (95% CI)
Hospital mortality					**Low SOE**
5 (355)	RCT/Good	Inconsistent	Direct	Imprecise	OR = 0.32 (0.08 to 1.33) RD = NA
Reintubation rate					**Low SOE**
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					**Moderate SOE**
5 (354)[a]	RCT/Good	Inconsistent	Direct	Imprecise	OR = 0.33 (0.13 to 0.84) RD = 167 fewer per 1,000 (33 to 233)

[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 ES-5. Summary of the strength of evidence for KQ 3—NPPV versus supportive care to prevent postextubation respiratory failure

Number of Studies (Subjects)	Domains Pertaining to SOE				Strength of Evidence (SOE)
	Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	Effect Estimate (95% CI)
Hospital mortality					**Low SOE**
5 (667)	RCT/Good	Inconsistent	Direct	Imprecise	OR = 0.89 (0.52 to 1.55) RD = NA
Reintubation rate					**Low SOE**
6 (760)	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**
4 (446)	RCT/Good	Consistent	Indirect	Imprecise	Not estimable; No study found a statistically significant difference in LOS
Medical utilization: ICU length of stay (LOS)					**Insufficient**
5 (667)[a]	RCT/Good	Consistent	Indirect	Imprecise	Not estimable; No study found a statistically significant difference in LOS
Hospital acquired pneumonia					**Low SOE**
3 (349)[a]	RCT/Fair	Consistent	Direct	Imprecise	OR = 0.64 (0.36 to 1.15)

[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

Of the 66 studies included in this report, 62 included information about the clinical setting in which NPPV was initiated, 2 provided specific information about the experience or training of study clinicians, 1 reported patients' mean body mass index, 16 reported data on patients' neurological or mental status, 16 reported a measure of disease burden, and 27 reported mean baseline Acute Physiology And Chronic Health Evaluation (APACHE) II or APACHE III scores for predicted ICU mortality. The only variable listed in KQ 4 that was reported in a sufficient number of studies to justify subgroup analysis is the clinical setting in which NPPV was initiated. Of the 47 studies that pertain to KQ 1, NPPV was initiated in the emergency department (ED) setting in 11 studies and in the ICU setting in 24 studies. In the remaining 12 studies, clinical setting was either not reported, or NPPV was initiated in another setting such as a general medicine ward or ambulance. Most studies were classified as mixed efficacy-effectiveness studies; only two were classified as effectiveness studies.

Table ES-6 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 ES-6. 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 (SOE)
	Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	Summary of effect
Different treatment effects by study effectiveness characteristics					**Low SOE**
42 (4341)[a]	Observational	Inconsistent	Direct	Imprecise	OR (95% CI) for mortality: Efficacy trial: 0.56 (0.27 to 1.02) Mixed trial: 0.50 (0.44 to 0.65) 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 (0.20 to 0.41) Effectiveness trial: 0.38 (0.16 to 2.13)
Different treatment effects across clinical settings					**Low SOE**
42 (4341)*	Observational	Consistent	Direct	Imprecise	OR (95% CI) for mortality: ED: 0.65 (0.38 to 1.09) ICU: 0.50 (0.37 to 0.67) OR (95% CI) for intubation: ED: 0.55 (0.28 to 1.09) ICU: 0.22 (0.15 to 0.34)
Different treatment effects across geographical regions					**Low SOE**

Number of Studies (Subjects)	Domains Pertaining to SOE				Strength of Evidence (SOE)
	Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	Summary of effect
42 (4341)*	Observational	Consistent	Direct	Imprecise	OR (95% CI) for mortality: Europe: 0.56 (0.44 to 0.71) USA/Canada: 0.58 (0.25 to 1.33) OR (95% CI) for intubation: Europe: 0.32 (0.21 to 0.48) USA/Canada: 0.36 (0.20 to 0.66)

[a]37 studies and 3666 patients for analyses of intubation rates.

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 66 trials that that compared NPPV to other common treatment strategies (supportive care and conventional mechanical ventilation). We also included trials that compared different types of NPPV with one another (CPAP versus BPAP). We included common outcomes of interest such as mortality and adverse events, but also examine more challenging 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 consistent across different populations including those with acute cardiogenic pulmonary edema, COPD, 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 to invasive ventilation in only 405 subjects, a finding itself likely related to widespread contemporary clinician belief that because avoiding invasive ventilation is strongly desired, invasive ventilation therefore represents a suboptimal comparator to NPPV. Compared to invasive ventilation, NPPV lowered hospital-acquired pneumonia but did not reduce mortality or length of stay. Compared to 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 recurrent acute respiratory failure post-extubation. We found low SOE for a nonstatistically significant benefit on mortality or reintubation rates. Because summary odds ratios favored benefit and confidence intervals were wide, clinically and statistically significant benefit remains possible. NPPV was associated with lower rates of hospital-acquired pneumonia when used to facilitate weaning from invasive ventilator support. 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 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 Relationship to What is Already Known

Our results are generally consistent with previous systematic reviews and clinical guidelines. Previous reviews have found similar benefits on mortality and intubation rates in patients with respiratory failure due to ACPE[24,39,40] and severe exacerbations of COPD.[24,38] 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 post-operative, post-transplant, or who have acute respiratory failure in the context of obesity-hypoventilation 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.[48-51] 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. Because of the small number of available RCTs, we combined trials examining NPPV for both the prevention and treatment of extubation failure. It could be reasonably argued that these are distinct scenarios and typically differ in the timing of NPPV application. 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 percent) conducted in Europe. There is a longer clinical experience with NPPV in Europe compared to 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 66 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 often descriptions of the interventions that were 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 to 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.[52] to identify gaps in evidence and classify why these gaps exist (Table ES-7). 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. Lack of blinding could introduce 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. 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 ES-7. Evidence gaps and future research

Evidence Gap	Reason	Type of Studies to Consider
Effects versus supportive care in patients with asthma, interstitial lung disease, pneumonia, 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
Effects on resource utilization of NPPV compared to 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
Effectiveness of NPPV as implemented in usual care (outside of RCTs)	Insufficient information	Observational studies Better reporting of the detailed application of NPPV
Uncertainty about the effects of training, staffing composition/ratios, and use of algorithms on NPPV effectiveness	Insufficient information	Observational studies Better reporting of these characteristics in trials
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

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 to supportive care alone. BPAP has been studied more rigorously, but CPAP and BPAP have 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. However, the evidence for these indications is weaker. Limited evidence shows similar treatment effects across different settings and the possibility of less benefit in trials designed to replicate usual clinical practice.

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
CDSR Cochrane Database of Systematic Reviews
CER Comparative Effectiveness Review
CI confidence interval
COPD chronic obstructive pulmonary disease

CPAP	continuous positive airway pressure
ED	emergency department
FDA	U.S. Food and Drug Administration
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
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.

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 associate 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) which 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 to 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 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. 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. Also, 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 trials 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 implemented in more typical clinical settings.

Scope and Key Questions

Scope of the 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.[26,27] 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.[25] 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 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 comparative effectiveness review are:

- **KQ 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:
    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 to NPPV with continuous positive airway pressure (CPAP), associated with less morbidity, lower mortality, lower 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?

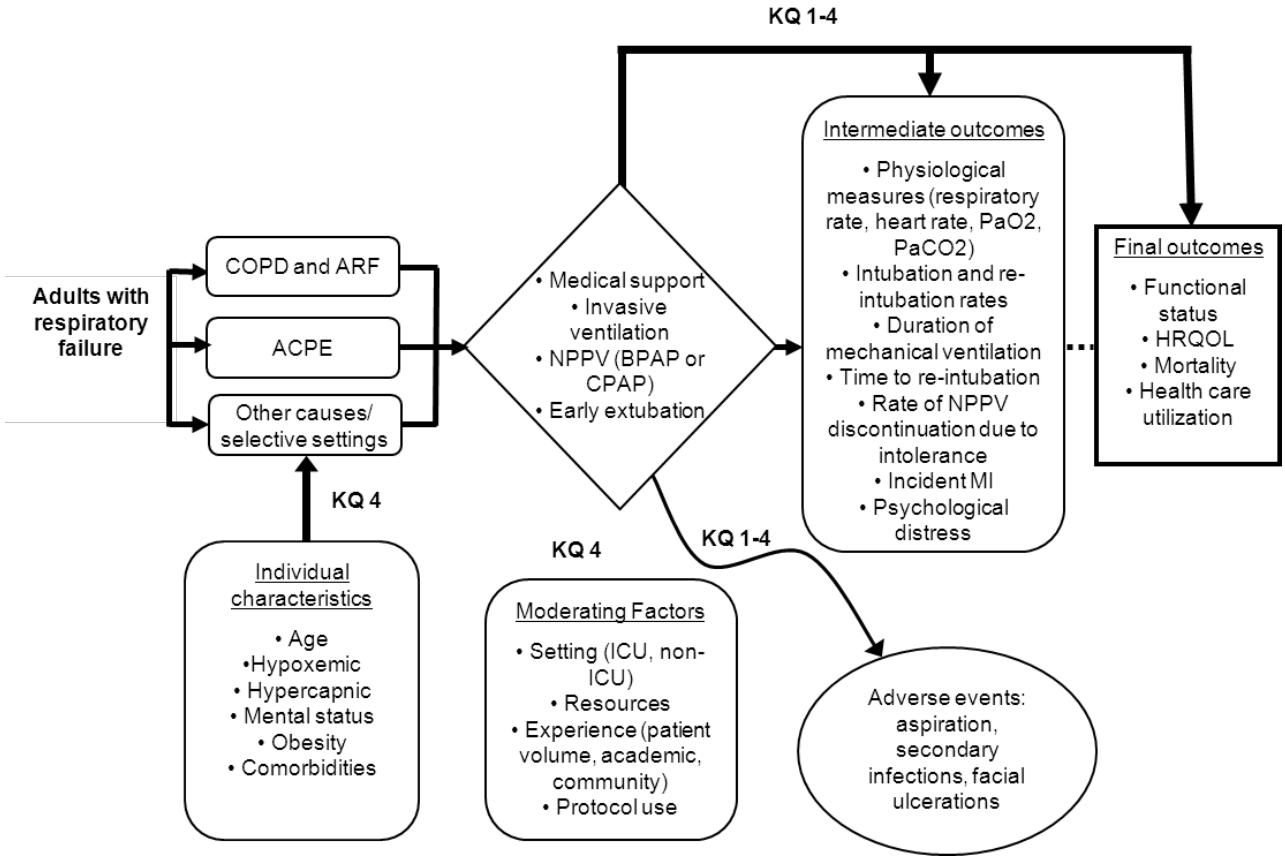
- **KQ 3:** Is early extubation to NPPV, compared to usual care, associated with less morbidity, lower mortality, lower adverse events, or lower medical utilization:
    a) In adults with COPD and acute respiratory failure?
    b) In adults with ACPE?
    c) In adults with acute respiratory failure due 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 versus supportive medical therapy or invasive ventilation (KQ 1), patients receiving NPPV with BPAP versus NPPV with CPAP (KQ 2), and patients receiving early extubation to NPPV versus 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*).[28] 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 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.[29]

Literature Search Strategy

Search Strategy

We searched PubMed®, Embase®, and the Cochrane Database of Systematic Reviews (CDSR) 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[30]). We included studies conducted in adults and published in English from 1990 on. We limited studies to 1990 forwards 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.[25,31-43] 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). While the draft report is under peer review, we will update all of the above-descried searches and include any eligible studies in the final report.

We used two approaches to identifying relevant gray 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 (FDA) 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. 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
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	• 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)

Study Characteristic	Inclusion Criteria	Exclusion Criteria
	• 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	
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
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 gray 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), we excluded non-English articles. It is the opinion of the investigators that the resources required for translation of non-English articles would not be justified by the low potential likelihood of identifying relevant data unavailable from English-language sources.

[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 gray 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 over-read the article and the accompanying abstraction form 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[44]) 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 0–7. 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 (http://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*.[28] 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*[28] 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 over-read 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 were often highly skewed for this outcome and were thought not to be amenable to quantitative synthesis. 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; Biotstat, 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 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).[45] If these analyses suggested significant publication bias, we computed an adjusted summary estimate using Duval's trim-and-fill method.[46]

We anticipated that intervention effects may be heterogeneous. We hypothesized that the methodological quality of individual studies, efficacy-effectiveness score, 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 and/or meta-regression 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.[44] In addition, 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 to 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[47] 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*.[28,48] 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.[49] 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*.[28,50] 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 to 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 is 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, have been invited to provide external peer review of this draft report; AHRQ and an associate editor will also provide comments. The draft report will be posted on the AHRQ Web site for 4 weeks to elicit public comment. We will address all reviewer comments, revising the text as appropriate, and will document everything in a disposition of comments report that will be made available 3 months after the Agency posts the final report on the AHRQ Web site. We will include a list of peer reviewers submitting comments on this draft in the final 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.

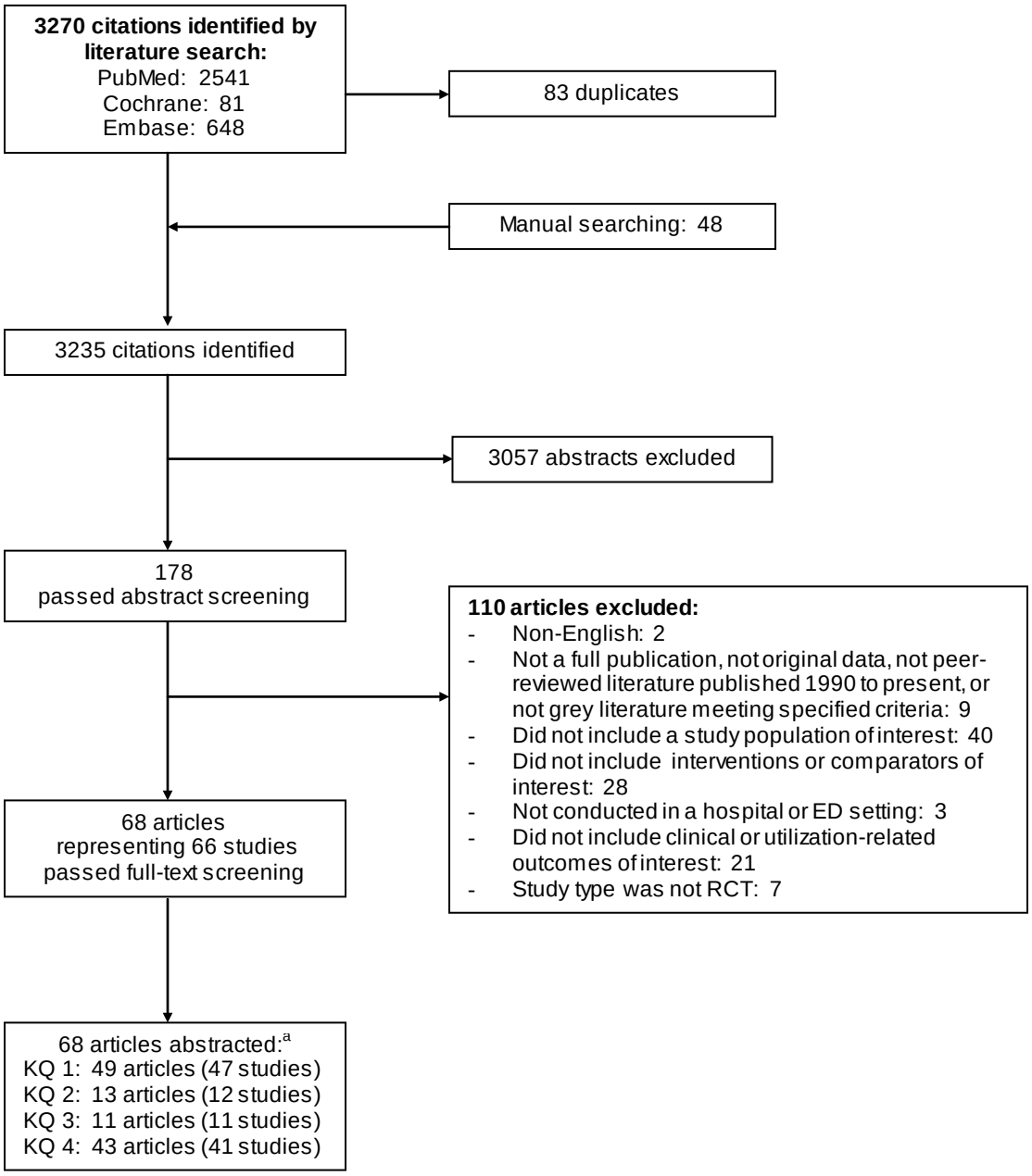
A list of abbreviations and acronyms used in this chapter is provided at the end of the report.

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 (CDSR) yielded 3270 citations, 83 of which were duplicate citations. Manual searching identified 48 additional citations, for a total of 3235 citations. After applying inclusion/exclusion criteria at the title-and-abstract level, 178 full-text articles were retrieved and screened. Of these, 110 were excluded at the full-text screening stage, leaving 68 articles (representing 66 unique studies) for data abstraction. As indicated in Figure 2, many articles/studies were relevant to more than one KQ.

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 68 articles/66 studies.

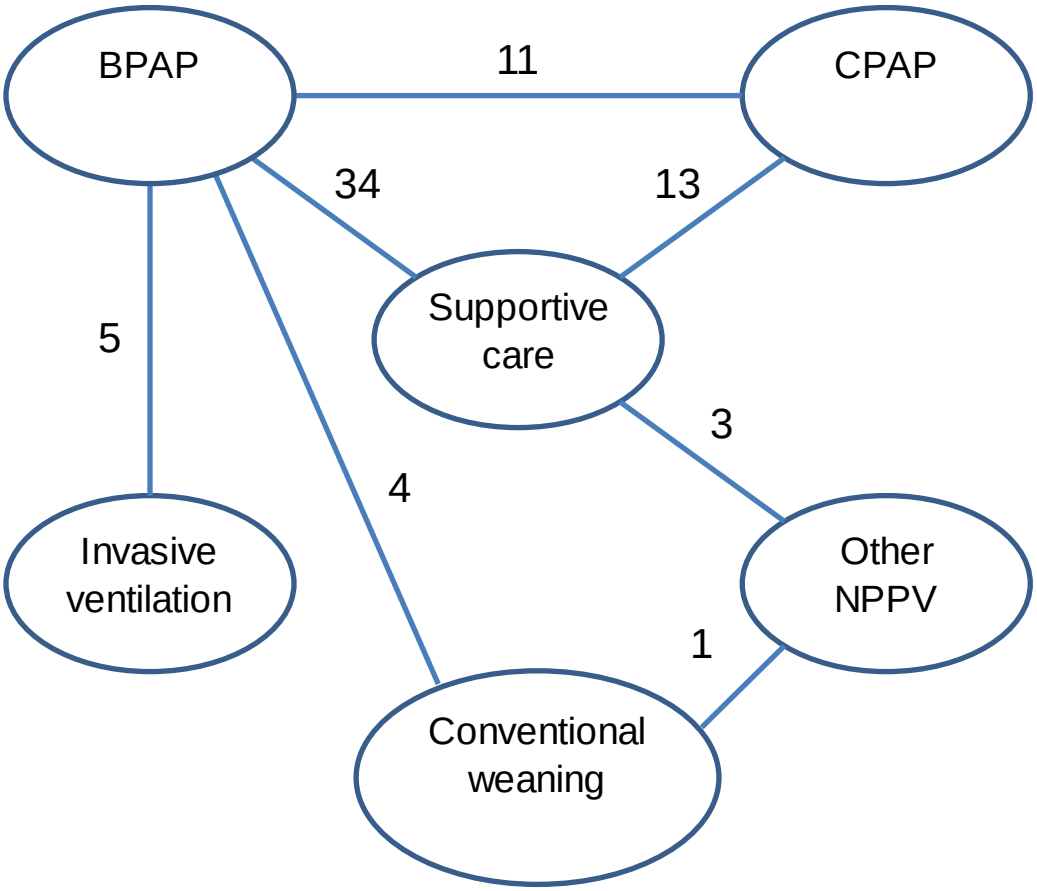
Abbreviations: KQ = key question; RCT = randomized controlled trial

Description of Included Studies

Overall, we included 66 studies, some of which were relevant to more than one KQ: 47 studies were relevant to KQ 1, 12 to KQ 2, and 11 to KQ 3. Studies were conducted in Europe (62 percent); Asia (14 percent); the United States or Canada (12 percent); and South America, Australia, Africa or multiple continents (12 percent). One-third of studies enrolled patients with acute cardiogenic pulmonary edema (ACPE) and another one-third patients with acute respiratory failure due to COPD. NPPV was evaluated infrequently in patients with asthma (five percent) and in patients with acute respiratory failure in the postoperative (three percent) or post-transplant setting (three percent).

Figure 3 maps the direct comparisons between treatments evaluated in this report. The most common comparisons were between BPAP and supportive care (48 percent of comparisons), followed by CPAP versus supportive care (18 percent) and BPAP versus CPAP (15 percent). Relatively few studies compared CPAP to supportive care (18 percent), or any mode of NPPV to invasive ventilation or to conventional weaning (both 7 percent).

Figure 3. Treatment comparisons evaluated in this CER



Abbreviations: Abbreviations: BPAP = bilevel positive airway pressure; CER = comparative effectiveness review; CPAP = continuous positive airway pressure; NPPV = noninvasive positive pressure ventilation

Of the 66 studies, 29 (44 percent) were judged to be of good quality, 29 (44 percent) of fair quality, and 8 (12 percent) 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 many outcomes (e.g., death, intubation) 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 117 citations. A single reviewer identified 32 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, lower adverse events, or lower medical utilization when compared to 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 ACPE and COPD, but limited evidence supports an effect in the postoperative or post-transplant settings.
- In patients treated for acute respiratory failure, current evidence supports a reduction in intubation rates and pneumonia when NPPV plus supportive care is used versus supportive care alone. The evidence does not support an increase in rate of myocardial infarction related to NPPV.
- Evidence for treatment effects is sparse or absent in many diagnostic groups, including those with asthma, interstitial lung disease, postoperative and post-transplant settings.
- In patients with mixed etiologies for acute respiratory failure, current evidence does not suggest a difference in mortality or myocardial infarction for patients treated with NPPV compared to invasive ventilation. However, there is a marked reduction in hospital-acquired pneumonia.
- Effects 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 seven (47) studies involving 4401 patients met our inclusion criteria.[51-97] Study characteristics are summarized in Table 4. Six studies were conducted in the United States or Canada.[68,71,73,75,78,87] Of the 47 studies, 21 (45 percent) were of good methodological quality,[51-53,56-59,61,62,65-67,71,73,81,83,86-88,93,97] 20 (43 percent) were of fair quality,[55,60,64,68-70,72,74-79,82,84,85,89-92] and 6 (13 percent) were of poor quality.[54,63,80,94-96] 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, 41 studies reported mortality,[51-56,58,59,61-65,67,69-75,77-81,83-97] 37 studies reported intubation rates,[51,53-59,61-65,67,68,71-81,83-85,87,88,92-94,96,97] 7 studies reported myocardial infarction,[56,61,65,75,81,87,93] and 8 studies reported rates of hospital-acquired pneumonia.[51,56,64,67,71,83,87,89] 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 47 studies, 38 compared NPPV plus supportive medical therapy to supportive medical therapy alone, 5 compared NPPV to invasive ventilation,[52,60,69,70,91] and 4 were 3-arm trials comparing CPAP, BPAP, and supportive care.[61,65,80,92] BPAP was the most common modality used and, when described, was applied with an inspiratory pressure ranging from 6–20 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 two studies[65,66] described training or provider experience and these studies reported substantial training or high levels of experience with NPPV among providers, and 11 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	1813 (45%)	234 (58%)
Female	1699 (43%)	112 (28%)
Not reported	484 (12%)	59 (15%)
Race: n (%)		
African-American	30 (< 1%)	0
White	75 (2%)	0
Other	17 (< 1%)	0
Not reported	3874 (97%)	405 (100%)
Setting: No. of studies (no. of participants)		
ICU	17 (954)	5 (405)
ED	10 (1616)	0
Postoperative	2 (257)	0
Mixed/Other	13 (1139)	0
NPPV modality: No. of studies (no. of participants)		
BPAP	26 (1767)	5 (405)
CPAP	9 (725)	0
Mixed/Other	7 (1504)	0
Diagnoses: No. of studies (no. of participants)		
COPD	15 (1228)	3 (277)
ACPE	14 (1926)	0
Asthma	3 (121)	0
Postoperative	2 (257)	0
Post-transplant	2 (92)	0
Mixed	6 (372)	2 (128)
Geographical region: No. of studies (no. of participants)		
U.S.A./Canada	6 (244)	0
Europe	23 (2777)	5 (405)
South America	2 (209)	0
Asia	9 (710)	0
Multiple continents	1 (123)	0
Other/NR	1 (33)	0
Funding source: No. of studies (no. of participants)[a]		
Government	7 (1744)	3 (292)
Industry	3 (243)	0
Professional society/Foundation	3 (138)	0
Not reported/Unclear	29 (1871)	2 (113)
Study quality: No. of studies (no. of participants)		
Good	20 (2918)	1 (64)
Fair	16 (875)	4 (341)
Poor	6 (203)	0

[a]Some studies had multiple funding sources; therefore, totals may not sum to the total number of studies.

Abbreviations: ACPE = acute cardiogenic pulmonary edema; COPD = chronic obstructive pulmonary disease; ED = emergency department; ICU = intensive care unit; IVS = invasive ventilatory support; KQ = key question; NPPV = non-invasive positive pressure ventilation; NR = not reported; RCT = randomized controlled trial

Detailed Synthesis

Mortality

Overview

A total of 41 studies reported the effects of NPPV on mortality and were included in our analyses; 37 compared NPPV with usual supportive care,[51,53,55,56,58,59,61-65,67,71-75,77-81,83-90,92-97] and 4 compared NPPV with invasive ventilation.[52,69,70,91] The majority of studies were relatively small in size, with only 9 having ≥ 100 subjects;[58,62,64,65,70,77,81,83,92,93] one study[65] 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, or who were post-transplant or postoperative. As measured by morbidity indices that rely primarily on physiological measures, the median predicted mortality for enrolled patients was approximately 25 percent.

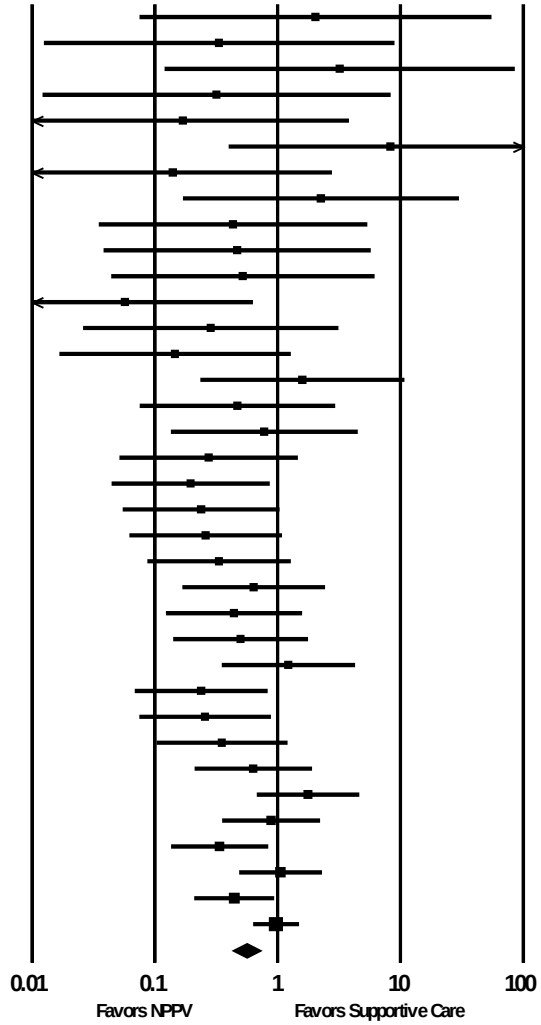
NPPV Versus Supportive Care

Mortality rates ranged from 0–33 percent for NPPV and 0–80 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 ($Q = 41.9$, $df = 35$, $p = 0.20$; $I^2 =$ 16 percent); funnel plots and test statistics did not suggest publication bias (Appendix D). Because the study by Gray et al.[65] contributed a larger 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 five 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 ($p =$ 0.29 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.

Effects on longer term mortality were reported at 30 to 120 days in four studies.[53,59,64,65] NPPV was associated with a nonstatistically significant reduction in mortality (summary OR 0.58; 95 percent CI, 0.31 to 1.06; $Q = 6.1$, $df = 3$, $p = 0.11$, $I^2 = 51$ percent).

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

Study name	Dead / Total		Year	Statistics for each study			Relative weight
	Control	NPPV		Odds ratio	Lower limit	Upper limit	
Park #1720	0 / 10	1 / 16	2001	2.03	0.08	54.83	0.57
Dhamija #3287	1 / 15	0 / 14	2005	0.33	0.01	8.88	0.57
Celikel #3289	0 / 15	1 / 15	1998	3.21	0.12	85.20	0.58
Pastaka #2953	1 / 21	0 / 21	2007	0.32	0.01	8.26	0.58
Masip #1384	2 / 18	0 / 19	2000	0.17	0.01	3.78	0.64
Wood #2466	0 / 11	4 / 16	1998	8.28	0.40	171.29	0.67
Squadrone #2140	3 / 105	0 / 104	2005	0.14	0.01	2.75	0.69
Thys #2254	1 / 10	2 / 10	2002	2.25	0.17	29.77	0.91
Kramer #1167	2 / 15	1 / 16	1995	0.43	0.04	5.35	0.96
Dikensoy #503	2 / 17	1 / 17	2002	0.47	0.04	5.72	0.97
Keenan #1086	2 / 27	1 / 25	2005	0.52	0.04	6.13	1.00
Takeda #2214	7 / 11	1 / 11	1998	0.06	0.01	0.63	1.05
Takeda #2215	3 / 15	1 / 15	1997	0.29	0.03	3.12	1.06
Nava #3293	6 / 41	1 / 41	2011	0.15	0.02	1.27	1.27
Khilnani #2726	2 / 20	3 / 20	2010	1.59	0.24	10.70	1.61
Bersten #205	4 / 20	2 / 19	1991	0.47	0.08	2.93	1.74
Levitt #1260	3 / 17	3 / 21	2001	0.78	0.14	4.46	1.89
Kelly #1096	7 / 31	2 / 27	2002	0.27	0.05	1.45	2.05
Park #3272	6 / 26	3 / 54	2004	0.20	0.04	0.86	2.53
Auriant #107	9 / 24	3 / 24	2001	0.24	0.06	1.03	2.58
Bott #3288	9 / 30	3 / 30	1993	0.26	0.06	1.08	2.70
Crane #434	6 / 20	5 / 40	2004	0.33	0.09	1.27	3.01
Lin #1286	6 / 50	4 / 50	1995	0.64	0.17	2.41	3.04
Antonelli #74	11 / 20	7 / 20	2000	0.44	0.12	1.57	3.27
Wysocki #2481	10 / 20	7 / 21	1995	0.50	0.14	1.77	3.32
Confalonieri #406	6 / 28	7 / 28	1999	1.22	0.35	4.24	3.40
Hilbert #891	21 / 26	13 / 26	2001	0.24	0.07	0.82	3.41
Brochard #273	12 / 42	4 / 43	1995	0.26	0.08	0.88	3.48
Martin #1370	10 / 29	5 / 32	2000	0.35	0.10	1.20	3.49
Nava #3277	9 / 65	6 / 65	2003	0.63	0.21	1.89	4.17
Anonymous #402	7 / 171	12 / 171	2005	1.77	0.68	4.61	5.12
L'Her #1198	14 / 46	12 / 43	2004	0.88	0.35	2.21	5.47
Ferrer #629	21 / 54	9 / 51	2003	0.34	0.14	0.83	5.57
Delclaux #482	18 / 61	19 / 62	2000	1.06	0.49	2.28	6.92
Plant #1796	24 / 118	12 / 118	2000	0.44	0.21	0.94	7.20
Gray #780	36 / 367	67 / 702	2008	0.97	0.63	1.49	12.51
				0.56	0.43	0.72	



Abbreviations: CI = confidence interval; 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	Summary OR (95% CI)	Tests for Heterogeneity
All participants	NA	37 (3985)	0.56 (0.43 to 0.72)	Q = 41.9, df = 35, p = 0.20, I^2 = 16%
Study quality[a]	Good	18 (3045)	0.62 (0.43 to 0.88)	Q = 25.37, df = 17, p = 0.09, I^2 = 33%
	Fair	13 (741)	0.44 (0.29 to 0.67)	Q = 9.92, df = 12, p = 0.62, I^2 = 0%
	Poor	6 (199)	0.46 (0.17 to 1.31)	Q = 2.79, df = 4, p = 0.59, I^2 = 0%
Diagnosis[b]	ACPE	13 (1778)	0.60 (0.41 to 0.88)	Q = 13.9, df = 12, p = 0.31, I^2 = 14%
	COPD	14 (1486)	0.52 (0.33 to 0.81)	Q = 13.04, df = 13, p = 0.37, I^2 = 8%
	Mixed	6 (372)	0.81 (0.42 to 1.56)	Q = 7.86, df = 5, p = 0.16, I^2 = 36%
	Postoperative	2 (257)	0.22 (0.06 to 0.80)	Q = 0.10, df = 1, p = 0.75, I^2 = 0%
	Post-transplant	2 (92)	0.32 (0.13 to 0.78)	Q = 0.46, df = 1, p = 0.50, I^2 = 0%

[a]p = 0.47 for differences in treatment effect by study quality.

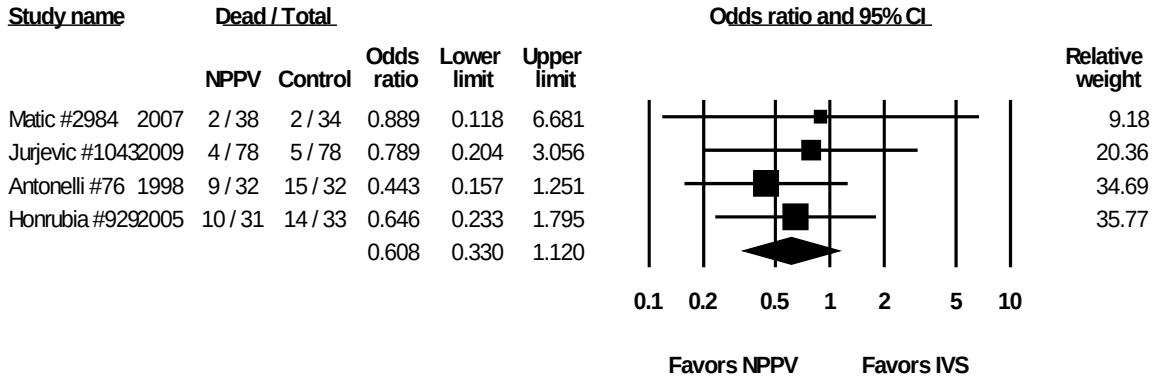
[b]p = 0.29 for differences in treatment effect by diagnosis.

Abbreviations: ACPE = acute cardiogenic pulmonary edema; CI = confidence interval; COPD = chronic obstructive pulmonary disease; df = degrees of freedom; NA = not applicable; NPPV = non-invasive positive pressure ventilation; OR = odds ratio

NPPV Versus Invasive Ventilation

Four studies compared NPPV to invasive ventilation and reported effects on mortality.[52,69,70,91] Etiology of acute respiratory failure was COPD (2 studies) and mixed (2 studies). One study was of good quality;[52] the others were of fair quality. The mortality rate for invasive ventilation ranged from 6–47 percent. Overall, there was no difference in mortality when NPPV was employed versus invasive ventilation (summary OR 0.61; 95 percent CI, 0.33 to 1.12; Figure 5). Effects were consistent across studies (Q = 0.65, df = 3, p = 0.89; I^2 = 0 percent). 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 vs. invasive ventilation



Abbreviations: CI = confidence interval; IVS = invasive ventilatory support; NPPV = noninvasive positive-pressure ventilation

Intubation

Overview

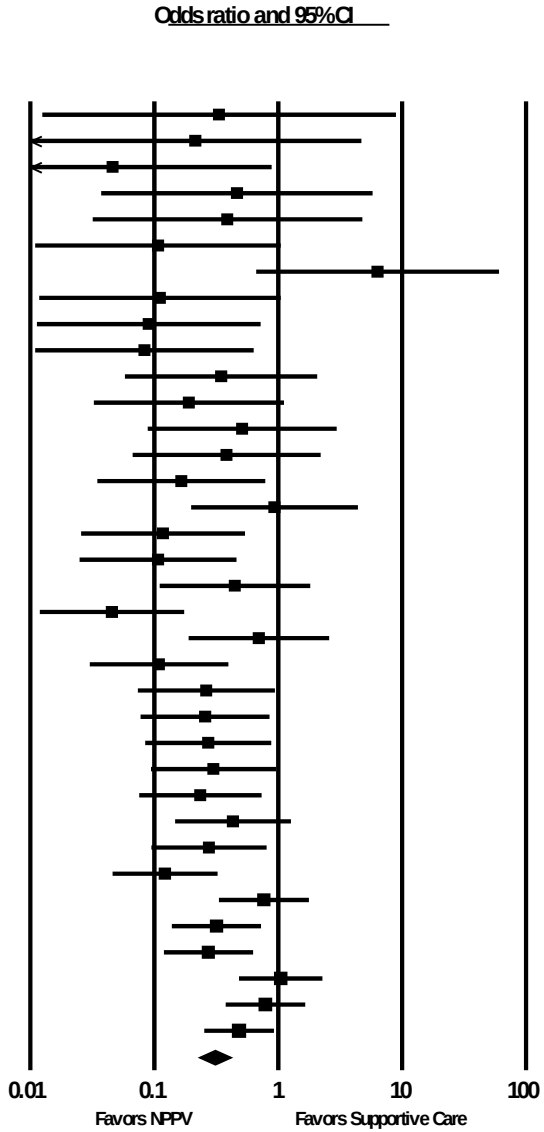
We identified 37 studies reporting on the relative effects of NPPV versus supportive care on intubation rates;[51,53,55-59,61-65,67,68,71-81,83-85,87-89,92-94,96,97] this outcome was not relevant for studies comparing NPPV with invasive ventilation.

NPPV Versus Supportive Care

Intubation rates ranged from 0–62 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 percent CI, 0.23 to 0.41; Figure 6). Tests for heterogeneity showed moderate variability in treatment effects across studies ($Q = 58.1$, $df = 35$, $p = 0.01$; $I^2 = 40$ percent). 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 = 0.40; 95 percent CI, 0.30 to 0.53). 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 vs. supportive care

Study name	Intub / Total		Year	Statistics for each study			Relative weight
	NPPV	Control		Odds ratio	Lower limit	Upper limit	
Dhamija #3287	0 / 14	1 / 15	2005	0.33	0.01	8.88	0.69
Kelly #1096	0 / 27	2 / 31	2002	0.21	0.01	4.67	0.78
Bersten #205	0 / 19	7 / 20	1991	0.05	0.00	0.88	0.84
Celikel #3289	1 / 15	2 / 15	1998	0.46	0.04	5.75	1.11
Holley #924	1 / 19	2 / 16	2001	0.39	0.03	4.74	1.12
Takeda #2215	1 / 15	6 / 15	1997	0.11	0.01	1.04	1.32
Crane #434	5 / 20	1 / 20	2004	6.33	0.67	60.16	1.34
Masip #1384	1 / 19	6 / 18	2000	0.11	0.01	1.04	1.35
Squadrone #2140	1 / 105	10 / 104	2005	0.09	0.01	0.72	1.53
Takeda #2214	2 / 11	8 / 11	1998	0.08	0.01	0.63	1.59
Park #1720	3 / 16	4 / 10	2001	0.35	0.06	2.06	1.94
Dikensoy #503	2 / 17	7 / 17	2002	0.19	0.03	1.11	1.98
L'Her #1198	2 / 43	4 / 46	2004	0.51	0.09	2.95	2.00
Keenan #1086	2 / 25	5 / 27	2005	0.38	0.07	2.18	2.01
Kramer #1167	5 / 16	11 / 15	1995	0.17	0.03	0.78	2.37
Wood #2466	7 / 16	5 / 11	1998	0.93	0.20	4.37	2.40
Khilnani #2726	3 / 20	12 / 20	2010	0.12	0.03	0.54	2.45
Antonelli #74	4 / 20	14 / 20	2000	0.11	0.03	0.46	2.60
Levitt MA	5 / 21	7 / 17	2001	0.45	0.11	1.80	2.75
Nava #3293	3 / 41	26 / 41	2011	0.05	0.01	0.17	2.91
Wysocki #2481	13 / 21	14 / 20	1995	0.70	0.19	2.56	3.01
Park #3272	4 / 54	11 / 26	2004	0.11	0.03	0.39	3.06
Auriant #107	5 / 24	12 / 24	2001	0.26	0.07	0.94	3.10
Hilbert #891	12 / 26	20 / 26	2001	0.26	0.08	0.85	3.33
Confalonieri #406	6 / 28	14 / 28	1999	0.27	0.08	0.88	3.42
Carrera #323	5 / 37	13 / 38	2009	0.30	0.09	0.96	3.46
Lin #1285	8 / 25	20 / 30	1991	0.24	0.08	0.73	3.54
Lin #1286	6 / 50	12 / 50	1995	0.43	0.15	1.26	3.76
Martin #1370	9 / 32	17 / 29	2000	0.28	0.09	0.80	3.77
Brochard #273	11 / 43	31 / 42	1995	0.12	0.05	0.32	4.15
Nava #3277	13 / 65	16 / 65	2003	0.77	0.33	1.75	4.77
Ferrer #629	13 / 51	28 / 54	2003	0.32	0.14	0.73	4.79
Anonymous #402	8 / 171	26 / 171	2005	0.27	0.12	0.62	4.80
Gray #780	20 / 702	10 / 367	2008	1.05	0.48	2.26	5.05
Delclaux #482	21 / 62	24 / 61	2000	0.79	0.38	1.65	5.22
Plant #1796	18 / 118	32 / 118	2000	0.48	0.25	0.92	5.67
				0.31	0.23	0.41	



Abbreviations: CI = confidence interval; 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	Summary OR (95% CI)	Tests for Heterogeneity
All participants	NA	37 (3666)	0.31 (0.23 to 0.41)	Q = 58.1, df = 35, p = 0.01, I^2 = 40%
Study quality[a]	Good	18 (2738)	0.36 (0.23 to 0.55)	Q = 44.3, df = 17, p < 0.001, I^2 = 62%
	Fair	14 (789)	0.24 (0.17 to 0.36)	Q = 8.77, df = 13, p = 0.79, I^2 = 0%
	Poor	5 (139)	0.29 (0.10 to 0.85)	Q = 0.40, df = 4, p = 0.94, I^2 = 0%
Diagnosis[b]	ACPE	14 (1813)	0.36 (0.21 to 0.64)	Q = 2.58, df = 13, p = 0.02, I^2 = 50%
	COPD	12 (1117)	0.23 (0.15 to 0.35)	Q = 14.4, df = 11, p = 0.22, I^2 = 23%
	Mixed	6 (352)	0.52 (0.32 to 0.84)	Q = 4.53, df = 5, p = 0.34, I^2 = 12%
	Asthma	1 (35)	0.39 (0.03 to 4.74)	NA
	Postoperative	2 (257)	0.20 (0.07 to 0.58)	Q = 0.74, df = 1, p = 0.39, I^2 = 0%
	Post-transplant	2 (92)	0.18 (0.07 to 0.46)	Q = 0.83, df = 1, p = 0.36, I^2 = 0%

[a]p = 0.44 for differences in treatment effect by study quality.

[b]p = 0.12 for differences in treatment effect by diagnosis.

Abbreviations: ACPE = acute cardiogenic pulmonary edema; CI = confidence interval; COPD = chronic obstructive pulmonary disease; df = degrees of freedom; NA = not applicable; NPPV = non-invasive positive pressure ventilation; OR = odds ratio

Myocardial Infarction

Overview

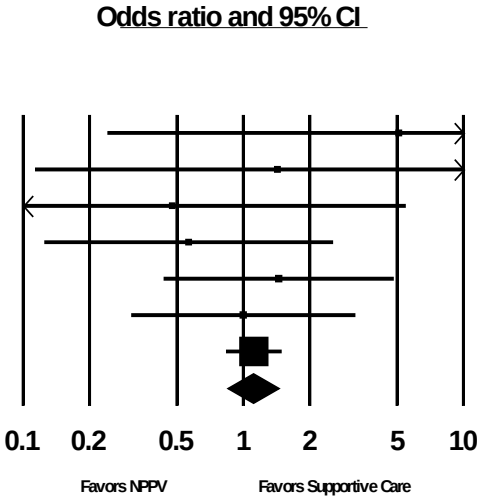
We identified seven studies reporting on the relative effects of NPPV versus supportive care on myocardial infarction rates.[56,61,65,75,81,87,93] Six of these were judged to be of good quality. Two studies (one good and one fair quality) reported this outcome for NPPV compared to invasive ventilation.[52,69]

NPPV Versus Supportive Care

Rates of myocardial infarction ranged from 2–30 percent for NPPV and from 0–30 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 vs. supportive care

Study name	Year	Intub / Total					Relative weight
		NPPV	Control	Odds ratio	Lower limit	Upper limit	
Plant #1796	2000	2 / 118	0 / 118	5.09	0.24	107.08	0.76
Wood #2466	1998	2 / 16	1 / 11	1.43	0.11	18.00	1.10
Brochard #273	1995	1 / 43	2 / 42	0.48	0.04	5.46	1.18
Levitt #1260	2001	4 / 21	5 / 17	0.56	0.12	2.55	3.10
Nava #3277	2003	7 / 65	5 / 65	1.45	0.43	4.82	4.86
Crane #434	2004	12 / 40	6 / 20	1.00	0.31	3.23	5.13
Gray #780	2008	189 / 702	91 / 367	1.12	0.84	1.49	83.87
				1.11	0.85	1.44	



Abbreviations: CI = confidence interval; Intub = intubated; 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)	Q = 2.45, df = 6, p = 0.87, I^2 = 0%
Diagnosis[a]	ACPE	4	1.10 (0.84 to 1.45)	Q = 1.76, df = 3, p = 0.62, I^2 = 0%
	COPD	2	0.81 (0.14 to 4.68)	Q = 0.38, df = 1, p = 0.54, I^2 = 0%
	Mixed	1	1.45 (0.44 to 4.82)	NA

[a]p = 0.85 for differences in treatment effect by diagnosis.

Abbreviations: ACPE = acute cardiogenic pulmonary edema; CI = confidence interval; COPD = chronic obstructive pulmonary disease; df = degrees of freedom; NA = not applicable; NPPV = non-invasive positive pressure ventilation; OR = odds ratio

NPPV Versus Invasive Ventilation

Only two studies comparing NPPV with invasive ventilation reported rates of myocardial infarction.[52,69] In each study, fewer patients in the NPPV-treated groups (1 of 31 and 2 of 32) had myocardial infarctions compared to invasive ventilation (2 of 33 and 4 of 32).

Hospital-Acquired Pneumonia

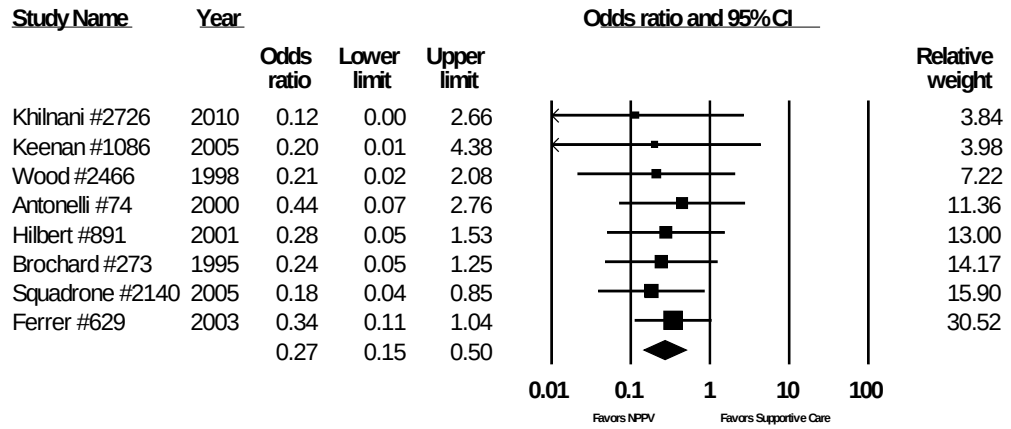
Overview

We identified eight studies reporting on the relative effects of NPPV versus supportive care on hospital-acquired pneumonia.[51,56,64,67,71,83,87,89] Six of these were judged to be of good quality. Four studies compared NPPV with invasive ventilation for this outcome.[52,60,69,70]

NPPV Versus Supportive Care

Rates of hospital-acquired pneumonia ranged from 0–10 percent for NPPV and from 7–24 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 = 7, p = 0.99; I^2 = 0 percent). 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 vs. supportive care



Abbreviations: CI = confidence interval; 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	8	0.27 (0.15 to 0.50)	Q = 1.09, df = 7, p = 0.99, I^2 = 0%
Study quality[a]	Good	6	0.25 (0.12 to 0.54)	Q = 0.60, df = 5, p = 0.99, I^2 = 0%
	Fair	2	0.30 (0.11 to 0.87)	Q = 0.41, df = 1, p = 0.52, I^2 = 0%
Diagnosis[b]	COPD	3	0.21 (0.06 to 0.77)	Q = 0.17, df = 2, p = 0.92, I^2 = 0%
	Mixed	2	0.31 (0.12 to 0.85)	Q = 0.14, df = 1, p = 0.71, I^2 = 0%
	Postoperative	1	0.18 (0.04 to 0.86)	NA
	Post-transplant	2	0.35 (0.10 to 1.20)	Q = 0.14, df = 1, p = 0.71, I^2 = 0%

[a]p = 0.78 for differences in treatment effect by study quality.

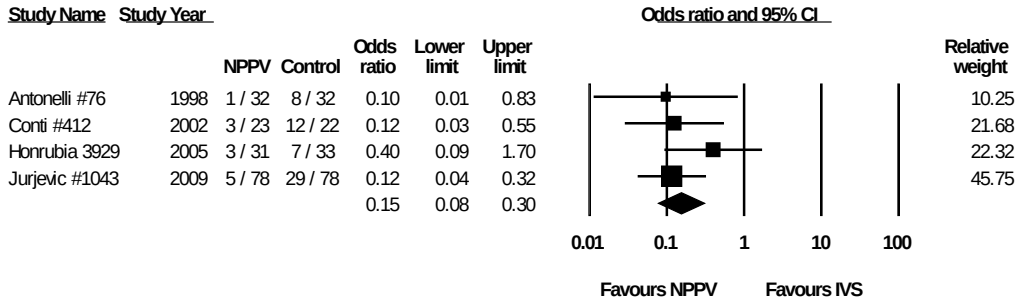
[b]p = 0.89 for differences in treatment effect by diagnosis.

Abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; df = degrees of freedom; NA = not applicable; NPPV = non-invasive 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 percent 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 percent).

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



Abbreviations: CI = confidence interval; IVS = invasive ventilatory support; NPPV = noninvasive positive-pressure ventilation

Length of Stay

NPPV Versus Supportive Care

Twenty-eight studies reported effects on hospital length of stay. Of these, we focused our analysis on the 10 studies with larger sample sizes.[57,58,64,65,74,77,81,83,93,95,97] Mean length of stay varied substantially across studies, from 8.5–20.7 days for NPPV-treated patients and from 5.1–26.8 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 difference in length of stay between survivors and nonsurvivors.

ICU length of stay was reported in 13 studies. We focused our analyses on the five largest of these.[59,64,66,77,83] Mean ICU length of stay range from 1.4–10 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.[59,66]

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.[52,60,69,70] Mean ICU length of stay range from 5–22 days in NPPV-treated patients and from 9.3–21 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 percent). 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[65,83] and 8.4 percent for BPAP.[65] Rates of facial abrasions or ulcerations were

reported in 14 studies and varied widely, ranging from 0–47 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[93] and 25.5 percent.[64]

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 to either supportive care or invasive ventilation. Antonelli et al.[52] 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[59] and no effect in the other.[67] Duration of invasive ventilation was reported in two studies comparing NPPV to invasive ventilation, one showing a statistically significant shorter duration,[70] with no effect in the other.[60] 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).[60]

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, lower 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

- Thirteen RCTs of varied quality showed no statistically significant difference between providing noninvasive positive airway pressure ventilation (NPPV) with bilevel positive airway pressure (BPAP) compared with continuous positive airway pressure (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). This limits the applicability of these findings to those with chronic obstructive pulmonary disease (COPD) and other causes of acute respiratory failure, 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.[61,65,80,92,98-105] Important study characteristics are summarized in Table 9. Nine studies enrolled patients from emergency departments,[61,65,92,98-101,104,105] two from an unclear setting,[80,103] and one from a high-dependency unit.[102] Seven studies were performed in Europe,[61,65,98,99,101,102,104] two in Brazil,[80,92] one in Tunisia,[105] one in Canada,[103] and one in Australia.[100] Of these, four were of good quality,[61,65,101,105] six were of fair quality,[92,98-100,102,104] and two were of poor quality.[80,103] The funding source was reported in five studies.[65,100,102,104,105] Studies enrolled patients between 1994 and 2008. The number of patients included in studies ranged from 26[80] to 1156,[65] with a total of 1996 patients. The mean age of study participants ranged from 64–78 years. The proportion of female patients included ranged from 48–67 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,[100] only 30 (30 percent) did not have pulmonary edema as their admission diagnosis; these included patients with COPD (21 percent), pneumonia (8 percent), and asthma (1 percent). Therefore, no studies included in these analyses addressed obesity hypoventilation syndrome, interstitial lung disease, or the postoperative or post-transplant setting.

Four studies included three treatment arms (BPAP, CPAP, and supportive care with supplemental oxygen),[61,65,80,92] while the remainder compared BPAP to CPAP alone. NPPV was delivered by nasal mask in one study,[103] 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.[61]

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

Characteristic	Values
Mean age of sample: Median (range)	76.5 (63.5–77.6)
Sex: n (%)	
Male	561 (38.3%)
Female	721 (49.3%)
Not reported	181 (12.4%)
Race: n (%)	
Not reported	1463 (100%)
Setting: No. of studies (no. of participants)	
ED	9 (1420)
High-dependency unit	1 (52)
Not reported	2 (524)
Diagnoses: No. of studies (no. of participants)	
ACPE	12 (1966)
COPD	1 (21)
Pneumonia	1 (8)
Asthma	1 (1)

Characteristic	Values
Geographical region: No. of studies (no. of participants)	
U.S.A./Canada	1 (27)
Europe	7 (1553)
Brazil	2 (106)
Africa	1 (200)
Funding source: No. of studies (no. of participants)	
Government	3 (1378)
Industry	0
Other	0
None or not reported	9 (718)
Study quality: No. of studies (no. of participants)	
Good	4 (1409)
Fair	6 (424)
Poor	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

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 (No. of Participants)	Summary OR (95% CI)	Tests for Heterogeneity
Mortality	10 (1731)	0.89 (0.58 to 1.35)	Q = 9.28, df = 9, p = 0.41; I^2 = 3%
Intubation	12 (1996)	0.84 (0.51 to 1.38)	Q = 8.73, df = 11, p = 0.65; I^2 = 0%
Myocardial infarction	7 (1423)	0.69 (0.34 to 1.40)	Q = 1 1.1, df = 6, p = 0.09; I^2 = 46%

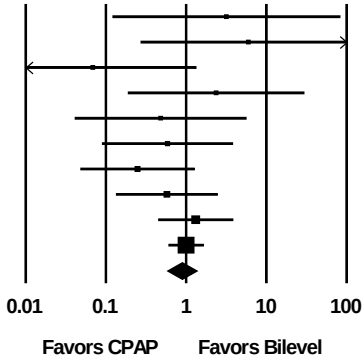
Abbreviations: BPAP = bilevel positive airway pressure; CI = confidence interval; df = degrees of freedom; CPAP = continuous positive airway pressure; df = degrees of freedom; OR = odds ratio

Mortality

In-hospital mortality ranged from 0–25 percent for BPAP, 0–21 percent for CPAP, and 0–30 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 percent CI, 0.58 to1.35) 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.[65]

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

Study name	Year	Dead / Total CPAP	Dead / Total BiPAP	Odds ratio	Lower limit	Upper limit	Relative weight
Bellone #179	2005	1 / 18	0 / 18	3.17	0.12	83.17	1.65
Bellone #177	2004	2 / 22	0 / 24	5.98	0.27	131.66	1.84
Crane #434	2004	0 / 20	5 / 20	0.07	0.00	1.34	2.00
Mehta #1429	1997	2 / 13	1 / 14	2.36	0.19	29.71	2.74
Park #3272	2004	1 / 27	2 / 27	0.48	0.04	5.64	2.89
Ferrari #626	2007	2 / 27	3 / 25	0.59	0.09	3.84	4.93
Ferrari #625	2010	2 / 40	7 / 40	0.25	0.05	1.28	6.44
Nouira #2661	2011	3 / 101	5 / 99	0.58	0.13	2.48	8.08
Cross #438	2004	9 / 51	7 / 50	1.32	0.45	3.86	14.48
Gray #780	2008	33 / 346	34 / 356	1.00	0.60	1.65	54.94
				0.89	0.58	1.35	



Abbreviations: CI = confidence interval; CPAP = continuous positive airway pressure

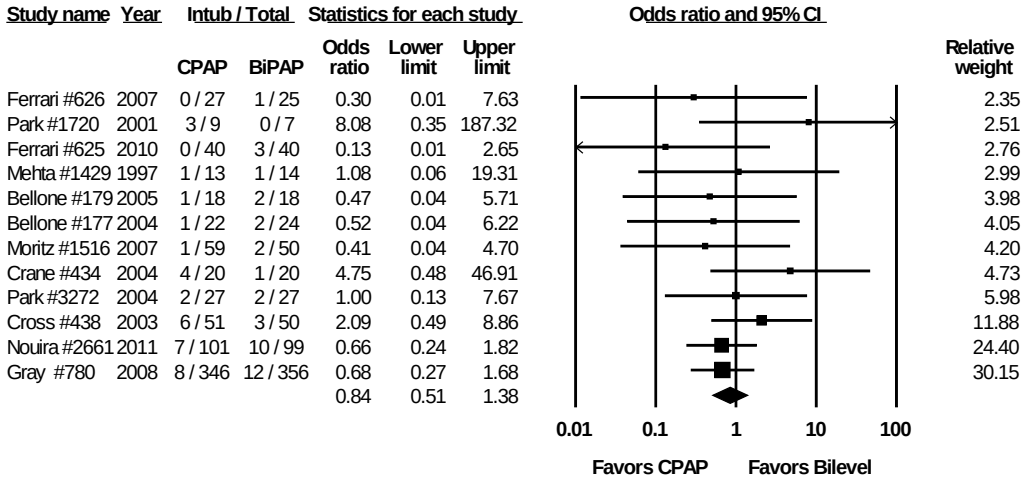
There are caveats and limitations to consider. One study alone accounted for 58 percent of all patients included in these analyses.[65] This study included three treatment arms (BPAP, CPAP, and supplemental oxygen only). Study investigators found that there was no difference in 7-day mortality between oxygen and NPPV (9.8 percent vs. 9.5 percent, 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 percent vs. 11.7 percent, p = 0.81). Nevertheless, even after removing Gray, analyses did not show a clinically or statistically important intervention effect (OR 0.88; 95 percent CI 0.39 to 1.48). Second, fewer than two percent of patients enrolled in these studies carried a primary diagnosis other than ACPE. Therefore, 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.

Intubation

Endotracheal intubation rates ranged from 0–29 percent for BPAP, 0–33 percent for CPAP, and 2.8–42 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 percent 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 percent). 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[100] had undue influence of the overall summary estimate. Removing this study lowed the point estimate for treatment effect, although this was not statistically significant (OR 0.74; 95 percent 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 vs. CPAP



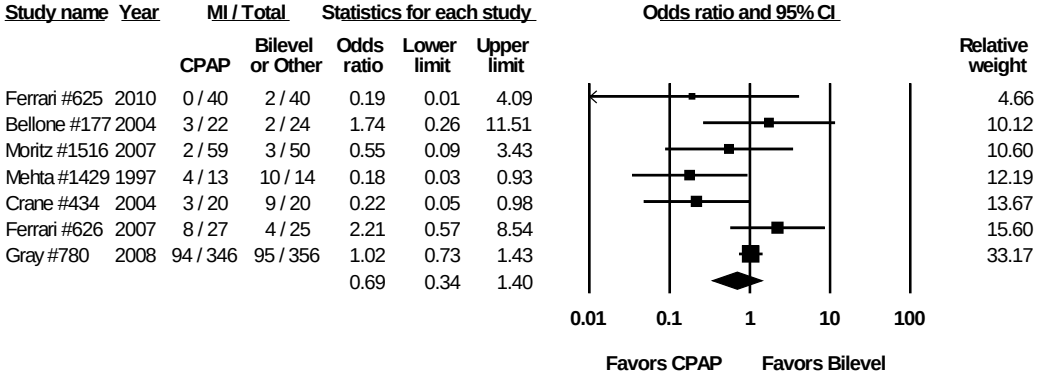
Abbreviations: CI = confidence interval; CPAP = continuous positive airway pressure

Myocardial Infarction

Seven studies included myocardial infarction as a treatment outcome. Myocardial infarction rates ranged from 0–71 percent for BPAP, 7–31 percent for CPAP, and 0–30 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 percent 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 percent).

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



Abbreviations: CI = confidence interval; CPAP = continuous positive airway pressure

Length of Stay in Hospital and ICU

Six studies reported hospital length of stay as an outcome.[92,100-104] Mean length of stay varied substantially across studies, from 4–13.6 days in CPAP-treated patients and 5–11.3 days for BPAP-treated patients. Of thee six studies, only three[100,101,104] 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.[100,103] Median length of ICU stay was zero days in both arms of one study,[100] while mean ICU length of stay was 2.3 and 2.7 days in the CPAP and BPAP arms, respectively, in the other.[103] 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.[61,65,101,103] All used full face masks except for one,[103] which used a nasal mask. No intolerance was observed in either CPAP or bilevel NPPV in one study[101] 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,[65] and in this study the rates were 5.2 percent for CPAP-treated patients compared with 8.4 percent for BPAP, a difference of 3.2 percent, but which did not reach statistical significance ($p = 0.09$).

A single study reported the incidence of facial ulcerations in both CPAP and BPAP arms.[103] 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.[100], 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], $p = 0.206$).

Key Question 3. Early Extubation to NPPV

KQ3. Is early extubation to NPPV, compared to usual care, associated with less morbidity, lower mortality, lower 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

- In mixed populations of patients intubated for acute respiratory failure, current evidence shows a nonstatistically significant reduction in mortality but no effect on reintubation rates when bilevel positive airway pressure (BPAP) is used facilitate early extubation versus usual care. However, early extubation to BPAP is associated with lower rates of hospital-acquired pneumonia.
- Few studies had adequate sample sizes to adequately 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.
- In patients at high risk for or with recurrent acute respiratory failure, use of BPAP postextubation was not associated with statistically significant lower mortality, reintubation rates, or hospital-acquired pneumonia rates compared with supportive care. However, summary estimates of treatment effects favored BPAP, and a clinically important benefit cannot be excluded.
- In patients at high risk for or with recurrent acute respiratory failure, use of BPAP postextubation was not associated with lower hospital or ICU length of stay compared with supportive care. However, few studies reported this outcome, and length of stay varied widely.
- No studies reported data on myocardial infarction, psychological response, functional status, or health-related quality of life.
- No studies used CPAP as the NPPV mode.

Description of Included Studies

Eleven (11) studies, involving 1114 patients met our inclusion criteria.[106-116] One study was conducted in Canada,[113] and one multicenter study included sites in the United States;[107] all others were carried out in Europe or Asia. Of the 11 studies, 6 (55 percent) were of good methodological quality,[107,109,113-116] 4 (36 percent) were of fair quality,[106,108,110,111] and 1 (9 percent) was of poor quality.[112] All studies reported effects on reintubation, and 10 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[110] reported a 15-year experience, and one[113] 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 six 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. Seven 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, and a third study had greater than 70 percent of patients with COPD. One study included patients with a diagnosis of ACPE.

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 versus extubation prior to meeting extubation criteria but with the application of NPPV as a bridge to liberation from invasive mechanical ventilation).[106,108,111,114,116] A second category of studies (four studies) describes the use of NPPV versus supportive care in preventing extubation failure in those deemed at higher than average risk for requiring reintubation.[109,110,112,115] Finally, two studies examined the use of NPPV versus supportive care in the treatment of recurrent, postextubation acute respiratory failure.[107,113] For the purpose of our analyses, we combined the last two groups into a general "postextubation—NPPV versus supportive care" category.

Table 11. Study characteristics by treatment comparison

Characteristic	Weaning: NPPV vs. "Usual" Strategy	Postextubation: NPPV vs. Supportive Care
Mean age of sample: Median age (range)	68.6 (64.2–70.7)	68.5 (54.6–72.7)
Sex: n (%)		
Male	184 (52%)	442 (58%)
Female	87 (25%)	237 (31%)
Not reported	83 (23%)	81 (11%)
Race: n (%)		
Not reported	354 (100%)	760 (100%)
Setting: No. of studies (no. of participants)		
ICU	5 (354)	6 (760)
High-dependency unit	0	0

Characteristic	Weaning: NPPV vs. "Usual" Strategy	Postextubation: NPPV vs. Supportive Care
NPPV modality: No. of studies (no. of participants)		
BPAP	5 (354)	6 (760)
CPAP	0	0
Diagnoses: No. of studies (no. of participants)		
Mixed	3 (214)	4 (573)
COPD	2 (140)	1 (106)
ACPE	0	1 (81)
Geographical region: No. of studies (no. of participants)		
U.S.A./Canada	0	1 (81)
Europe	4 (264)	3 (365)
Asia	1 (90)	1 (93)
Multiple continents	0	1 (221)
Funding source:[a] No. of studies (no. of participants)		
Government	1 (138)	3 (408)
Industry	0 (0)	1 (81)
Professional society/Foundation	0 (0)	2 (187)
Not reported/Unclear	4 (216)	2 (190)
Study quality: No. of studies (no. of participants)		
Good	2 (188)	4 (505)
Fair	3 (166)	1 (162)
Poor	0	1 (93)

[a]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; 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.[106,108,111,114,116] All studies used BPAP. Table 12 summarizes the pooled treatment effects. Hospital-acquired pneumonia was significantly reduced with early extubation to NPPV. Neither mortality nor reintubation was significant decreased with NPPV, but the point estimate favored early weaning to NPPV in each case. 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

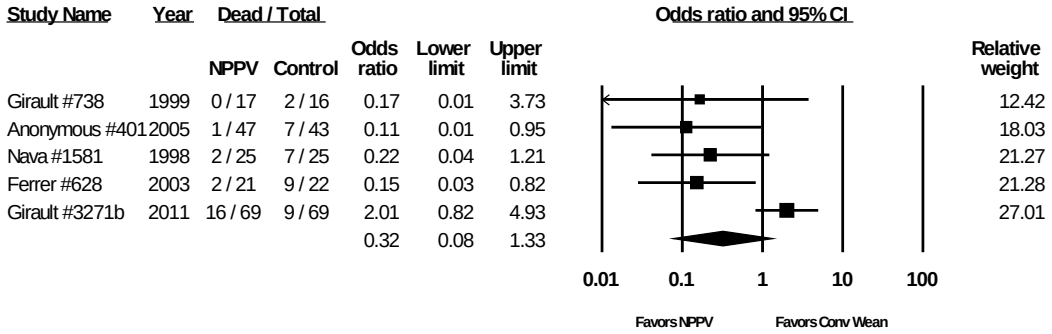
Outcome	No. of Studies (No. of Patients)	Summary OR (95% CI)	Tests for Heterogeneity
Mortality	5 (354)	0.32 (0.08 to 1.33)	Q = 13.8, df = 4, p = 0.01; I^2 = 69%
Reintubation	4 (303)	0.83 (0.48 to 1.44)	Q = 2.72, df = 3, p = 0.44; I^2 = 0%
Hospital-acquired pneumonia	5 (354)	0.33 (0.13 to 0.84)	Q = 7.17, df = 4, p = 0.13; I^2 = 44%
Myocardial infarction	0 (0)	NR	NR

Abbreviations: CI = confidence interval; NPPV = noninvasive positive pressure ventilation; NR = not reported; OR = odds ratio

Mortality

Mortality ranged from 0–23 percent for early extubation to NPPV and 13–41 percent for conventional weaning in five studies.[106,108,111,114,116] Overall, there was a nonstatistically significant reduction in mortality between early extubation to NPPV and usual weaning practices (summary OR 0.32; 95 percent CI, 0.08 to 1.33; Figure 13). However, the confidence interval was wide, and the number of patients randomized and events (55 deaths) were small. Tests of heterogeneity suggested important variability in treatment effects across studies (Q = 13.8, df = 4, p = 0.01, I^2 = 69 percent). There were too few studies to explore potential reasons for heterogeneity quantitatively. However, qualitative analyses show that Girault 2011,[116] 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 vs. conventional weaning

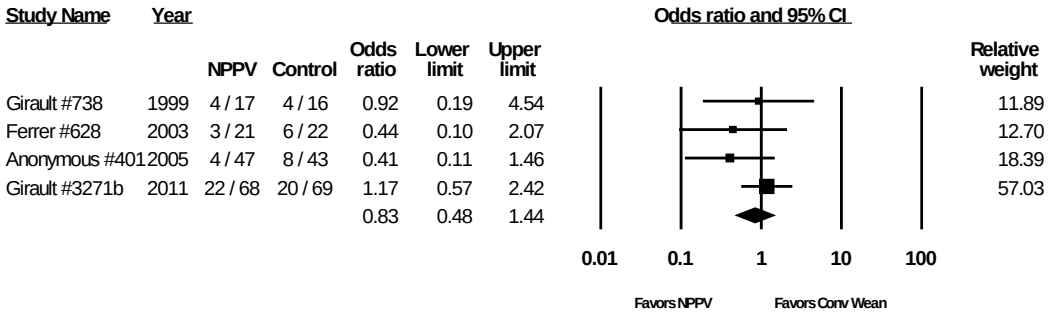


Abbreviations: CI = confidence interval; Conv Wean = conventional weaning; NPPV = noninvasive positive pressure ventilation

Reintubation

Four studies[106,108,111,116] 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 percent 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 percent).

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

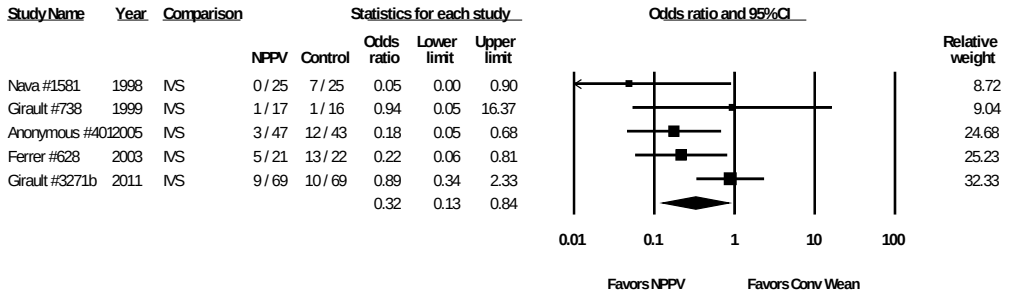


Abbreviations: CI = confidence interval; Conv Wean = conventional weaning; NPPV = noninvasive positive pressure ventilation

Hospital-Acquired Pneumonia

Hospital-acquired pneumonia ranged from 0–24 percent for NPPV and 6–59 percent for usual care. Overall, early extubation to NPPV reduced hospital-acquired pneumonia (OR 0.32; 95 percent CI, 0.13 to 0.84; Figure 15). Tests for heterogeneity suggested moderate variability in treatment effects ($Q = 7.17$, $df = 4$, $p = 0.13$, $I^2 = 44$ percent). Qualitative analyses did not suggest a reason for the variability in treatment effects.

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



Abbreviations: CI = confidence interval; Conv Wean = conventional weaning; NPPV = noninvasive positive pressure ventilation

Length of Stay

Four studies reported effects on hospital length of stay.[106,108,111,116] Mean length of stay varied substantially across studies, from 18–28 days in NPPV-treated patients and 20–41 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 8–15 days in NPPV-treated patients and 8–25 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.[114] found a shorter mean (SD) length of stay of 15.1 (5.4) with NPPV versus 24.0 (13.7) days with conventional weaning (p = 0.005). A fair-quality study[106] 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,[116] 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 six 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.[107,109,110,112,113,115] All studies used BPAP. Study quality was judged to be good in four studies, fair in one study, and poor in one study. Table 13 summarizes the pooled treatment effects. When there were sufficient studies, we report effects in two subgroups: those at high risk for recurrent acute respiratory failure and those with recurrent acute respiratory failure. 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 postextubation

Outcome	Group	No. of Studies (No. of Patients)	Summary OR (95% CI)	Tests for Heterogeneity
Mortality[a]	All	5 (667)	0.89 (0.52 to 1.55)	Q = 7.40, df = 4, p = 0.12; I^2 = 46%
	High risk	3 (365)	0.60 (0.34 to 1.04)	Q = 0.28, df = 2, p = 0.87; I^2 = 0%
	Recurrent ARF	2 (302)	0.87 (0.57 to 1.34)	Q = 1.37, df = 1, p = 0.24; I^2 = 27%
Reintubation[b]	All	6 (760)	0.79 (0.47 to 1.32)	Q = 9.73, df = 5, p = 0.08; I^2 = 49%
	High risk	4 (458)	0.70 (0.46 to 1.08)	Q = 7.69, df = 3, p = 0.05; I^2 = 61%
	Recurrent ARF	2 (302)	1.03 (0.84 to 1.25)	Q = 0.34, df = 1, p = 0.85; I^2 = 0%
Hospital-acquired pneumonia	All	3 (349)	0.64 (0.36 to 1.15)	Q = 2.48, df = 2, p = 0.29; I^2 = 19%
Myocardial infarction	All	0 (0)	NR	NR

[a]p = 0.04 for differences in treatment effect on mortality by high risk versus recurrent ARF groups.

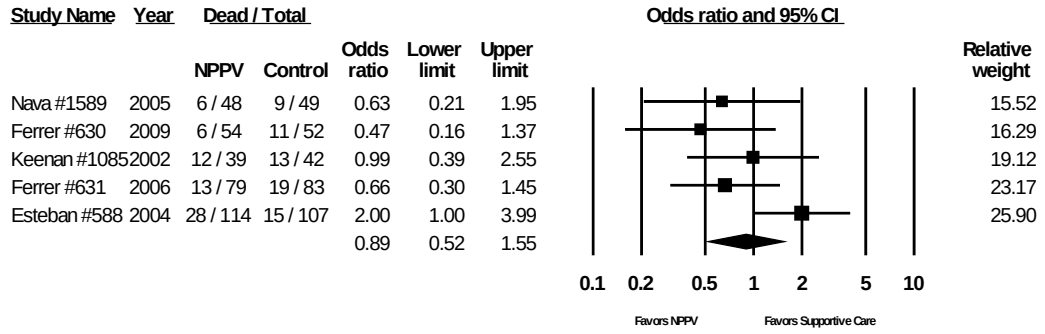
[b]p = 0.29 for differences in treatment effect reintubation by high risk versus recurrent ARF groups.

Abbreviations: ARF = acute respiratory failure; CI = confidence interval; df = degrees of freedom; NPPV = noninvasive positive pressure ventilation; NR = not reported; OR = odds ratio

Mortality

Mortality ranged from 14–31 percent for usual care and 11–31 percent for NPPV in five studies.[107,109,110,113,115] Overall, NPPV postextubation did not decrease mortality (OR 0.89; 95 percent CI, 0.52 to 1.55; Figure 16). Tests for heterogeneity suggested moderate variability in treatment effects across studies (Q = 7.40, df = 4, p = 0.12; I^2 = 46 percent). Subgroup analyses by those at risk for recurrent acute respiratory failure versus those with recurrent acute respiratory failure showed less variability in treatment effects for the subgroups than when the groups were combined.

Figure 16. Random-effects analysis of data on mortality—NPPV vs. supportive care postextubation

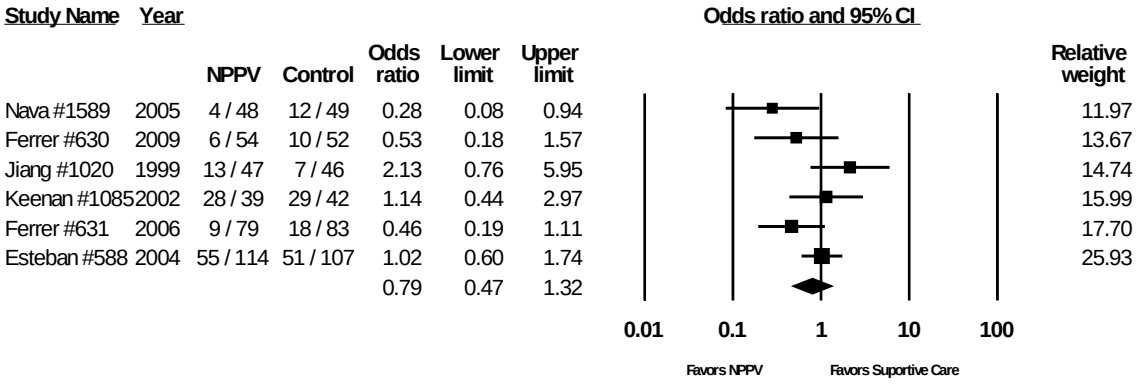


Abbreviations: CI = confidence interval; NPPV = noninvasive positive pressure ventilation

Reintubation

Six studies reported reintubation rates ranging from 8–72 percent for NPPV to 15–69 percent for usual care. Overall, NPPV postextubation did not decrease reintubation rates compared to usual supportive care (OR 0.79; 95 percent CI, 0.47 to 1.32; Figure 17). Tests for heterogeneity suggested moderate variability in treatment effects across studies (Q = 9.73, df = 5, p = 0.08, I^2 = 49 percent). Subgroup analyses by those at risk for recurrent acute respiratory failure versus those with recurrent acute respiratory failure did not explain the variability in treatment effects.

Figure 17. Random-effects analysis of data on reintubation rates—NPPV vs. supportive care postextubation

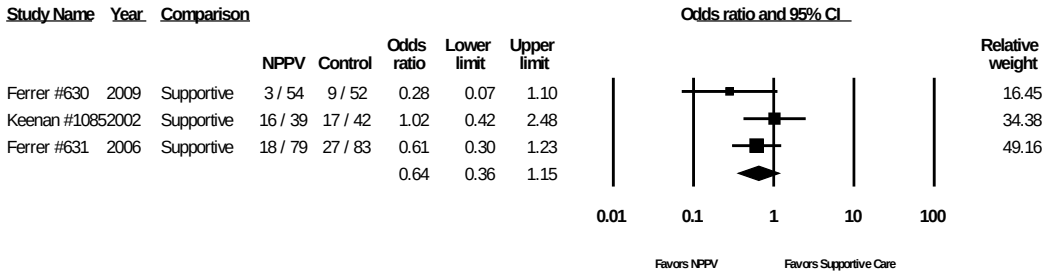


Abbreviations: CI = confidence interval; NPPV = noninvasive positive pressure ventilation

Hospital-Acquired Pneumonia

Three studies reported rates of hospital-acquired pneumonia, ranging from 6–41 percent for NPPV and 17–41 percent for usual care. Overall, NPPV post-extubation did not decrease hospital-acquired pneumonia rates compared to usual supportive care (OR = 0.64; 95 percent CI 0.36 to 1.15) (Figure 18). Tests for heterogeneity suggested no significant variability in treatment effects (Q = 2.48, df = 2, p = 0.29, I^2 = 19 percent).

Figure 18. Random-effects analysis of data on hospital-acquired pneumonia rates—NPPV vs. supportive care postextubation



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

Length of Stay

Five studies reported effects on hospital length of stay.[107,109,110,113,115] Mean length of stay varied from 18–32 days in NPPV-treated patients and 18–30 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 the same five studies; mean ICU length of stay ranged from 9–18 days in NPPV-treated patients and 10–19 days with supportive care. Of the five 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.

Other Outcomes (Weaning and Postextubation Studies)

Intolerance and Facial Ulcerations

Three studies[107,109,113] 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 4.4–25.6 percent). Rates of facial abrasions or ulcerations were reported in four studies[108,110,112,113] and varied widely, ranging from 2.1–26 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,[116] 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 to conventional weaning. The mean duration of mechanical ventilation ranged from 4.6–10.2 days for NPPV weaning and 7.7–20.1 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.[113] This good-quality study, conducted with 81 patients with ACPE, found a nonstatistically significant decrease in ventilator days with NPPV compared to supportive care (median 6.7 [range 0.5–28.6] versus 8.9 [range 2.0–146.7, $p = 0.12$]). One study reported the rate of ventilator dependence at hospital discharge for NPPV weaning (0 of 25) compared to conventional weaning (2 of 25, p-value not reported).[115]

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 emergency department (ED), but these findings are based on indirect comparisons (low strength of evidence).
- Few studies reported details about clinical setting and associated resources, experience and training of clinicians, or the use of clinical protocols. With the occasional 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 to effectiveness trials, but only two effectiveness trials were included in the analysis and the 95 percent CIs overlapped (low strength of evidence).
- 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 (low strength of evidence).
- With the exception of the clinical setting in studies that compared NPPV to 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 (insufficient strength of evidence).

Description of Included Studies

Of the 66 eligible studies, 62 (94 percent) reported information about the clinical setting in which NPPV was initiated, 2 (3 percent) provided specific information about the experience or training of study clinicians, 1 (1 percent) reported patients' mean body mass index, 16 (24 percent) reported data on patients' neurological or mental status, 16 (24 percent) reported a measure of disease burden, and 27 (41 percent) reported mean baseline Acute Physiology And Chronic Health Evaluation (APACHE) II or APACHE III scores for predicted ICU mortality.

The only variable listed in KQ 4 that was reported in a sufficient number of studies to justify subgroup analysis is the clinical setting in which NPPV was initiated. Of the 47 studies that pertain to KQ 1, NPPV was initiated in the ED setting in 11 studies (23 percent) and in the ICU setting in 24 studies (51 percent). In the remaining 12 studies (26 percent), clinical setting was either not reported, or NPPV was initiated in another setting such as a general medicine ward or ambulance. Forty-four studies compared NPPV to supportive care; of these 37 (84 percent) reported mortality rates and 37 (84 percent) reported intubation rates.

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 to usual supportive care or invasive ventilator support (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 0.65 (95 percent CI, 0.38 to 1.09) in studies in which NPPV was initiated in the ED and 0.50 (95 percent CI, 0.37 to 0.67) in studies in which NPPV was initiated in the ICU (Table 14). 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 percent CI, 0.43 to 0.99). The difference in pooled ORs across the three settings (ED, ICU, other) was not statistically significant ($Q = 1.43$, $df = 2$, $p = 0.49$). An analysis that examined risk of intubation showed differences in treatment effect that approached statistical significance: the ORs for intubation were 0.55 (95 percent CI, 0.28 to 1.09), 0.22 (0.15 to 0.34), and 0.35 (0.24 to 0.51) for NPPV initiated in the ED, ICU, or mixed/unreported, respectively ($Q = 5.74$, $df = 2$, $p = 0.06$). 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 14. Risk of mortality or intubation by clinical setting, NPPV vs. usual supportive care or invasive ventilation[a]

Clinical Setting	Mortality[b] (n = 42) Odds Ratio (95% CI)	Intubation[c] (n = 38) Odds Ratio (95% CI)
Emergency department	0.65 (0.38 to 1.09)	0.55 (0.28 to 1.09)
ICU	0.50 (0.37 to 0.67)	0.22 (0.15 to 0.34)
Mixed, other, or not reported	0.65 (0.43 to 0.99)	0.35 (0.24 to 0.51)

[a]Studies that compared NPPV to 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; $p = 0.49$ for differences in treatment effect by clinical setting.

[c]Does not include studies that compared NPPV to invasive ventilation; $p = 0.06$ 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.[44] and assigned a scale score of 0–7 to each study, as described above in the Methods section. We defined studies with a score of 0 to 2 as efficacy trials and studies with a score of 6 to 7 as effectiveness trials. Studies with scores of 3 to 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 41 studies that compared NPPV to usual supportive care or invasive ventilation and reported mortality rates, 11 (27 percent) were efficacy trials, 2 (5 percent) were effectiveness trials, and 28 (68 percent) were mixed efficacy-effectiveness trials. The pooled ORs for mortality were 0.56 (95 percent 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 0.50 (95 percent CI, 0.39, 0.65) (Table 15). 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 percent CI, 0.19 to 0.46), 0.58 (0.16 to 2.13), and 0.29 (0.20 to 0.41) (Table 15). 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 = 1.01, p = 0.60). For both mortality and intubation, there were only two effectiveness trials, thereby potentially rendering the pooled OR an unreliable estimate. The 95 percent CIs associated with the efficacy and effectiveness studies overlapped for both mortality and intubation.

Table 15. Risk of mortality or intubation by effectiveness rating, NPPV vs. usual supportive care or invasive ventilation[a]

Effectiveness Rating	Mortality[b] (n = 42) Odds Ratio (95% CI)	Intubation[c] (n = 38) Odds Ratio (95% CI)
Efficacy trial	0.56 (0.27 to 1.02)	0.29 (0.19 to 0.46)
Mixed efficacy-effectiveness trial	0.50 (0.44 to 0.65)	0.29 (0.20 to 0.41)
Effectiveness trial	0.99 (0.66 to 1.49)	0.58 (0.16 to 2.13)

[a]Studies that compared NPPV to 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 to invasive ventilation; p = 0.60 for differences in treatment effect by effectiveness rating.

Abbreviations: CI = confidence interval; ICU = intensive care unit; KQ = key question; 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

to studies conducted in the U.S. or Canada. We conducted meta-analyses of the 41 studies that pertain to KQ 1 that reported mortality and the 37 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 16. The pooled OR for mortality for the 24 studies conducted in Europe is 0.56 (95 percent CI, 0.44 to 0.71), compared with 0.58 (95 percent CI, 0.25 to 1.33) for the 5 studies conducted in the U.S. or Canada and 0.71 (95 percent CI, 0.41 to 1.24) for the 12 studies conducted in other countries. The difference in pooled ORs for mortality across the three categories of countries was not statistically significant (Q = 1.66, df = 2, p = 0.44 for mortality). For the 37 studies that pertain to KQ 1 and reported intubation rates, the pooled OR was 0.32 (95 percent CI, 0.21 to 0.48) for the 18 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 percent CI, 0.14 to 0.45) for the 13 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 16. Risk of mortality or intubation by geographical location, NPPV vs. usual supportive care or invasive ventilation[a]

Geographical location	Mortality[b] (n = 42) Odds Ratio (95 percent CI)	Intubation[c] (n = 38) Odds Ratio (95% CI)
Europe	0.56 (0.44 to 0.71)	0.32 (0.21 to 0.48)
USA or Canada	0.58 (0.25 to 1.33)	0.36 (0.20 to 0.66)
Other countries	0.71 (0.41 to 1.24)	0.25 (0.14 to 0.45)

[a]Studies that compared NPPV to usual supportive care or invasive ventilatory 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 = 0.44 for differences in treatment effect by geographical location'

[c]Does not include studies that compared NPPV to invasive ventilation; p = 0.70 for differences in treatment effect by geographical location.

Abbreviations: CI = confidence interval; ICU = intensive care unit; KQ = key question; 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 0.50; 95 percent CI, 0.37 to 0.67) and intubation rates (OR 0.22; 95 percent CI, 0.15 to0.34). The 95 percent CIs for the pooled ORs for mortality (0.67) or intubation (0.55) 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 percent 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 66 trials that that compared NPPV to other common treatment strategies (supportive care and conventional mechanical ventilation). We also included trials that compared different types of NPPV with one another (CPAP versus BPAP). We included common outcomes of interest such as mortality and adverse events but also examined more challenging 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)[48,49] are summarized in Tables 17 and 18. 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 COPD. Few studies enrolled patients with asthma, 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, reduced hospital-acquired pneumonia, and comparable effects for CPAP and BPAP. We found insufficient evidence for 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 to 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 17. Summary of the strength of evidence for KQ 1—NPPV versus supportive care

Number of Studies (Subjects)	Domains Pertaining to SOE				Strength of Evidence (SOE)
	Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	Effect Estimate (95% CI)
Hospital mortality					**High SOE**
37 (3985)	RCT/Good	Consistent	Direct	Precise	OR = 0.56 (0.43 to 0.72) RD = 64 fewer per 1000 (40 to 85)
Intubation rate					**High SOE**
37 (3666)	RCT/Good	Inconsistent	Direct	Precise	OR = 0.31 (0.23 to 0.41) RD = 227 fewer per 1000 (184 to 265)
Myocardial infarction					**Moderate SOE**
7 (1645)	RCT/Good	Consistent	Direct	Imprecise	OR = 1.11 (0.85 to 1.44) RD = not applicable
Medical utilization: Hospital length of stay (LOS)					**Low SOE**

Number of Studies (Subjects)	Domains Pertaining to SOE				Strength of Evidence (SOE)
	Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	Effect Estimate (95% CI)
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 SOE**
8 (610)	RCT/Good	Consistent	Direct	Imprecise	OR = 0.27 (0.15 to 0.50) RD = 131 fewer per 1,000 (86 to 158)

[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 18. Summary of the strength of evidence for KQ 2—CPAP versus BPAP

Number of Studies (Subjects)	Domains Pertaining to SOE				Strength of Evidence (SOE)
	Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	Effect Estimate (95% CI)
Hospital mortality					**Moderate SOE**
10 (1338)	RCT/Good	Consistent	Direct	Imprecise	OR = 0.89 (0.58 to 1.35) RD = NA
Intubation rate					**Moderate SOE**
12 (1463)	RCT/Good	Consistent	Direct	Imprecise	OR = 0.84 (0.51 to 1.38) RD = NA
Myocardial infarction					**Low SOE**
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; LOS = length of stay; NA = not applicable; OR = odds ratio; RCT = randomized controlled trial; RD = risk difference; SOE = strength of evidence

Compared to 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 recurrent acute respiratory failure postextubation. Results for these comparisons, along with ratings for the SOE are summarized in Tables 19 and 20. When compared to conventional weaning, we found low SOE for a nonstatistically significant reduction in mortality and no benefit for reintubation rates. However, summary odds ratios (ORs) favored benefit and confidence intervals (CIs) were wide; clinically important benefit remains possible. NPPV was associated with lower rates of hospital-acquired pneumonia (SOE = low) when used to facilitate

weaning from invasive ventilator support. Evidence was insufficient to estimate effects for other outcomes.

Table 19. 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 (SOE)
	Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	Effect Estimate (95% CI)
Hospital mortality					**Low SOE**
5 (355)	RCT/Good	Inconsistent	Direct	Imprecise	OR = 0.32 (0.08 to 1.33) RD = NA
Reintubation rate					**Low SOE**
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					**Moderate SOE**
5 (354)[a]	RCT/Good	Inconsistent	Direct	Imprecise	OR = 0.33 (0.13 to 0.84) RD = 167 fewer per 1,000 (33 to 233)

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

Number of Studies (Subjects)	Domains Pertaining to SOE				Strength of Evidence (SOE)
	Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	Effect Estimate (95% CI)
Hospital mortality					**Low SOE**
5 (667)	RCT/Good	Inconsistent	Direct	Imprecise	OR = 0.89 (0.52 to 1.55) RD = NA
Reintubation rate					**Low SOE**
6 (760)	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**
4 (446)	RCT/Good	Consistent	Indirect	Imprecise	Not estimable; No study found a statistically significant difference in LOS
Medical utilization: ICU length of stay (LOS)					**Insufficient**

Number of Studies (Subjects)	Domains Pertaining to SOE				Strength of Evidence (SOE)
	Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	Effect Estimate (95% CI)
5 (667)[a]	RCT/Good	Consistent	Indirect	Imprecise	Not estimable; No study found a statistically significant difference in LOS
Hospital acquired pneumonia					**Low SOE**
3 (349)[a]	RCT/Fair	Consistent	Direct	Imprecise	OR = 0.64 (0.36 to 1.15)

[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 21). 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 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 21. 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 (SOE)
	Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	Summary of effect
Different treatment effects by study effectiveness characteristics					**Low SOE**
42 (4341)[a]	Observational	Inconsistent	Direct	Imprecise	<u>OR (95% CI) for mortality:</u> Efficacy trial: 0.56 (0.27 to 1.02) Mixed trial: 0.50 (0.44 to 0.65) Effectiveness trial: 0.99 (0.66 to 1.49) <u>OR (95% CI) for intubation:</u> Efficacy trial: 0.29 (0.19 to 0.46) Mixed trial: 0.29 (0.20 to 0.41) Effectiveness trial: 0.38 (0.16 to 2.13)
Different treatment effects across clinical settings					**Low SOE**
42 (4341)*	Observational	Consistent	Direct	Imprecise	<u>OR (95% CI) for mortality:</u> ED: 0.65 (0.38 to 1.09) ICU: 0.50 (0.37 to 0.67) <u>OR (95% CI) for intubation:</u> ED: 0.55 (0.28 to 1.09) ICU: 0.22 (0.15 to 0.34)
Different treatment effects across geographical regions					**Low SOE**

Number of Studies (Subjects)	Domains Pertaining to SOE				Strength of Evidence (SOE)
	Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	Summary of effect
42 (4341)*	Observational	Consistent	Direct	Imprecise	OR (95% CI) for mortality: Europe: 0.56 (0.44 to 0.71) USA/Canada: 0.58 (0.25 to 1.33) OR (95% CI) for intubation: Europe: 0.32 (0.21 to 0.48) USA/Canada: 0.36 (0.20 to 0.66)

[a]37 studies and 3666 patients for analyses of intubation rates.

Abbreviations: KQ = key question; OR = odds ratio; SOE = strength of evidence; ED = emergency department; ICU = intensive care unit

Findings in Relationship to What is Already Known

Our results are generally consistent with previous systematic reviews and clinical guidelines. Previous reviews have found similar benefits on mortality and intubation rates in patients with respiratory failure due to ACPE[26,41,42] and severe exacerbations of COPD.[26,40] 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 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.

There are several other considerations that warrant further discussion. Regarding NPPV for ACPE, our positive findings are in contrast with 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.[65,117] 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.

A systematic review and meta-analysis by Burns et al. demonstrated a consistent positive effect of NPPV weaning on mortality and ventilator-associated pneumonia, which is in contrast to our findings of no significant effect.[33] 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 quasiexperimental studies, non-English language studies, and studies presented only in abstract form. Our review also has limitations when evaluating this question. Because of the small number of available randomized controlled trials (RCTs), we combined trials examining NPPV for both the prevention and treatment of extubation failure. It could be reasonably argued

that these are distinct scenarios and typically differ in the timing of NPPV application. Additionally, the two trials examining "rescue" NPPV for postextubation respiratory failure are remarkable in their inclusion of a low proportion of patients with COPD and a long time period between the development of respiratory distress and use of NPPV.[107,113] We performed an exploratory analysis which segregated the studies looking at NPPV to prevent extubation failure versus treating recurrent acute respiratory failure and, although the data must be interpreted with caution, it suggests that NPPV may be beneficial in the former scenario.

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 percent) conducted in Europe. There is a longer clinical experience with NPPV in Europe compared to 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. 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 66 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.[26] Guidelines groups from the United States have made weaker recommendations to use NPPV in patients with CHF[118] or have not addressed the use of NPPV.[119] 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. A survey of respiratory care directors in two northeastern states showed relatively low use of NPPV (20 percent of ventilator starts) and high variability in estimated use across hospitals (none to greater than 50 percent).[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.[120,121] 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.[121]

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 often descriptions of the interventions that were 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 to Burns et al.[33] 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

We used the framework recommended by Robinson et al.[122] 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 22. 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. Lack of blinding could introduce 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. 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 22. Evidence gaps and future research

Evidence Gap	Reason	Type of Studies to Consider
Effects versus supportive care in patients with asthma, interstitial lung disease, pneumonia, 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
Effects on resource utilization NPPV compared to 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
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
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

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 to supportive care alone. BPAP has been studied more rigorously, but CPAP and BPAP have 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. However, the evidence for these indications is weaker. 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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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
BPAP	bilevel positive airway pressure
CDSR	Cochrane Database of Systematic Reviews
CER	comparative effectiveness review
CHF	congestive heart failure
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
ED	emergency department
FDA	U.S. Food and Drug Administration
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
SD	standard deviation
TEP	Technical Expert Panel
TOO	Task Order Officer