Non-invasive positive pressure ventilation (CPAP or bilevel NPPV) for cardiogenic pulmonary oedema

Review information

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Dates

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What's new

Date	Event	Description
10 December 2018	New citation: conclusions changed	We include seven new studies in our review update. We have excluded 15 previously-included studies from the update. Our conclusions now include strength-of-evidence recommendations and have been updated.
30 October 2018	Updated	A new review team has updated this review and meta-analysis. We compared non-invasive positive pressure ventilation to standard medical care for acute cardiogenic pulmonary oedema. Our inclusion criteria have been updated and we include RCTs only. We performed our updated literature search from database inception to 20 September 2018. We identified new articles for inclusion and have fully revised this systematic review.

History

Date	Event	Description
12 November 2012	Updated	New search in April 2011 found 11 new studies
1 December 2011	Updated	Eleven new studies have been included in this review update.
		Background section has been updated.
		No changes have been made to the methodology. The search strategies have been modified in MEDLINE and EMBASE, and the dates over which the databases were searched were updated.
		The conclusions have been amended slightly. The use of CPAP produces fewer adverse events compared to the standard treatment or compared the Bilevel NPPV, but the main thrust of the review has not changed.
17 April 2008	Amended	Converted to new review format.

Abstract

Background

Non-invasive positive pressure ventilation (NPPV) has been used to treat respiratory distress due to acute cardiogenic pulmonary oedema (ACPE). We performed a systematic review and meta-analysis update on NPPV for adults presenting with ACPE.

Objectives

To evaluate the safety and effectiveness of NPPV compared to standard medical care (SMC) for adults with ACPE. The primary outcome was hospital mortality. Important secondary outcomes were endotracheal intubation, treatment intolerance, hospital and intensive care unit length of stay, rates of acute myocardial infarction, and adverse event rates.

Search methods

We searched CENTRAL (CRS Web, 20 September 2018), MEDLINE (Ovid, 1946 to 19 September 2018), Embase (Ovid, 1974 to 19 September 2018), CINAHL Plus (EBSCO, 1937 to 19 September 2018), LILACS, WHO ICTRP, and clinicaltrials.gov. We also reviewed reference lists of included studies. We applied no language restrictions.

Selection criteria

We included blinded or unblinded randomised controlled trials in adults with ACPE. Participants had to be randomised to NPPV (continuous positive airway pressure (CPAP) or bilevel NPPV) plus standard medical care (SMC) compared with SMC alone.

Data collection and analysis

Two review authors independently screened and selected articles for inclusion. We extracted data with a standardised data collection form. We evaluated the risks of bias of each study using the Cochrane 'Risk of bias' tool. We assessed evidence quality for each outcome using the GRADE recommendations.

Main results

We included 24 studies (2664 participants) of adult participants (older than 18 years of age) with respiratory distress due to ACPE, not requiring immediate mechanical ventilation. People with ACPE presented either to an Emergency Department or were inpatients. ACPE treatment was provided in an intensive care or Emergency Department setting. There was a median follow-up of 13 days for hospital mortality, one day for endotracheal intubation, and three days for acute myocardial infarction. Compared with SMC, NPPV may reduce hospital mortality (risk ratio (RR) 0.65, 95% confidence interval (CI) 0.51 to 0.82; participants = 2484; studies = 21; I^2 = 6%; low quality of evidence) with a number needed to treat for an additional beneficial outcome (NNTB) of 17 (NNTB 12 to 32). NPPV probably reduces endotracheal intubation rates (RR 0.49, 95% CI 0.38 to 0.62; participants = 2449; studies = 20; I^2 = 0%; moderate quality of evidence) with a NNTB of 13 (NNTB 11 to 18). There is probably little or no difference in acute myocardial infarction (AMI) incidence with NPPV compared to SMC for ACPE (RR 1.03, 95% CI 0.91 to 1.16; participants = 1313; studies = 5; I^2 = 0%; moderate quality of evidence). We are uncertain as to whether NPPV increases hospital length of stay (mean difference (MD) ?0.31 days, 95% CI ?1.23 to 0.61; participants = 1714; studies = 11; I^2 = 55%; very low quality of evidence). Adverse events were generally similar between NPPV and SMC groups, but evidence was of low quality.

Authors' conclusions

Our review provides support for continued clinical application of NPPV for ACPE, to improve outcomes such as hospital mortality and intubation rates. NPPV is a safe intervention with similar adverse event rates to SMC alone. Additional

research is needed to determine if specific subgroups of people with ACPE have greater benefit of NPPV compared to SMC. Future research should explore the benefit of NPPV for ACPE patients with hypercapnia.

Plain language summary

A breathing intervention for shortness of breath due to heart failure

Background

Heart failure is one of the leading causes of hospital admission in the world. People with heart failure often experience shortness of breath and leg swelling. These symptoms may develop over hours to weeks, or rapidly over a few hours. Such rapid deterioration is called acute cardiogenic pulmonary oedema.

Providing air under pressure through a face or nose mask can treat shortness of breath. This treatment is called non-invasive ventilation and its use in heart failure is controversial.

Study characteristics

Randomised controlled studies compare treatments to find out if they are truly effective. We searched for randomised studies comparing non-invasive ventilation to routine care for adults with acute cardiogenic pulmonary oedema. We compared studies treating people with non-invasive ventilation versus medical care. Medical care includes therapies such as providing extra oxygen and water pills to patients. The evidence upon which this review is based is current to September 2018.

Review question

We sought to address if non-invasive ventilation in adults with acute cardiogenic pulmonary oedema reduces rates of deaths, the need for a breathing tube, and heart attacks.

Key results and quality of evidence

We found 24 studies with 2664 participants comparing non-invasive ventilation to medical care alone. Non-invasive ventilation may decrease the chances of dying in hospital. The quality of results for studies reporting death in hospital was low. Studies were poorly conducted, and results were not similar across studies. In addition, non-invasive ventilation probably reduces the chances of needing a breathing tube. The quality of results for studies reporting breathing tube rates was moderate. Studies evaluating breathing tube rates were poorly conducted. Non-invasive ventilation probably has little or no effect on getting a heart attack. The quality of results for studies reporting heart attack rates was moderate, and studies had inconsistent results for this outcome. We are unsure if the length of hospital stay is improved with non-invasive ventilation. The quality of results for studies reporting hospital length of stay was very low, which was due to poor study conduct and inconsistent results. Finally, non-invasive ventilation may make little or no difference to adverse events (complications), compared to medical care. The quality of results for studies reporting adverse events was low. Studies evaluating adverse events were poorly conducted and had inconsistent results.

Background

Description of the condition

Abnormal heart function in heart failure (HF) can produce signs and symptoms of reduced cardiac output (Ezekowitz 2017). A rapid deterioration in HF symptoms is called congestive heart failure (CHF) or acute cardiogenic pulmonary oedema (ACPE). Symptoms of ACPE can include dyspnoea, orthopnoea, peripheral oedema, cough, fatigue, and weight gain (Wang 2005). Signs of ACPE can include the presence of a third heart sound, jugular venous distension, rales, lower extremity oedema, wheezing, and ascites (Wang 2005). Approximately one million people a year are discharged from hospitals in the United States with HF (Benjamin 2017). ACPE severity is variable, but the presence of hypoxia, respiratory failure, and hypotension can indicate a higher risk presentation (Ponikowski 2016). Many conditions can trigger ACPE, such as acute coronary syndrome (ACS), tachyarrhythmia, valvular heart disease, and hypertension (Ponikowski 2016). Importantly, ACPE is also associated with an in-hospital mortality of approximately 10% and one-year mortality of 30% (Rudiger 2005).

ACPE can be conceptualised as left ventricular failure with elevated left ventricular filling pressures. Elevated filling pressures produce higher pulmonary capillary pressures and fluid extravasation into alveoli due to overwhelmed lymphatic vessel absorption capacity (Allison 1991; Packer 1993). Pulmonary oedema fluid can dilute surfactant and neutralise its lubricating properties, causing a reduction in lung compliance and increased work of breathing (Allison 1991; Park 2001). In the upright position, oedema accumulates at the lung bases, causing a ventilation-perfusion (V-Q) mismatch, which can cause hypoxia (Allison 1991).

Description of the intervention

ACPE treatment guidelines have been prepared in several countries, including Canada (Ezekowitz 2017) and Europe (Ponikowski 2016). Treatment options include: loop diuretics (e.g. furosemide), vasodilators (e.g. nitroglycerin), supplemental oxygen, non-invasive positive pressure ventilation (NPPV), and endotracheal intubation (Ezekowitz 2017; Ponikowski 2016). Treating the underlying cause of ACPE is also necessary (e.g. antihypertensives for hypertension, coronary angiography for ST elevation myocardial infarction) (Ezekowitz 2017; Ponikowski 2016; Yancy 2013).

Endotracheal intubation raises the risk for adverse events, such as nosocomial infections (e.g. pneumonia), tracheal injury, and prolonged hospital length of stay (Gay 2009). In contrast to the invasiveness of endotracheal intubation, NPPV can be provided in the form of continuous positive airway pressure (CPAP) and bilevel NPPV (BiPAP® -

Respironics, Inc, Murrysville, PA) using face or nasal masks. CPAP maintains a constant positive airway pressure throughout the respiratory cycle. In contrast, bilevel NPPV provides additional inspiratory positive airway pressure and positive end-expiratory pressure (Nava 2009).

How the intervention might work

The cardiovascular and pulmonary systems work together to maintain homeostasis. During normal inhalation contraction of the diaphragm and intercostal muscles produces a more negative pleural pressure compared to the lungs at rest (Alviar 2018). This negative pleural pressure reduces left ventricular pressure relative to systemic arterial pressure (Alviar 2018). In contrast, during positive pressure ventilation, inhalation involves a positive pleural pressure which raises left ventricular pressure relative to systemic arterial pressure and reduces left ventricular afterload due to a baroreceptor reflex (Alviar 2018; Buda 1979). Intrapleural pressure influences right ventricular inflow and left ventricular outflow. The difference between airway pressure and intrapleural pressure (transpulmonary pressure gradient) affects pulmonary vasculature, which in turn influences left ventricular inflow and right ventricular outflow (Alviar 2018). NPPV reduces pulmonary workload, improves cardiac output, and enhances lung compliance (Baratz 1992; Lenique 1997). During ACPE interstitial and alveolar oedema reduce lung compliance. Application of positive pressure at end expiration can force fluid out of alveoli, improving pulmonary vascular resistance and enhancing gas exchange (Alviar 2018). In addition, positive pressure ventilation could prevent alveolar collapse and enhance alveolar expansion with inspiration improving airway compliance (Alviar 2018). This mechanism could explain how NPPV applied during ACPE can lead to improved oxygenation (Räsänen 1985). During respiratory distress without NPPV the intrapleural pressure becomes more negative and left ventricular afterload is increased, because left ventricular systolic pressure is more negative compared to the systemic circulation (Alviar 2018; Magder 1983). In terms of left ventricular function, NPPV reduces preload, afterload, myocardial oxygen demand, and enhances hydrostatic displacement of alveolar oedema (Alviar 2018). In left ventricular failure, NPPV can improve cardiac output by reducing left ventricular afterload. In contrast, in right ventricular failure, NPPV reduces right ventricular preload and can reduce right ventricular cardiac output (Alviar 2018). The net benefit of NPPV in heart failure will depend on the relative left and right ventricular functions, and afterload (Alviar 2018). Furthermore, NPPV use in ACPE may prevent endotracheal intubation without significant adverse events (Nava 2009). Mechanical ventilation can be life-saving for people with respiratory failure needing airway protection and with severe hypoxia associated with failed NPPV therapy (Alviar 2018). However, mechanical ventilation is associated with additional adverse events, such as endotracheal tube complications (Tobin 1994), ventilator-associated lung injury (Slutsky 2013), ventilator-associated pneumonia (Spalding 2017), barotrauma (e.g. pneumothorax) (Anzueto 2004), and ventilator-induced diaphragmatic dysfunction (Levine 2008).

Why it is important to do this review

Since the increased clinical use of NPPV in the 1980s, many studies have evaluated NPPV's effectiveness for ACPE, and have reported mixed results (Nava 2009). Furthermore, current heart failure guidelines differ in their NPPV recommendations. Canadian guidelines recommend against routine use of NPPV, and suggest that NPPV could be used for ACPE with persistent hypoxia despite standard medical care (Ezekowitz 2017). In addition, Canadian guidelines warn of the clinical risks of NPPV, including worsening right heart failure, worsening hypercapnia, aspiration, and pneumothorax (Ezekowitz 2017). In contrast, European guidelines (Ponikowski 2016) suggest NPPV be considered and started quickly in people with ACPE who present with tachypnoea (respiratory rate greater than 25 breaths a minute) and hypoxia (SpO_2 less than 90%). Furthermore, they are of the opinion that NPPV can reduce respiratory distress and endotracheal intubation. The main risk of NPPV emphasised by the European guidelines is hypotension (Ponikowski 2016). American guidelines do not provide treatment guidance for ACPE (Yancy 2013). Given the differences in opinion between these two major heart failure guidelines on the use of NPPV for ACPE, we have updated our systematic review and meta-analysis.

Objectives

To evaluate the safety and effectiveness of NPPV compared to standard medical care (SMC) for adults with ACPE. The primary outcome was hospital mortality. Important secondary outcomes were endotracheal intubation, treatment intolerance, hospital and intensive care unit length of stay, rates of acute myocardial infarction, and adverse event rates.

Methods

Criteria for considering studies for this review

Types of studies

For inclusion, studies had to be randomised controlled trials (RCTs). We excluded studies that were cluster-randomised or used a cross-over design. We ruled out cluster-randomised studies to avoid heterogeneity in study design, heterogeneity from the unit of randomisation (e.g. intensive care unit (ICU) versus emergency room (ER)), and variation in eligibility criteria at the individual level compared to a cluster level. We ruled out cross-over studies because we did not consider them an appropriate design for acute cardiogenic pulmonary oedema (ACPE). In a cross-over study, a carry-over effect from the initial therapy (e.g. medical therapy or NPPV) could influence the second intervention (e.g. medical therapy or NPPV), such that participants entering the second intervention differ from those during the first intervention. To avoid publication bias, we included studies irrespective of final publication status. We also included studies reported as full text, abstract only, and unpublished data.

Types of participants

We included trials reporting on adults (18 years and older) with ACPE. A diagnosis of ACPE can have symptoms and clinical signs of hypoperfusion or congestion, or both, such as dyspnoea, pulmonary congestion, jugular venous distension, congestive hepatomegaly, peripheral oedema, confusion, oliguria, and cool extremities (Wang 2005; Yancy 2013). The clinical diagnosis could be supported by a chest radiograph, electrocardiograms, serum biomarkers (e.g. troponin for acute myocardial infarction or Brain natriuretic peptide / N-terminal-pro hormone Brain natriuretic peptide for HF), or echocardiography. We excluded trials investigating NPPV for people with a primary diagnosis of pneumonia, alternative aetiologies of respiratory failure (e.g. endocarditis, cardiac surgery patients, unknown cause), or its use as a weaning strategy.

Types of interventions

For inclusion, the intervention group had to have received nasal or face mask NPPV (CPAP, or bilevel NPPV, or both) with standard medical care (SMC). In contrast, the control group had to have received the same SMC alone (Ponikowski 2016; Yancy 2013).

Types of outcome measures

Primary outcomes

- Hospital mortality

Secondary outcomes

- Endotracheal intubation
- Incidence of acute myocardial infarction (AMI) during hospitalisation, after starting treatment, (e.g. cardiac biomarker elevation creatinine kinase (CK) or troponin) with or without electrocardiographic (ECG) changes or symptoms of myocardial ischaemia
- Intolerance to allocated treatment (e.g. early treatment discontinuation in people not meeting criteria for endotracheal intubation)
- Treatment failure (the combination of mortality, intubation, and intolerance to the allocated treatment)
- Hospital length of stay (from hospital admission to hospital discharge or death)
- ICU length of stay (from ICU admission to ICU discharge or death)
- Vital signs: blood pressure one hour post-intervention, respiratory rate
- Arterial blood gases (PaO$_2$) one hour post-intervention
- Adverse events

For inclusion, studies had to report one or more of the clinical outcomes of interest. We sought additional information from principal investigators as required, including for outcomes that were measured but not reported in the final publication.

Search methods for identification of studies

Electronic searches

We identified trials through systematic searches of the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) (CRS Web, 20 September 2018).
- Database of Abstracts of Reviews Effectiveness (DARE) in the Cochrane Library (Issue 2 of 4, 2015).
- MEDLINE (Ovid, 1946 to 19 September 2018).
- Embase (Ovid, 1974 to 19 September 2018).
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) Plus (EBSCO, 1937 to 20 September 2018).
- LILACS (1982 to 20 September 2018).
- WHO International Clinical Trials Registry Platform (ICTRP; apps.who.int/trialsearch/) (searched 20 September 2018).
- Clinicaltrials.gov (searched 20 September 2018)

The RCT filter for MEDLINE is the Cochrane sensitivity-maximising RCT filter and, for Embase search terms as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* were applied. (Lefebvre 2011). We searched all databases from their inception to the present, without language restriction or consideration of final publication status. We present the search strategies for each database in Appendix 1. Finally, we also considered studies that were ongoing or awaiting classification at the time of the last version of this review.

Searching other resources

We checked the bibliographies of retrieved articles to identify related published and unpublished studies.

Data collection and analysis

We followed the recommendations outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* in preparing this review (Higgins 2011; Higgins 2017).

Selection of studies

In our updated search, two review authors (NB, MC) independently screened citations and selected trials that met the inclusion criteria. We resolved disagreements by consensus with a third review author (YW). In the previous version of this review, two review authors (FV and ML) independently screened citations and selected trials meeting the inclusion criteria with disagreements resolved by a third review author (AA) (Vital 2013).

Data extraction and management

We used a standardised and piloted data collection form to record data on study characteristics, risks of bias, and outcomes. Two review authors (NB, YW) independently extracted:

- characteristics of the study (design, methods of randomisation, withdrawals and dropouts, intention-to-treat analysis (ITT), informed consent, place and multicentre study, funding, conflicts of interest, study dates);
- participants (age, gender, number, diagnostic criteria, inclusion and exclusion criteria);
- interventions (type of NPPV, timing and duration of therapy, co-interventions, SMC (intervention and dose); and
- outcomes reported.

We requested unpublished data from primary authors to supplement outcomes where needed. Two review authors (NB, YW) performed data extraction for all selected study reports independently, with partial extraction by an additional two review authors (CG and MA). We resolved disagreements by consensus with a third senior review author (MC).

Assessment of risk of bias in included studies

Two review authors (NB, YW) independently assessed risks of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreements by consensus with a third review author (MC). We assessed risks of bias according to the following domains, using the Cochrane 'Risk of bias' tool:

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Completeness of outcome data.
- Selective reporting bias.
- Other bias (any other sources of potential bias, e.g. trial prematurely stopped)

We graded each potential source of bias as high, low, or unclear and provide a justification for our judgement in the 'Risk of bias' table. We summarise the 'Risk of bias' judgements across different studies for each of the domains listed. If unpublished data were used in the 'Risk of bias' assessment, we noted this in the 'Risk of bias' table. When we considered treatment effects, we took into account the risks of bias for studies that contributed to that outcome.

Assessment of bias in conducting the systematic review
We conducted the review according to our published protocol and report any deviations from it in the Differences between protocol and review section of the review.

Measures of treatment effect

We analysed dichotomous data as risk ratios (RRs) with 95% confidence intervals (CIs), and continuous data as mean difference (MDs) with 95% CIs.

Unit of analysis issues

We included RCTs with a parallel design. If the same outcome was measured at repeated time points, we selected the longest time point for inclusion in the review, to avoid double counting. In trials with multiple intervention arms, we included the control group with SMC and combined the treatment groups if they had a similar intervention (NPPV: CPAP or BiPAP). For subgroup analysis in studies comparing CPAP, bilevel NPPV, and SMC we divided the control group evenly between groups, as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dealing with missing data

We contacted investigators or study sponsors to obtain missing numerical outcome data where required (e.g. when a study was reported as an abstract only). Where this was not possible and the missing data were thought to introduce serious bias, we explored the impact of study inclusion in the overall assessment of results by performing a sensitivity analysis.

Assessment of heterogeneity

We quantified the impact of statistical heterogeneity using the I^2 statistic (Higgins 2011). An I^2 of 0 to 40% may represent low heterogeneity, 30% to 60% may represent moderate heterogeneity, 50% to 90% may represent substantial heterogeneity, and 75% to 100% may represent considerable heterogeneity. In interpreting the heterogeneity values, we also considered the magnitude and direction of effects and strength of evidence for heterogeneity (e.g. P value from the Chi^2 test or a confidence interval for I^2). In addition, we inspected forest plots for signs of heterogeneity. If substantial heterogeneity was present, we reported it and conducted exploratory analyses to identify sources of heterogeneity (e.g. participants, treatments and study quality). We hypothesised that age, gender, and co-morbidities may represent potential sources of heterogeneity among participants. Furthermore, heterogeneity may be related to the initial treatment(s) used, the levels of pressure applied with NPPV, or treatment duration.

Assessment of reporting biases

Funnel plots allowed us to examine and explore small-study biases and publication bias (Egger 1997). We generated funnel plots for each outcome with at least 10 studies.

Data synthesis

We undertook meta-analysis only where studies were sufficiently similar for results to be clinically meaningful and if we identified more than two trials reporting data for that outcome. For these studies, we pooled dichotomous and

continuous variables using a random-effects model. We chose a random-effects model, as we anticipated heterogeneity in study participants, interventions, and outcomes of included studies. We presented the number needed to treat for an additional beneficial outcome (NNTB) when an effect was indicated by meta-analysis. We report summary estimates of treatment effect with their associated 95% CIs. We conducted all analyses using Cochrane statistical software (Review Manager 2014).

'Summary of findings' table

We created a 'Summary of findings' table for the main outcomes of the review: hospital mortality, endotracheal intubation (ETI), acute myocardial infarction (AMI), intolerance to allocated treatment, hospital length of stay, ICU length of stay and adverse events. We generated these tables using GRADEpro software (gradepro.org/) and imported them into Review Manager 5.

GRADE

We used the five GRADE domains (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies. For this process, we used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011; Higgins 2017). We justified all decisions to downgrade the quality of evidence using footnotes provided in the 'Summary of findings' table (Guyatt 2008; Higgins 2011).

Two review authors (NB, YW) working independently, made judgements about evidence quality, with disagreements resolved by consensus with a third senior review author (MC).

Subgroup analysis and investigation of heterogeneity

We performed subgroup analyses for the following outcomes: hospital mortality, ETI, AMI, intolerance to allocated treatment, and hospital length of stay. Subgroups of interest included: type of NPPV (CPAP or bilevel NPPV), location of therapy (ER versus ICU), baseline hypercapnia status. In addition, for AMI we planned a subgroup analysis by time of event relative to treatment (AMI before or after initiation of treatment). Unfortunately, our planned AMI subgroup analysis was not possible, due to inconsistent definitions of AMI between studies. Please see Differences between protocol and review for further details. For mean, systolic, and diastolic blood pressure after one hour of therapy we performed a subgroup analysis by NPPV type (CPAP or bilevel NPPV). We used the test for subgroup differences to detect whether the effect estimate differed between groups of studies. We used a P value of less than 0.05 for this test, as suggesting a true difference between subgroups, but acknowledge that this test has limited power when there are few studies.

Sensitivity analysis

We decided a priori to perform sensitivity analyses on hospital mortality, ETI, and adverse events. These sensitivity analyses covered:

- including studies with only low risk of bias.
- including studies without missing data.
- including only studies with a final diagnosis of cardiogenic pulmonary oedema being present in 50% or more of included participants.

For mortality, we considered a trial to be at low risk of bias if it met the criteria for low risk of bias in the following domains: random sequence generation and incomplete outcome data. For ETI and adverse events, we rated trials at low risk of bias if they met the low-risk-of-bias criteria for the following domains: random sequence generation and allocation concealment.

Reaching conclusions

We base our conclusions only on findings from the quantitative or narrative synthesis of studies included in this review. In addition, we outline the gaps in the evidence for NPPV in ACPE, and suggest future directions for research.

Results

Description of studies

Results of the search

Our updated search identified 3791 references (CENTRAL 905, DARE 12, MEDLINE 1266, Embase 878, LILACS 67, CINAHL Plus 397, WHO ICTRP 168, and clinicaltrials.gov 98). After de-duplication and reviewing reference lists from included articles, we screened 2807 references for inclusion. After screening, we obtained full-text articles for 94 references. Ultimately, we have included in this review update 24 studies (37 references) with a total of 2664 participants treated with NPPV versus SMC for ACPE. We excluded 43 studies (57 references). Our review update includes seven new studies since May 2013 (Austin 2013; Ducros 2011; El-Refay 2016; Hao 2002; Li 2005; Moritz 2003; Zokaei 2016) and excludes 15 previously included studies (Bautin 2005; Bellone 2004; Bellone 2005; Bersten 1991; Delclaux 2000; Ferrer 2003; Ferrari 2007; Ferrari 2010; Fontanella 2010; Liesching 2014; Martin-Bermudez 2002; Mehta 1997; Moritz 2007; Sharon 2000; Weitz 2007). Our PRISMA flowchart summarises the study selection process (Figure 1). We provide additional information on included and excluded studies in the following sections: Characteristics of included studies; Characteristics of excluded studies.

Included studies

Study design

We included 24 parallel-design RCTs in this review update (Agmy 2008; Austin 2013; Crane 2004; Ducros 2011; El-Refay 2016; Frontin 2011; Gray 2008; Hao 2002; Kelly 2002; L'Her 2004; Levitt 2001; Li 2005; Lin 1991; Lin 1995; Masip 2000; Moritz 2003; Nava 2003; Park 2001; Park 2004; Räsänen 1985; Takeda 1997; Takeda 1998; Thys 2002; Zokaei 2016). The funding sources for seven studies was public (Agmy 2008; Austin 2013; Ducros 2011; Frontin 2011; Gray 2008; Masip 2000; Thys 2002). One study reported receiving funds from a nonprofit organisation (Kelly 2002). Two studies were funded by device manufacturers (Crane 2004; L'Her 2004) and 14 studies provided no details on funding sources (El-Refay 2016; Hao 2002; Levitt 2001; Li 2005; Lin 1991; Lin 1995; Moritz 2003; Nava 2003; Park 2001; Park 2004; Räsänen 1985; Takeda 1997; Takeda 1998; Zokaei 2016). We summarise each study in our Characteristics of included studies tables.

Population

The mean participant age in our review was 73.3 ± 9.0 years. Our review includes studies from 14 countries: Australia, Belgium, Brazil, China, Egypt, Finland, France, Iran, Italy, Japan, Spain, Taiwan, the UK, and the USA. Furthermore, five studies were multicentre (Crane 2004; Ducros 2011; Gray 2008; L'Her 2004; Nava 2003). Studies varied in size from eight to 1069 participants, with a median and mean study size of 55 and 114 participants respectively. Ten studies were conducted in an emergency department (ED or ER) setting (Crane 2004; El-Refay 2016; Gray 2008; Kelly 2002; Levitt 2001; L'Her 2004; Moritz 2003; Nava 2003; Park 2004; Thys 2002), eight studies were conducted in an ICU setting (Agmy 2008; Lin 1991; Lin 1995; Masip 2000; Räsänen 1985; Takeda 1997; Takeda 1998; Zokaei 2016), and three studies did not reference a specific study location (Hao 2002; Li 2005; Park 2001). Three studies were started in the pre-hospital setting with further care in the ER and the ICU if required (Austin 2013; Ducros 2011; Frontin 2011).

Intervention

Six studies compared all three interventions: CPAP, bilevel NPPV, and SMC (Agmy 2008; Crane 2004; El-Refay 2016; Gray 2008; Park 2001; Park 2004). Twelve studies compared CPAP against SMC (Austin 2013; Ducros 2011; Frontin 2011; Hao 2002; Kelly 2002; L'Her 2004; Lin 1991; Lin 1995; Moritz 2003; Räsänen 1985; Takeda 1997; Takeda 1998). Six studies compared bilevel NPPV against SMC (Levitt 2001; Li 2005; Masip 2000; Nava 2003; Thys 2002; Zokaei 2016). We summarise the NPPV settings including mask type, inspiratory positive airway pressure (IPAP), expiratory positive airway pressure (EPAP), positive end-expiratory pressure (PEEP), and duration of NPPV in Table 1. The NPPV patient-ventilator interface varied between exclusive use of nasal masks (Takeda 1997; Takeda 1998), a choice between a nasal or face mask (Levitt 2001; Park 2001; Zokaei 2016), and exclusive use of face masks. We have summarised the SMC provided in each trial in Table 2. SMC included supplemental oxygen and pharmacologic treatments. SMC pharmacologic treatments included loop diuretics (furosemide), nitrates (e.g. nitroglycerin, isosorbide dinitrate), opioids (e.g. morphine), and ionotropes if required.

Outcomes

Commonly-reported outcomes included hospital mortality, endotracheal intubation (ETI), acute myocardial infarction (AMI), hospital length of stay, ICU length of stay, change in systolic blood pressure (SBP) and respiratory rate (RR) during treatment, and change in arterial blood glasses (PaO_2). In reviewing the methodology for each study, we found that only three studies (Austin 2013; Ducros 2011; Gray 2008) provided a power calculation to detect a mortality difference. In addition, hospital mortality was reported at variable time periods. We summarise the time point at which hospital mortality was measured in Table 3. The median length of follow-up for hospital mortality was 13 days. AMI during the study period was reported by five studies (Crane 2004; Gray 2008; Levitt 2001; Nava 2003; Park 2001). AMI definitions were inconsistent, varying between new ST segment elevation on ECG, to myocardial enzyme elevation (e.g. CK, troponin) with ECG changes, and myocardial enzyme elevation alone. Treatment intolerance or early treatment discontinuation was reported by Agmy 2008. Explicit definitions for treatment failure as an indicator for potential endotracheal intubation are summarised in Table 4.

Several outcomes, including systolic blood pressure, mean blood pressure, diastolic blood pressure, PaO_2, and respiratory rate, are reported as continuous outcomes. For these outcomes, we used the reported mean and standard deviations. Certain data were only available in graphical format and we extracted them by measuring the graph: PaO_2 (Lin 1995). We converted arterial blood gas data from kilopascals (kPa) to millimetres of mercury (mmHg) for three studies (Crane 2004; Gray 2008; Kelly 2002), using the conversion of 1 kPA to 7.50 mmHg (Zumdahl 2002).

Excluded studies

We excluded citations if they were duplicates of the same study (N = 27), an ineligible intervention (N = 14), an ineligible population (N = 5), a quasi-randomised controlled trial (N = 4), an ineligible study type (N = 17), and if the study was withdrawn after study registration (N = 3). We have excluded 15 studies included in the previous version of this review. Of these, we excluded three studies conducted on an inappropriate population (Bautin 2005; Delclaux 2000; Ferrer 2003). We excluded four quasi-randomised controlled trials (Bersten 1991; Moritz 2007; Sharon 2000; Weitz 2007). Finally, we excluded eight studies which compared bilevel NPPV against CPAP, without an additional comparison against SMC (Bellone 2004; Bellone 2005; Ferrari 2007; Ferrari 2010; Fontanella 2010; Liesching 2014; Martin-Bermudez 2002; Mehta 1997). We provide additional details explaining each excluded study in Characteristics of excluded studies tables.

Risk of bias in included studies

We present our 'Risk of bias' assessments in Characteristics of included studies tables. We provide a graphic

summary of our assessments (Figure 2; Figure 3).

Allocation (selection bias)

All included studies had randomly-allocated treatments. Randomisation sequence generation was at low risk of bias in eight studies (Austin 2013; Crane 2004; Frontin 2011; Gray 2008; L'Her 2004; Levitt 2001; Masip 2000; Nava 2003) and at unclear risk of bias in 16 studies (Agmy 2008; Ducros 2011; El-Refay 2016; Hao 2002; Kelly 2002; Li 2005; Lin 1991; Lin 1995; Moritz 2003; Park 2001; Park 2004; Räsänen 1985; Takeda 1997; Takeda 1998; Thys 2002; Zokaei 2016).

Allocation concealment was at low risk of bias in seven studies (Austin 2013; Crane 2004; Frontin 2011; Gray 2008; L'Her 2004; Nava 2003; Thys 2002), at unclear risk of bias in 16 studies (Agmy 2008; Ducros 2011; El-Refay 2016; Hao 2002; Kelly 2002; Levitt 2001; Li 2005; Lin 1991; Lin 1995; Moritz 2003; Park 2001; Park 2004; Räsänen 1985; Takeda 1997; Takeda 1998; Zokaei 2016), and at high risk of bias in one study (Masip 2000).

Blinding (performance bias and detection bias)

Blinding of participants and personnel was not possible for most studies, given the nature of the intervention. Twelve studies were at unclear risk of bias, as they did not state whether or not they had blinded participants and personnel (Hao 2002; Kelly 2002; Levitt 2001; Li 2005; Moritz 2003; Nava 2003; Park 2001; Park 2004; Räsänen 1985; Takeda 1997; Takeda 1998; Zokaei 2016). Twelve studies did not blind participants and personnel (Agmy 2008; Austin 2013; Crane 2004; Ducros 2011; El-Refay 2016; Frontin 2011; Gray 2008; L'Her 2004; Lin 1991; Lin 1995; Masip 2000; Thys 2002).

Blinding of outcome assessments was not explicitly stated for most studies. Three studies were at low risk of bias for outcome assessment blinding (Austin 2013; Ducros 2011; El-Refay 2016), 19 studies were at unclear risk of bias (Agmy 2008; Crane 2004; Frontin 2011; Hao 2002; Kelly 2002; Levitt 2001; Li 2005; Lin 1991; Lin 1995; Masip 2000; Moritz 2003; Nava 2003; Park 2001; Park 2004; Räsänen 1985; Takeda 1997; Takeda 1998; Thys 2002; Zokaei 2016), and two studies were at high risk of bias (Gray 2008; L'Her 2004).

Incomplete outcome data (attrition bias)

Three studies had high risk of bias due to incomplete outcome data (El-Refay 2016; Lin 1991; Park 2004). These studies excluded a significant number of participants after randomisation. Seven studies did not present enough information to judge the completeness of outcome data and were rated at unclear risk (Hao 2002; Levitt 2001; Li 2005; Moritz 2003; Park 2001; Takeda 1997; Zokaei 2016). Fourteen studies presented complete outcome data and were at low risk of bias (Agmy 2008; Austin 2013; Crane 2004; Ducros 2011; Frontin 2011; Gray 2008; Kelly 2002; L'Her 2004; Lin 1995; Masip 2000; Nava 2003; Räsänen 1985; Takeda 1998; Thys 2002).

Selective reporting (reporting bias)

Most studies did not provide enough information to judge whether they included all planned outcomes. Three studies (Austin 2013; Frontin 2011; Gray 2008) were at low risk of bias for selective reporting, given that the authors performed prospective trial registration and reported all their prespecified outcomes. Eighteen studies did not present enough information to determine if the outcomes presented were prespecified, and were at unclear risk of bias (Crane 2004; El-Refay 2016; Hao 2002; Kelly 2002; L'Her 2004; Levitt 2001; Li 2005; Lin 1991; Lin 1995; Masip 2000; Moritz 2003; Nava 2003; Park 2001; Park 2004; Räsänen 1985; Takeda 1997; Takeda 1998; Thys 2002). Three studies were at high risk of bias, as they failed to report prespecified outcomes or the outcomes reported were not in an extractable format (Agmy 2008; Ducros 2011; Zokaei 2016).

Other potential sources of bias

Two studies were reported in abstract form only (Agmy 2008; Austin 2013). Seven studies had high risk of other potential sources of bias (Agmy 2008; Ducros 2011; El-Refay 2016; Hao 2002; L'Her 2004; Levitt 2001; Li 2005). Agmy 2008 was reported as a personal communication in addition to abstracts which did not have quantitative data. There is a discrepancy between counts reported on clinicaltrials.gov and the personal communication data. We have used the personal communication data in our analysis. Other potential sources of bias included study termination due to poor recruitment, low likelihood of significant findings, or presenting data without a measure of variance (e.g. standard deviation). Our funnel plot of hospital mortality for NPPV versus SMC demonstrates some asymmetry for studies of intermediate sample size, which may indicate the presence of publication bias (see Figure 4).

Effects of interventions

Hospital mortality

NPPV may reduce hospital mortality compared to SMC alone (RR 0.65, 95% CI 0.51 to 0.82; participants = 2484; studies = 21; I^2 = 6%; Analysis 1.1; low quality of evidence), with a number needed to treat for an additional beneficial outcome (NNTB) of 17 (NNTB 12 to NNTB 32). We summarise our findings in Summary of findings table 1. We downgraded the evidence for hospital mortality by one level due to serious risk of bias (unclear or high risk of bias for randomisation sequence, allocation concealment, and other significant bias), and by one level due to imprecision (most trials had few participants and events, with a wide confidence interval).

We performed subgroup analysis by NPPV type (CPAP or bilevel), and found no significant difference between CPAP or bilevel NPPV (Analysis 1.2), based on the test for differences between subgroups (P = 0.64). Park 2001 reported no deaths in the bilevel NPPV arm and the SMC arm. El-Refay 2016 reported no deaths in the CPAP or bilevel NPPV arms. CPAP may reduce hospital mortality (RR 0.65, 95% CI 0.48 to 0.88; participants = 1454; studies = 16; I^2 = 9%) and bilevel

NPPV may reduce hospital mortality (RR 0.72, 95% CI 0.53 to 0.98; participants = 1030; studies = 11; I^2 = 0%).

Our treatment location subgroup analysis (Analysis 1.3) revealed no significant difference between participants treated with NPPV in the ER compared to the ICU, based on the test for differences between subgroups (P = 0.51). People treated with NPPV in the ICU may have reduced hospital mortality compared to SMC (RR 0.52, 95% CI 0.35 to 0.77; participants = 862; studies = 10; I^2 = 0%). Similarly, people treated with NPPV in the ER may have reduced hospital mortality compared to SMC (RR 0.66, 95% CI 0.47 to 0.93; participants = 1596; studies = 10; I^2 = 18%). Baseline $PaCO_2$ subgroup analysis (Analysis 1.4) revealed a significant subgroup difference between studies with baseline eucapnia or hypercapnia (test for differences between subgroups P = 0.005). People with eucapnia treated with NPPV compared to SMC may have reduced hospital mortality (RR 0.41, 95% CI 0.27 to 0.63; participants = 581; studies = 10; I^2 = 0%). In contrast, hypercapnic people may not benefit from NPPV compared to SMC (RR 0.82, 95% CI 0.65 to 1.03; participants = 1903; studies = 11; I^2 = 0%).

Low-risk-of-bias sensitivity analysis eliminated the observed reduction in hospital mortality with NPPV compared to SMC (RR 0.81, 95% CI 0.61 to 1.06; participants = 1505; studies = 7; Analysis 1.5; I^2 = 6%). A sensitivity analysis that excluded studies with missing data (RR 0.68, 95% CI 0.54 to 0.86; participants = 2283; studies = 18; Analysis 1.6; I^2 = 5%) indicates that NPPV may reduce hospital mortality. Finally, changing our statistical model from random-effects to fixed-effect also indicates that NPPV may reduce hospital mortality compared to SMC alone (RR 0.67, 95% CI 0.55 to 0.81; participants = 2484; studies = 21; Analysis 1.7; I^2 = 6%).

Endotracheal intubation (ETI)

NPPV compared to SMC probably reduces ETI (RR 0.49, 95% CI 0.38 to 0.62; participants = 2449; studies = 20; Analysis 1.8; I^2 = 0%; moderate quality of evidence) with a NNTB of 13 (NNTB 11 to NNTB 18). Two studies contributed data from only one of their three study arms: Kelly 2002 reported no ETI events for CPAP or SMC arms, and El-Refay 2016 reported no ETI events for CPAP or bilevel NPPV.

Our subgroup analysis by NPPV type indicates no significant difference between CPAP or bilevel NPPV compared to SMC (test for differences between subgroups P = 0.75). Both CPAP compared to SMC (RR 0.46, 95% CI 0.34 to 0.62; participants = 1413; studies = 15; I^2 = 0%) and bilevel NPPV compared to SMC (RR 0.50, 95% CI 0.31 to 0.81; participants = 1036; studies = 11; I^2 = 23%) probably reduce ETI (Analysis 1.9). Treatment location subgroup analysis (ER or ICU, Analysis 1.10) revealed no significant difference between participants treated in the ER or ICU with NPPV compared to SMC (test for differences between subgroups P = 0.40). NPPV use in the ER setting probably reduces ETI (RR 0.60, 95% CI 0.37 to 0.96; participants = 1561; studies = 9; I^2 = 21%). Participants treated with NPPV in the ICU setting probably have reduced ETI (RR 0.40, 95% CI 0.29 to 0.56; participants = 862; studies = 10; I^2 = 0%). Our $PaCO_2$ subgroup analysis (Analysis 1.11) revealed a significant difference between baseline eucapnic and hypercapnic studies (test for differences between subgroups P = 0.03). Both eucapnic participants treated with NPPV (RR 0.37, 95% CI 0.26 to 0.52; participants = 523; studies = 9; I^2 = 0%) and hypercapnic participants treated with NPPV (RR 0.64, 95% CI 0.46 to 0.91; participants = 1926; studies = 11; I^2 = 0%) probably have reduced ETI rates compared to SMC, but the effect was larger in those with $PaCO_2$? 45 mmHg.

Low-risk-of-bias sensitivity analysis indicates there was probably no ETI rate reduction with NPPV compared to SMC (RR 0.85, 95% CI 0.55 to 1.32; participants = 1491; studies = 6; Analysis 1.12; I^2 = 0%). In contrast, sensitivity analysis that excluded studies with missing data (Analysis 1.13) indicates that NPPV probably reduces ETI rates compared to SMC (RR 0.52, 95% CI 0.40 to 0.69; participants = 2248; studies = 17; I^2 = 0%). We performed additional post hoc analysis exploring the effect of exclusive use of face masks to deliver NPPV compared to studies with permissive use of nasal or face masks (Analysis 1.14). We found no significant subgroup differences. Exclusive face mask use (RR 0.52, 95% CI 0.40 to 0.69; participants = 2213; studies = 15; I^2 = 0%) or permissive use of nasal masks (RR 0.35, 95% CI 0.20 to 0.62; participants = 236; studies = 5; I^2 = 0%) probably reduced ETI.

Incidence of acute myocardial infarction (AMI)

There is probably little or no difference in AMI incidence with NPPV compared to SMC for ACPE (RR 1.03, 95% CI 0.91 to 1.16; participants = 1313; studies = 5; Analysis 1.15; I^2 = 0%; moderate quality of evidence). The median length of follow-up for AMI was three days. Subgroup analysis by NPPV type revealed no significant differences between CPAP or bilevel NPPV (Analysis 1.16; test for differences between subgroups P = 0.30). Both CPAP (RR 0.96, 95% CI 0.80 to 1.14; participants = 569; studies = 3; I^2 = 0%) and bilevel NPPV (RR 1.09, 95% CI 0.92 to 1.29; participants = 744; studies = 5; I^2 = 0%) probably have little or no difference in AMI incidence compared to SMC. Several trials reported no AMI events in either treatment arm: CPAP versus bilevel versus SMC (Park 2004), and bilevel NPPV versus SMC (Park 2001; Thys 2002). Study location subgroup analysis was not possible, as only one study (Park 2001) was conducted in an unknown location while the remaining studies were conducted in the ER. Baseline $PaCO_2$ subgroup analysis was not possible, as only one study (Park 2001) had baseline eucapnia while the remaining studies had baseline hypercapnia. Our planned subgroup analysis comparing AMI rates before and after NPPV intervention was not possible, due to inconsistent AMI definitions (e.g. STEMI, NSTEMI, angina).

Intolerance to allocated treatment

We were interested in obtaining information on treatment intolerance of NPPV compared to SMC. Unfortunately, this outcome was inconsistently defined. Potential outcomes providing similar information included:

- Treatment failure. This outcome was more commonly reported. Treatment failure could indicate the need for endotracheal intubation. This outcome was inconsistently defined and was often a clinical diagnosis. Criteria for endotracheal intubation

are summarised in Table 4.

- Crane 2004 reported on treatment failure, which was defined as worsening respiratory function or reduced level of consciousness. Treatment failure occurred in one SMC participant, four CPAP participants, and one bilevel NPPV participant. Only one CPAP participant and one bilevel NPPV participant were intubated.
- Ducros 2011 reported on the presence of intubation criteria, which they defined as medically refractory hypoxaemia, loss of consciousness, psychomotor agitation, or haemodynamic instability. They reported 13 SMC participants and four CPAP participants meeting intubation criteria. Only six SMC participants and three CPAP participants were intubated.
- Kelly 2002 reported no treatment failures in the CPAP group and two treatment failures in the SMC group.
- L'Her 2004 reported no treatment failures or changes to the assigned treated after one hour of therapy. After 12 hours of treatment there were 11 SMC participants with coma and one CPAP participant with coma.
- Lin 1991 reported treatment failure in five CPAP participants and 10 SMC participants during the first three hours of treatment, leading to endotracheal intubation.
- Lin 1995 reported nine CPAP participants and 17 SMC participants meeting treatment failure criteria. Only six CPAP participants and 12 SMC participants were ultimately intubated, as the final decision was based on clinical judgement.
- Räsänen 1985 reported on treatment failure after three hours of therapy in 13 SMC participants and seven CPAP participants.
- Thys 2002 defined treatment failure based on clinical deterioration assessed by the clinician. Thys 2002 reported that all five participants assigned to SMC had treatment failure with placebo NPPV, and were switched over to active NPPV therapy.

- Treatment intolerance was inconsistently defined.
  - Agmy 2008 reported one event in each treatment group (CPAP, bilevel NPPV, and SMC) of NPPV intolerance leading to ETI.
  - Gray 2008 reported rates of participants changing to a new treatment, i.e. 65 of 363 SMC participants, 55 of 340 CPAP participants, and 85 of 352 participants for bilevel NPPV.

Given the heterogeneity in clinical definitions of treatment failure and our desired outcome being intolerance to allocated treatment, we are unable to draw any conclusions on the effect of NPPV compared to SMC for ACPE.

Hospital and ICU length of stay

We are uncertain whether NPPV reduces hospital length of stay compared to SMC for ACPE (MD ?0.31 days, 95% CI ?1.23 to 0.61; participants = 1714; studies = 11; Analysis 1.17; I^2 = 55%; very low quality of evidence). The mean hospital length of stay was 9.65 days. Subgroup analysis by NPPV type found no significant subgroup differences (P = 0.22) between participants treated with CPAP (MD ?0.52 days, 95% CI ?1.77 to 0.72; participants = 943; studies = 7; I^2 = 59%) or with bilevel NPPV (MD 0.39 days, 95% CI ?0.35 to 1.13; participants = 771; studies = 6; I^2 = 0%) compared to SMC for hospital length of stay (Analysis 1.18). Treatment location subgroup analysis identified no significant difference (P = 0.84) between ACPE participants treated with NPPV in the ER (MD ?0.38 days, 95% CI ?1.70 to 0.93; participants = 1455; studies = 8; I^2 = 68%) compared to the ICU (MD ?0.21 days, 95% CI ?1.30 to 0.89; participants = 259; studies = 3; Analysis 1.19; I^2 = 0%). Subgroup analysis by baseline $PaCO_2$ (Analysis 1.20) found a significant difference (P = 0.01) in hospital length of stay between eucapnic ACPE participants (MD ?1.18 days, 95% CI ?2.33 to ?0.04; participants = 397; studies = 5; I^2 = 44%) and hypercapnic ACPE participants (MD 0.60 days, 95% CI ?0.15 to 1.34; participants = 1317; studies = 6; I^2 = 7%). However, the evidence quality was very low, and we are uncertain whether eucapnic or hypercapnic ACPE participants had reduced hospital lengths of stay.

We are uncertain whether NPPV reduces ICU length of stay compared to SMC for ACPE. We found significant heterogeneity with ICU length-of-stay data which were reported by six studies (Ducros 2011; Frontin 2011; Lin 1995; Takeda 1997; Thys 2002; Zokaei 2016). In addition, the quality of evidence was very low. We did not pool ICU length-of-stay data, due to significant heterogeneity (Analysis 1.21). We downgraded the quality of evidence for ICU length of stay by one level due to serious risk of bias. Most information was from studies at low or unclear risk of bias. Furthermore, lack of blinding was likely to lower confidence in our ICU length-of-stay findings. We also downgraded the evidence quality by one level due to data inconsistency. ICU length-of stay-data were heterogeneous with an I^2 of 99% and visually-evident heterogeneity. Finally, we downgraded by one level for imprecision, because most of the trials had few participants, with the confidence interval crossing a mean difference of 0.

Vital signs one hour after intervention

Systolic blood pressure (SBP)

There is probably little or no difference in SBP after one hour in people with ACPE treated with NPPV compared to SMC (MD ?1.72 mmHg, 95% CI ?5.03 to 1.58; participants = 1408; studies = 7; Analysis 1.22; I^2 = 0%; moderate quality of evidence). The mean SBP was 128.4 mmHg in the SMC group. We downgraded the quality of evidence for SBP by one level for imprecision, as the included studies had few participants and wide confidence intervals. Subgroup analysis by NPPV type (Analysis 1.23) found no significant subgroup difference (P = 0.95) between SBP in people with ACPE treated with CPAP (MD ?1.65 mmHg, 95% CI ?5.58 to 2.28; participants = 866; studies = 7; I^2 = 0%) or bilevel NPPV (MD ?1.89 mmHg, 95% CI ?8.01 to 4.23; participants = 542; studies = 3; I^2 = 0%) compared to SMC.

Diastolic blood pressure (DBP)

People with ACPE treated with NPPV compared to SMC probably have little or no difference in DBP after one hour of

treatment (MD 1.46 mmHg, 95% CI −1.86 to 4.78; participants = 1361; studies = 6; Analysis 1.24; I = 42%; moderate quality of evidence). The mean DBP was 71.9 mmHg in the SMC group. We downgraded DBP quality of evidence by one level for imprecision, because the included studies had few participants and wide confidence intervals. Subgroup analysis by NPPV type (Analysis 1.25) demonstrated no significant subgroup difference (P = 0.96) between DBP in people with ACPE treated with CPAP (MD 0.92 mmHg, 95% CI −3.92 to 5.75; participants = 823; studies = 6; I^2 = 64%) or bilevel NPPV (MD 1.08, 95% CI −2.88 to 5.04; participants = 538; studies = 3; I^2 = 0%) compared to SMC.

Mean blood pressure (MBP)

There is probably little or no difference in MBP after one hour for people with ACPE treated with NPPV compared to SMC (MD -2.50 mmHg, 95% CI -8.29 to 3.30; participants = 251; studies = 3; I^2 = 20%; Analysis 1.26; moderate quality of evidence). The mean MBP was 101 mmHg. We downgraded MBP quality of evidence by one level for imprecision, because the included studies had few participants and wide confidence intervals. We did not perform subgroup analysis by NPPV type, due to the small number of studies.

Respiratory rate (RR)

NPPV for ACPE probably reduces the RR after one hour of treatment compared to SMC (MD −1.87 breaths a minute, 95% CI −2.70 to −1.03; participants = 1636; studies = 10; Analysis 1.27; I^2 = 17%; moderate quality of evidence). The mean RR after one hour of therapy was 27.4 breaths a minute in the SMC group. We downgraded RR quality of evidence by one level for imprecision, because the included studies had few participants and wide confidence intervals. Subgroup analysis by NPPV type (Analysis 1.28) demonstrated no significant subgroup differences (P = 0.70) in RR after one hour between CPAP compared to SMC (MD −1.64 breaths a minute, 95% CI −2.41 to −0.87; participants = 1107; studies = 10; I^2 = 0%) and bilevel NPPV compared to SMC (MD −2.17 breaths a minute, 95% CI −4.69 to 0.35; participants = 529; studies = 3; I^2 = 38%).

Arterial oxygen concentration (PaO$_2$) after one hour of intervention

NPPV compared to SMC for ACPE may improve PaO$_2$ after one hour of therapy (MD 16.19 mmHg, 95% CI 3.54 to 28.84; participants = 1428; studies = 10; Analysis 1.29; I^2 = 91%; low quality of evidence). The mean PaO$_2$ after one hour of therapy was 133.9 mmHg in the SMC group. We downgraded PaO$_2$ quality of evidence by one level due to imprecision. Most trials had few participants and the confidence interval crossed the line of no effect. We downgraded by an additional level for inconsistency, because the PaO$_2$ data were visually heterogeneous, with an I^2 of 91%. Our subgroup analysis by NPPV type (Analysis 1.30) demonstrated no significant subgroup differences (P = 0.42) in PaO$_2$ after one hour between CPAP compared to SMC (MD 9.55 mmHg, 95% CI −9.10 to 28.19; participants = 761; studies = 8; I^2 = 88%) and bilevel NPPV compared to SMC (MD 19.50 mmHg, 95% CI 4.29 to 34.71; participants = 667; studies = 6; I^2 = 86%). We did not pool PaCO$_2$ and pH after one hour of treatment, as these outcomes require assessment compared to baseline values. In addition, we were unable to pool the treatment failure outcome, as this composite outcome of mortality, ETI rate, and treatment intolerance was not reported.

Adverse events

Eleven trials (Agmy 2008; Crane 2004; Ducros 2011; Frontin 2011; Gray 2008; L'Her 2004; Lin 1995; Masip 2000; Nava 2003; Park 2004; Räsänen 1985) compared NPPV against SMC for ACPE and reported adverse events (Analysis 1.31). There were 228 adverse events reported in 1230 NPPV participants compared to 116 adverse events for 808 SMC participants. Adverse events included skin damage, pneumonia, gastrointestinal bleeding, gastric distention, vomiting, pneumothorax, sinusitis, mask discomfort, hypotension, arrhythmia, cardiorespiratory arrest, gastric aspiration, stroke, seizures, claustrophobia, and hypercapnia.

Three trials (Gray 2008; Masip 2000; Nava 2003) reported that participants treated with NPPV probably have increased mask discomfort compared to SMC (RR 12.59, 95% CI 2.39 to 66.28; participants = 1100; studies = 3; I^2 = 0%; moderate quality of evidence). We downgraded the evidence for mask discomfort by one level for imprecision, because there were few events and wide confidence intervals.

Three trials (Agmy 2008; Nava 2003; Räsänen 1985) reported worsening hypercapnia with treatment. Participants treated with NPPV or SMC for ACPE probably have little or no difference in rates of worsening hypercapnia. We downgraded the evidence quality for hypercapnia by one level for imprecision, due to few events and wide confidence intervals.

Park 2004 (n = 83) reported a higher incidence of gastric distention in the NPPV group (13/56 in NPPV group, 0/27 in SMC group; RR 13.26, 95% CI 0.82 to 215.12), but the number of events was low and the confidence interval wide. There was some weak evidence of a lower incidence of cardiorespiratory arrest in the NPPV group (24/836 (NPPV) versus 26/516 (SMC); RR 0.60, 95% CI 0.34 to 1.05). There was no evidence of a difference between groups for the other adverse events.

Overall, we assessed the evidence for adverse events to be of low quality. We downgraded the evidence by one level for serious risk of bias (unclear or high risk of bias in at least one domain), and by one additional level for imprecision (the included studies had few participants and wide confidence intervals).

Discussion

Summary of main results

Our updated systematic review and meta-analysis includes 24 RCTs with 2664 participants. Compared to standard medical care (SMC), the use of non-invasive positive pressure ventilation (NPPV) for acute cardiogenic pulmonary oedema (ACPE)

may reduce hospital mortality and probably reduces endotracheal intubation (ETI) rates. In addition, there was probably little or no difference between NPPV and SMC for rates of acute myocardial infarction (AMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), or mean blood pressure (MBP) after one hour of therapy. We are uncertain if NPPV reduces hospital length of stay. However, NPPV (compared to SMC) probably improves respiratory rate after one hour of treatment, may slightly improve PaO_2 after one hour of therapy, and probably increases mask discomfort.

NPPV use for ACPE may reduce hospital mortality compared to SMC alone, with a number needed to treat for an additional beneficial outcome (NNTB) of 17 (NNTB 12 to NNTB 32) (Summary of findings table 1). Our subgroup analysis by NPPV type identified no significant difference between continuous positive airway pressure (CPAP) and bilevel NPPV subgroups. Both NPPV forms may reduce hospital mortality compared to SMC. We found no significant difference between people with ACPE treated in the Emergency Room (ER) or intensive care unit (ICU) in our subgroup analysis. NPPV may reduce hospital mortality compared to SMC in both treatment locations. Our baseline $PaCO_2$ subgroup analysis for people with ACPE treated with NPPV compared to SMC revealed a significant difference between studies with baseline average eucapnia and hypercapnia. Eucapnic people with ACPE treated with NPPV may have reduced hospital mortality, while hypercapnic people may have little or no difference in hospital mortality. The non-significant hospital mortality benefit with hypercapnia may have been due to the greater weight of the trial by Gray 2008 (conducted in the ER setting with baseline hypercapnia), which did not show any hospital mortality benefit with NPPV. Prior smaller studies have suggested enhanced benefit for people with baseline hypercapnia, due to their higher risk of complications and NPPV potentially preventing endotracheal intubation (Masip 2000; Moritz 2007; Nava 2003). Our baseline $PaCO_2$ subgroup analysis did not support the idea that hypercapnic people with ACPE would benefit more compared to eucapnic people with ACPE. One possible reason for this discrepancy was that mean $PaCO_2$ values could hide hypercapnic people who derived significant benefit from NPPV or clinical worsening with SMC. Finally, our sensitivity analysis limited to low-risk-of-bias studies found NPPV may make little or no difference in hospital mortality compared to SMC. In contrast, our sensitivity analysis limited to studies without missing data indicated that NPPV for ACPE may reduce hospital mortality compared to SMC alone.

NPPV in ACPE probably reduces ETI compared to SMC alone, with a NNTB of 13 (NNTB 11 to 18). We did not find a significant difference between trials comparing CPAP or bilevel NPPV in our subgroup analysis. Both forms of NPPV probably reduce ETI compared to SMC. We found no significant difference between trials comparing NPPV in the ER or ICU setting in our subgroup analysis. People with ACPE treated with NPPV in the ER or ICU probably have reduced ETI compared to SMC. Baseline $PaCO_2$ subgroup analysis revealed a significant difference between baseline eucapnic and hypercapnic people with ACPE treated with NPPV compared to SMC. Both eucapnic and hypercapnic people with ACPE probably have reduced ETI compared to SMC. However, eucapnic people probably get more benefit compared to hypercapnic people. Sensitivity analysis limited to low-risk-of-bias studies found NPPV use probably makes little or no difference to ETI compared with SMC. In contrast, sensitivity analysis limited to studies without missing data indicated NPPV for ACPE probably reduces ETI compared to SMC alone. Our post hoc subgroup analysis which compared exclusive use of face masks to permissive use of nasal masks revealed no significant subgroup differences, and both NPPV subgroups probably reduce ETI compared to SMC alone.

Several trials (Mehta 1997; Rusterholtz 1999; Sharon 2000) reported increased AMI incidence with NPPV compared to SMC. We explored the safety of NPPV by identifying studies that reported AMI during or after NPPV initiation, compared to SMC. We found there was probably little or no difference in AMI incidence with NPPV. Subgroup analysis by NPPV type did not identify a difference between CPAP or bilevel NPPV studies. An important limitation of our AMI analysis was the inconsistent AMI definitions used across studies (e.g. ST elevation MI, ECG changes, biomarker positive, symptoms) and many studies only provided baseline AMI rates (Frontin 2011, L'Her 2004, Lin 1991, Lin 1995, Masip 2000, Räsänen 1985, Takeda 1997).

We were unable to perform an analysis of NPPV treatment intolerance compared to SMC in ACPE, due to the outcome not being reported. Furthermore, treatment failure which was reported had inconsistent definitions. Treatment failure data suggest that not all participants meeting treatment failure criteria were intubated. Possible reasons include changes to the underlying medical therapy, participant goals of care, and the difference between a quantitative description of failure based on vital signs and blood gas values and the clinical evaluation of treatment failure.

NPPV could reduce hospital and ICU length of stay for ACPE due to reduced ETI and avoidance of its complications (e.g. pneumonia and tracheal injury) (Gay 2009). Ideally, studies would have provided data on ICU or hospital-free days as participants who die early during the trial would have a short hospital or ICU length of stay, despite not benefiting from treatment. Unfortunately, hospital-free days were not reported. We are uncertain whether NPPV reduces hospital length of stay compared to SMC for ACPE. We found no subgroup differences between participants treated with CPAP or bilevel NPPV. In addition, we found no subgroup differences between studies comparing NPPV to SMC in the ER or ICU setting. Our subgroup analysis by baseline $PaCO_2$ indicated a significant difference between eucapnic and hypercapnic studies. However, given the very low quality of evidence we are uncertain whether NPPV reduces hospital length of stay in eucapnic people with ACPE. We were unable to pool ICU length-of-stay data due to significant heterogeneity. Based on the available data, we are uncertain whether NPPV reduces ICU length of stay.

We pooled mean blood pressure values obtained after one hour of therapy to identify differences between NPPV and SMC. In our comparison of NPPV to SMC in people with ACPE we found there is probably little or no difference between SBP, DBP, and MBP after one hour of therapy. These non-significant differences may represent a true lack of difference between therapies for reducing blood pressure, or the inability of mean blood pressure values to convey any potential benefit or harm with NPPV over SMC in individuals with significant hypertension or hypotension. Our analysis of mean respiratory rate data

after one hour of therapy with NPPV or SMC found that NPPV probably reduces the respiratory rate compared to SMC in ACPE. Furthermore, our analysis of PaO_2 after one hour of therapy demonstrated that NPPV may improve PaO_2 slightly compared to SMC. Finally, 16 adverse event types were reported in 11 studies. We found higher rates of face discomfort when using NPPV compared to SMC.

Overall completeness and applicability of evidence

Our objective in performing this systematic review and meta-analysis update was to evaluate the impact of new literature published since the last version of this review (May 2013, Vital 2013) on the safety and effectiveness of NPPV compared to SMC for ACPE. Furthermore, we have updated the protocol and conduct of the review to recently-revised Cochrane standards (Higgins 2018). We reassessed the literature and performed a new assessment for study eligibility, which identified 24 RCTs for inclusion. Of these, seven are new studies published since the last version of this review (Austin 2013; Ducros 2011; El-Refay 2016; Hao 2002; Li 2005; Moritz 2003; Zokaei 2016). Three newly-included studies are based on a reassessment of previously excluded studies (Hao 2002; Li 2005; Moritz 2003), which lacked extractable outcomes. The outcomes in these trials were measured on different time scales for our secondary outcomes: Li 2005 (PaO_2, respiratory rate), Hao 2002 (PaO_2, respiratory rate, SBP), and Moritz 2003 (SBP, DBP). Only Hao 2002 provided data on ETI as a primary outcome.

Importantly, we also excluded 15 studies that we had included in the previous version of this review but that no longer meet the revised inclusion criteria. For transparency, these were four quasi-randomised controlled trials (Bersten 1991; Moritz 2007; Sharon 2000; Weitz 2007), three studies conducted on an ineligible population (Bautin 2005; Delclaux 2000; Ferrer 2003) and eight studies which compared CPAP to bilevel NPPV without a SMC arm (Bellone 2004; Bellone 2005; Ferrari 2007; Ferrari 2010; Fontanella 2010; Liesching 2014; Martin-Bermudez 2002; Mehta 1997).

Overall, the evidence we identified was able to address our review objective. Studies that we identified focused on a single acute intervention (NPPV versus SMC) for people with ACPE provided during their hospital presentation. Our inclusion criteria for adults with ACPE were met. However, diagnosis of ACPE across studies was not standardised but based on a clinical assessment supported by clinical signs, chest x-ray, and exclusion of important alternative causes of dyspnoea (e.g. chronic obstructive pulmonary disease (COPD) and pneumonia). An important limitation of the studies we identified was the lack of baseline demographic data that could explain why certain recruited participants were at higher mortality risk than others (e.g. severe untreated valvular heart disease or AHA stage D heart failure). For example, the mortality rates reported by included studies were extremely disparate, ranging from 0 to 27.91% for NPPV (mean 9.64%) and 0 to 63.64% for SMC (mean 21.06%). These large variations in mortality may be influenced by the recruitment of ACPE participants with different underlying risks of mortality, regardless of their aggressive medical treatment with SMC or NPPV or both, and subtle differences in SMC between the different countries in which the included trials were performed.

Regarding the interventions under study, the trials included CPAP or bilevel NPPV or both, that had adjustable settings. We tried to ascertain whether the specific devices and pressure settings were reflective of contemporary practice. However, the NPPV device settings were not completely reported for all included trials. Where available, we have reported the mean inspiratory positive airway pressure (IPAP), expiratory positive airway pressure (EPAP), positive end-expiratory pressure (PEEP), and duration of NPPV used by each study (Table 1). For studies where this information was available, the devices and settings do reflect contemporary practice.

In addition, the ideal trial would have compared both forms of NPPV against SMC, given the possibility that CPAP versus bilevel NPPV may differ in their treatment efficacy. Only six of 24 included trials used a three-arm design. One such study (Gray 2008) was the largest RCT performed to date (N = 1069). The other five studies had smaller sample sizes (range 26 to 129; mean 73). The remaining studies compared one type of NPPV (bilevel NPPV or CPAP) against SMC. Subgroup analysis by type of NPPV did not reveal any significant differences for the primary or main secondary outcomes. Current ACPE treatment practices vary from targeting an oxygen saturation of greater than 92% by titration of FiO_2, initiation of NPPV, or endotracheal intubation (Ezekowitz 2017). Finally, we considered whether the SMC used in each trial reflected current treatment guidelines (Ezekowitz 2017; Ponikowski 2016). Such contemporary guidelines for acute heart failure recommend therapy with intravenous loop diuretics, supplemental oxygen, and nitrates, while maintaining an adequate blood pressure (Ezekowitz 2017; Ponikowski 2016). Our summary of the SMC used in each trial is listed in Table 2. All studies provided loop diuretics. However, the doses provided were unclear in nine studies. Nitrates were provided in all trials, but the form and dose was unclear in two studies. Similarly, each trial provided supplemental oxygen, but the specific FiO_2 used was unclear in two studies. In summary, the NPPV and SMC used by the included studies generally reflected contemporary clinical practice

Quality of the evidence

All outcomes were assessed according to GRADE recommendations (Guyatt 2008; Higgins 2017). For the main outcomes, evidence quality ranged from moderate (ETI, AMI), to low (hospital mortality, adverse events), to very low (hospital length of stay). Hospital mortality was assessed in 21 studies that compared NPPV versus SMC and included 2484 patients. Key methodological limitations of the meta-analysis include the clinical heterogeneity of included studies, such as variation in the aetiology of cardiogenic pulmonary oedema (e.g. myocardial ischaemia, severe valvular heart disease) and the lack of clinical context for each individual participant (e.g. home therapies, ACC/AHA heart failure grade). Additional limitations were the impracticality of blinding participants, personnel, and outcome assessment, given the nature of NPPV. Lack of blinding may have influenced objective outcomes (e.g. hospital mortality or ETI) because participants treated with SMC could potentially cross over to NPPV if they appeared to be clinically deteriorating, thereby attenuating the benefit of NPPV when using intention-to-treat analysis. Another limitation of the included studies was the unclear risk of selective reporting bias, as

reflected by the inconsistent reporting of outcomes. Finally, most studies recruited a low number of participants and their primary outcome was not hospital mortality. Interestingly, the well-powered study by Gray 2008 which had hospital mortality as a primary outcome did not detect a mortality difference between NPPV and SMC.

Our GRADE quality of evidence assessments for our primary outcomes were influenced by a number of factors, including risk of bias, imprecision, and inconsistency. Specifically, we rated the hospital mortality outcome as low quality, due to serious concerns with risks of bias and imprecision. We downgraded evidence quality by one level for risk of bias because most trials were rated as having unclear or high risk of bias for key domains, which included: randomisation sequence generation, allocation concealment, selective reporting bias, and other significant bias. We also downgraded this outcome for imprecision because there were few mortality events and the confidence interval included the appreciable benefit risk ratio of 0.75. The funnel plot for hospital mortality (Figure 4) was also asymmetrical, which suggests the presence of publication bias. However, we did not further downgrade the evidence for this outcome, as the asymmetry could be explained by the poor design of smaller studies included in our review, clinical heterogeneity, and sampling variation. Furthermore, the findings were consistent in a post hoc fixed-effect sensitivity analysis (Analysis 1.7; Sterne 2011).

We rated the quality of evidence for ETI as moderate. We downgraded this outcome by one level, due to serious concerns with risks of bias. Most trials that provided ETI evidence had unclear or high risk of bias for key domains, which included: randomisation sequence generation, allocation concealment, selective reporting bias, and other significant bias. Our ETI funnel plot (Figure 5) was symmetrical, which suggests the absence of graphical evidence of publication bias. For AMI, the quality of evidence was moderate. We downgraded the evidence by one level for serious concerns with imprecision. We downgraded for imprecision because few trials reported AMI events, the confidence interval crossed a risk ratio of 1, and the AMI definition varied between trials. We rated hospital length-of-stay evidence quality as very low, and downgraded it for the following reasons: serious risk of bias due to lack of blinding, visually heterogeneous data, and high imprecision with few participants and a confidence interval crossing a mean difference of 0. Our hospital length-of-stay funnel plot (Figure 6) was symmetrical and we therefore did not downgrade the evidence for publication bias. Adverse events evidence quality was low, and downgraded for the following reasons: serious risk of bias due to most studies having at least one domain at unclear or high risk of bias, and imprecision with wide confidence intervals crossing a risk ratio of 1 for many of the reported adverse events. For our secondary outcomes SBP, DBP, MBP, respiratory rate and PaO_2, the quality of evidence was moderate. We downgraded SBP, DBP, MBP, and respiratory rate evidence quality by one level for imprecision because the included studies had few participants and wide confidence intervals. We downgraded PaO_2 evidence quality by one level due to imprecision, because most trials had few participants and the confidence interval crossed a mean difference of 0. In summary, the quality of evidence was low or very low for most primary outcomes, except for ETI and AMI, which were moderate and have important clinical significance.

Potential biases in the review process

Our review is strengthened by using prespecified methods to reduce bias. We reduced bias in our search strategy by searching eight databases including clinical trial databases without language restrictions. After obtaining reference lists, we minimised bias through duplicate independent screening, duplicate data abstraction, and prespecified criteria for appraising methodological quality. In addition, the study protocol was established prospectively and followed the Cochrane format for systematic reviews (Higgins 2018; Jadad 2000; McKibbon 2004). Furthermore, two of our review authors (NB, FV) obtained additional data from study authors for outcomes incompletely described in their initial publication (Agmy 2008; Austin 2013; Crane 2004; Gray 2008; Kelly 2002; Masip 2000; Nava 2003; Park 2004; Räsänen 1985; Takeda 1998; Thys 2002). Our meta-analysis includes the largest number of trials exploring the role of NPPV compared to SMC in ACPE and had increased power in pooling outcomes compared to earlier reviews (Potts 2009; Weng 2010). We performed extensive analysis of the impact of NPPV on a broad range of clinically important outcomes and physiological parameters. Furthermore, our results were robust to the exclusion of studies with missing data. The generalisability of our findings is enhanced by the broad range of treatment locations and countries included, representing international experience with NPPV for ACPE.

The small number of events (e.g. mortality, ETI, AMI) within identified trials is one important limitation of our review and meta-analysis. Additionally, the underlying heterogeneity of included ACPE participants may have influenced our findings on hospital mortality and ETI. Several important prognostic factors were not clearly reported by trial investigators, such as the participants' underlying heart failure severity, compliance with guideline-appropriate home therapy, and presence of heart failure aetiologies requiring surgical interventions (e.g. severe valvular heart disease). Furthermore, there were slight variations in SMC among studies, which suggest that clinical heterogeneity may have influenced some of the treatment effects. Additionally, the definition of AMI was inconsistent across studies. Finally, intubation criteria were not standardised and variations in clinical practice could have influenced the observed differences in ETI.

Agreements and disagreements with other studies or reviews

The first systematic review on NPPV for ACPE included three trials and reported a significant reduction in ETI with CPAP compared to SMC (Pang 1998). Hess 2004 expressed concern about the use of NPPV for ACPE, due to greater AMI rates in two studies and no significant benefit for mortality or ETI. Nadar 2005 identified reduced ETI for CPAP compared to SMC with no significant mortality difference. Several meta-analyses have reported similar conclusions to our own (Collins 2006; Ho 2006; Masip 2005; Peter 2006; Weng 2010; Winck 2006), despite small differences in methodology. The results of previous systematic reviews were challenged by a large new RCT (Gray 2008), which found no significant differences in hospital mortality or ETI between CPAP, bilevel NPPV, and SMC. Important caveats within Gray 2008 include exclusion of people requiring an emergent intervention who could possibly benefit from NPPV, exclusion

of people with AMI undergoing an intervention, and cross-overs between treatment arms of 19.9% (SMC), 16.2% (CPAP), and 24.1% (bilevel NPPV) (Gray 2008). There was evidence in Gray 2008 that SMC cross-overs had more severe illness, and their cross-over to NPPV could have attenuated the benefit with NPPV compared to SMC. Nevertheless, as the largest single trial to date, Gray 2008 is an important trial in the meta-analysis and its results contrast with those of smaller included studies, which tend to show greater effect estimates favouring NPPV over SMC. The negative results of Gray 2008 make it imperative that we are cautious in interpreting the overall findings of our meta-analysis, which demonstrated that NPPV may reduce hospital mortality and probably reduces ETI when compared to SMC.

Our main findings are important and add support to current European heart failure guidelines (Ponikowski 2016). This guideline recommends that NPPV be considered and initiated promptly in people with ACPE presenting with tachypnoea (respiratory rate higher than 25 breaths a minute) and hypoxia (SpO$_2$ less than 90%). In contrast, our findings may challenge Canadian heart failure guidelines which recommend against routine use of NPPV in ACPE (Ezekowitz 2017). The Canadian heart failure guideline suggests starting with SMC and considering NPPV if there is persistent hypoxia (Ezekowitz 2017). Based on our findings, their recommendation may be too conservative. Furthermore, NPPV is a relatively benign intervention. The main harms that were evident in our review were increased mask discomfort compared to SMC. Overall, the results of our review suggest that people with ACPE may experience more benefits than harms from the addition of NPPV to SMC for ACPE.

Authors' conclusions

Implications for practice

Meta-analysis of the best available evidence for NPPV versus SMC to treat ACPE demonstrates that NPPV may reduce hospital mortality and probably reduces ETI. NPPV probably has little or no influence on rates of AMI compared to SMC. We are uncertain whether NPPV reduces hospital length of stay compared to SMC. When considering the type of NPPV, the included studies demonstrated no significant differences between CPAP or bilevel NPPV compared to SMC. Thus, it is reasonable to consider the initiation of NPPV in people with ACPE who are already receiving optimal SMC. Limitations in the current evidence did not allow us to identify patient subgroups (e.g., eucapnic people or people treated in the ER or ICU) that derived more (or less) benefit from the initiation of NPPV.

Implications for research

Current evidence has allowed us to draw conclusions about the efficacy of NPPV (versus SMC) for treating ACPE. Nevertheless, certain shortcomings of the included studies have left some clinical questions unanswered. First, the optimal dosing of diuretics as part of SMC was not clear within the included studies. It is possible that the benefits of NPPV identified herein may be different (e.g. reduced or null), based on the clinical experience of a clinician providing SMC for ACPE. Second, it remains to be seen if certain types of people with ACPE (e.g. those with more severe ACC/AHA heart failure grade) would derive more benefit from the initiation of NPPV (in addition to SMC). Future studies should be judicious about explicitly defining intubation criteria, characterising the aetiology of ACPE, the underlying severity of heart failure, and guideline adherence for home heart-failure therapies prior to admission. Finally, individual patient-level data for blood gases with prespecified subgroups for hypercapnia or eucapnia can better characterise whether NPPV influences clinically important outcomes to a greater degree in people with hypercapnia compared to eucapnia.

Acknowledgements

Contributions of authors

Nicolas Berbenetz proposed the systematic review update, updated the methods, performed study selection, data extraction, 'Risk of bias' assessment, GRADE quality assessment, co-ordinated the research team, and prepared and updated the review manuscript.

Yongjun Wang assisted with the review update, data extraction, 'Risk of bias' assessment, GRADE quality assessment, and reviewed the final manuscript.

Matthew Chong assisted with the review update, updated the methods, performed study selection, assisted in co-ordination of the research team, GRADE quality assessment, provided guidance with manuscript preparation, and edited the final manuscript.

Flávia Vital was involved as the lead author of the previous version of this review. She provided her correspondence with authors for unpublished findings.

Charlotte Godfrey assisted with data extraction and reviewed the final manuscript.
Mahmood Ahmad proposed the systematic review update, assisted with data extraction, and reviewed the final manuscript.
James Brown, Pier Lambiase, Amitava Banerjee, and Ameet Bakhai reviewed the final manuscript.

Declarations of interest

Nicolas Berbenetz: none known

Yongjun Wang: none known

James Brown: none known

Charlotte Godfrey: none known

Mahmood Ahmad: none known

Flávia Vital: none known

Pier Lambiase: receives speaker fees and educational grant funding from Boston Scientific, and educational grant funding from Medtronic for work unrelated to the content of this Cochrane review.

Amitava Banerjee: none known

Ameet Bakhai: is employed within the NHS and also advises third sector companies (pharma, device, diagnostics, digital and AI) on trial design, economic models, technology adoption and acts as lecturer for cardiovascular topics. As research director, he also recruits to trials and supports research partnership work for his NHS employer, which attracts commercial research recruitment funding. There are no direct conflicts to the work presented however.

Matthew Chong: none known

Differences between protocol and review

In the previous version of this review (Vital 2013), we stated that acute myocardial infarction (AMI) was an outcome during and after intervention. In this update, we have combined these outcomes, because treatment with SMC or NPPV was not reported in a manner which allowed us to make causal determinations on when AMI occurred relative to the trial intervention (e.g. AMI during or after intervention was not specified). We were unable to include a subgroup analysis comparing AMI at trial inclusion or after NPPV, as the data were not reported consistently. Multiple vital signs were reported as outcomes in the original version of this review. For this update, we have focused on the most clinically relevant outcomes: systolic blood pressure, diastolic blood pressure, and mean blood pressure, which could be a contra-indication to starting NPPV therapy if too low, and could be expected to decrease with NPPV. Other vital signs such as heart rate are not useful compared to more objective markers of respiratory status such as respiratory rate and PaO_2, which we have retained as outcomes. We did not perform a subgroup analysis of adverse events by study publication year before or after 2000. W did perform this analysis in the previous version of this review, but were unable to find a significant change in SMC or NPPV delivery which justified separating studies by any publication year.

Differences between review version from 2013 and this update

There has been a change in the authorship team since the last version of this review in 2013 (Vital 2013). In assuming authorship of this review, we have rerun searches of all databases outlined in the Methods section since 2013. We have also reassessed the inclusion criteria and risks of bias for all trials previously included. For data collection we have included means and standard deviations where available, if an outcome was reported as a median we have approximated it as being equivalent to the mean. We also converted standard error or interquartile ranges to standard deviations using formulae outlined in the *Cochrane Handbook* (Higgins 2011). In the previous version of this review we included quasi-randomised controlled trials. We defined quasi-randomised controlled trials as those where the allocation procedure was unlikely to be adequately randomised (e.g. randomisation according to odd or even numbers, day of the week, social security number, or medical record number). For this update, we have not included these studies, in order to use the highest level of evidence possible to guide the conclusions of our review.

Vital 2013 included studies comparing bilevel NPPV to CPAP without an additional standard medical therapy arm. In this update, we only include studies which compared bilevel NPPV or CPAP or both to standard medical care. These changes led to the inclusion of seven new studies and the exclusion of 15 previously included studies. Please see Included studies and Excluded studies for additional details.

The last authorship team (Vital 2013) performed a grey literature search by contacting authors of included articles for any additional articles on NPPV compared to SMC. We found all previously identified studies using our updated search strategy. In addition, we were able to identify seven new studies. We therefore did not repeat the grey literature search outside of the explicit databases named in our search strategy.

Published notes

Characteristics of studies

Characteristics of included studies

Agmy 2008

Methods	Single-centre randomised controlled trial, parallel design, unblinded, using ITT approach. No participants were lost to follow-up **Setting**: RICU or CCU **Country:** Egypt **Funding:** Assiut University **Study dates**: not reported **Conflicts of interest:** not reported
Participants	129 people with mean age 67 ± 4.8 (CPAP arm 66 ± 6.9, bilevel arm 68 ± 3.8, and SMC 69 ± 5.8). ACPE causes: systolic (N = 37), diastolic (N = 40) or valvular heart failure (N = 52) **Excluded**: immediate need for endotracheal intubation, acute MI, pneumothorax, contraindications to NPPV, severe renal failure, ventricular arrhythmias
Interventions	CPAP group (N = 44). Face mask interface. PEEP 5cm H_2O and titrated as tolerated. Bilevel NPPV group. IPAP 8 - 10 cm H_2O and EPAP 2 - 4cm H_2O increased as tolerated Control group (N = 41): standard medical care and oxygen mask (high-flow facemask - 60%) Co-intervention: morphine, diuretics, ACE and nitrates
Outcomes	1. Primary outcome: Endotracheal intubation rate 2. Mortality 3. Arterial blood gases (PaO_2, $PaCO_2$, pH) 4. Vital signs (RR, BP, HR) 5. Length of hospital stay 6. Length of ICU stay 7. Intrapulmonary shunt 8. A-a oxygen gradient 9. Cardiac output 10. Intolerance
Notes	Trial available in abstract form only. Additional data from personal communication.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias)	High risk	ClinicalTrials.gov "masking: none (Open label)"
Blinding of outcome assessment (detection bias)	Unclear risk	No details provided
Incomplete outcome data (attrition bias)	Low risk	No participants were lost to follow-up (personal communication)
Selective reporting (reporting bias)	High risk	Registered at ClinicalTrials.gov NCT00912158, unclear if prospectively. No data provided on duration of NPPV and mean settings. Outcomes reported as a personal communication
Other bias	High risk	Data discrepancy between personal communication and ClinicalTrials.gov entry for CPAP group intubation events

Austin 2013

Methods	Single-centre, parallel-group design, and unblinded RCT **Setting**: pre-hospital/Emergency Department **Country:** Tasmania, Australia Prospectively registered with ANZCTR. **Funding:** National Health and Medical Research Council, Ambulance Tasmania **Study dates**: July 2009 to July 2010 **Conflict of interest**: not reported
Participants	50 adults with ACPE, with mean age 79.8 ± 11.9 (control group 78.3 ± 11.8, CPAP group 81.5 ± 11.9) Pre-hospital setting with diagnosis of severe ACPE requiring ventilatory assistance. 2 independent physicians blinded to group allocation retrospectively reviewed randomised participant records to confirm they met the diagnostic criteria for severe ACPE (crackles on auscultation, acute onset shortness of breath and hypoxia requiring assisted ventilation) **Exclusion criteria**: other respiratory conditions (asthma, COPD), people with respiratory or cardiac arrest or with GCS < 12 or systolic BP < 90
Interventions	CPAP and standard medical therapy (N = 26). CPAP setting 10 cm H_2O delivered by "Whisperflow" Standard medical therapy (N = 24): nitrates, furosemide 40 mg IV if transit time > 20 minutes, high-flow oxygen 8 - 15 L per minute
Outcomes	1. Primary outcome: pre-hospital mortality, in-hospital mortality 2. Endotracheal intubation rate 3. Requirement for ICU admission 4. Vital signs (BP, RR, oxygen saturation, HR, GCS)
Notes	Trial available in abstract form only. Additional data from personal communication 19 January 2018

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated numbers
Allocation concealment (selection bias)	Low risk	Numbers placed on cards within sealed, sequentially-numbered opaque envelopes and placed with ventilation equipment
Blinding of participants and personnel (performance bias)	High risk	Masking not used
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessed by blinded physicians
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Prospectively registered with ANZCTR: ACTRN12609000410257. All prespecified outcomes were provided in a personal communication
Other bias	Low risk	The study appears to be free of other sources of bias

Crane 2004

Methods	Multicentre, parallel design, unblinded RCT conducted at 2 university hospitals. Used an ITT approach. No reported loss to follow-up. Participants or next-of-kin were aware through informed consent, but in 17 cases, the participant gave verbal consent Diagnosis of myocardial infarction if during 3 days after admission there were ECG changes or a CK rise (> 280) **Setting**: Emergency Department **Country:** United Kingdom **Funding:** ResMed, Abingdon, UK **Study dates:** May 2000 and September 2001 **Conflict of interest**: not reported
Participants	60 adults (23 men and 37 women) with mean age 75.1 ± 10.5 (74.6 ± 11.1 years in SMC group, 74.9 ± 12.2 in CPAP group and 76 ± 8.4 in bilevel group) **Inclusion criteria**: RR > 23 breaths a minute, diagnosis consistent with pulmonary oedema, pH < 7.35, widespread pulmonary crepitations and diaphoresis. History: HF, IHD, diabetes mellitus, hypertension, COPD **Exclusion criteria**: Hypotension (systolic BP < 90 mmHg), temperature > 38 °C, requiring thrombolysis for myocardial infarction or dialysis for renal impairment, people with impaired consciousness or with dementia
Interventions	CPAP group (N = 20): PEEP = 10 cmH$_2$O Bilevel group (N = 20): EPAP = 5 cmH$_2$O; IPAP= 15 cmH$_2$O Control group (N = 20): SMC and O$_2$ mask (to maintain SaO$_2$ > 90%); mask: full-face Co-interventions: furosemide, nitrates and diamorphine (without restriction)
Outcomes	1. Primary outcome: treatment success (RR < 23 a minute, SpO$_2$ > 90%, arterial pH > 7.35 after 2 hours of treatment) 2. Mortality 3. Endotracheal intubation rate 4. Arterial blood gases (PaO$_2$, PaCO$_2$, pH) 5. Vital signs (RR, BP, HR) 6. Incidence of acute myocardial infarction (follow-up) 7. Participant compliance 8. Treatment failure 9. Side effects
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation sequence was generated using random numbers produced by Microsoft Excel
Allocation concealment (selection bias)	Low risk	Assignments were concealed in an opaque envelope, which was then further concealed within another
Blinding of participants and personnel (performance bias)	High risk	Impossible to mask treatment allocation
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Low risk	All enrolled participants were accounted for
Selective reporting (reporting bias)	Unclear risk	Study was not prospectively registered in a trial registry. The primary outcome of treatment success was not a standard outcome used in similar trials, but includes secondary outcomes which could be used in the meta-analysis
Other bias	Unclear risk	No power calculation to explain the sample size used for the trial

Ducros 2011

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation sequence was generated using random numbers produced by Microsoft Excel

Methods	Multicentre, parallel-group, unblinded RCT conducted in the pre-hospital setting followed ITT analysis. Pre-hospital setting included mobile ICU/emergency medical services including a physician and a nurse. 2 a priori defined subgroups: hypercapnic status and left ventricular ejection fraction
	Setting: Pre-hospital setting mobile ICU and later transferred to cardiac ICU
	Country: Paris, France
	Funding: French Ministry of Health, Laurent Ducros conducted non-invasive ventilation training sessions funded by Respironics Philips France
	Study dates: October 2004 and October 2007
	Conflict of interest: Yes. Laurent Ducros conducted NIV training sessions funded by Respironics Philips France
Participants	207 people with ACPE were recruited. Mean age 80.5 ± 10.1 (81 ± 9 in control group, 80 ± 11 in CPAP group)
	Inclusion criteria: ACPE symptoms including: orthopnoea, diffuse crackles (Killip score ? III), RR > 25 a minute, and SpO_2 < 90% on room air
	Exclusion criteria: History of COPD, asthma, severe stenotic valve disease, immediate indication for intubation (severe impairment of consciousness, bradypnoea), cardiovascular collapse or suspicion of ST segment elevation acute coronary syndrome
Interventions	Pre-hospital applied CPAP with standard therapy or standard therapy alone
	CPAP group (N = 107): 2.5 to 10 cm H_2O provided by "Whisperflow" and delivered using a face mask
	Control group (N = 100): co-intervention only
	Co-interventions: lasix 40 mg - 120 mg IV or 1 - 3 mg bumetanide, nitroglycerin (1 mg per 3 min) and a continuous intravenous infusion unless systolic BP < 110 mmHg; supplemental oxygen 15 L per minute
Outcomes	1. Primary combined outcome: death, endotracheal intubation, persistence of all inclusion criteria or circulatory failure in hospital or reappearance in hospital during first 48 hours 2. Brain natriuretic factor value 3. Hospital mortality 4. Persistence of inclusion criteria 5. Acute MI rate 6. Adverse effects
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Did not describe the method, but indicated that randomisation was stratified using permuted block randomisation
Allocation concealment (selection bias)	Unclear risk	Used "sealed numbered envelopes kept in each ambulance and opened on-scene"
Blinding of participants and personnel (performance bias)	High risk	ClinicalTrials.gov: "Masking: None (Open Label)"
Blinding of outcome assessment (detection bias)	Low risk	Independent Critical Event Validation Committee assessed the endpoint
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data
Selective reporting (reporting bias)	High risk	Prospectively registered at ClinicalTrials.gov: NCT00554580. Acute MI rate is not reported, provide a median troponin for control and CPAP groups, which cannot be included in meta-analysis
Other bias	High risk	Premature termination due to poor recruitment

El-Refay 2016

Methods	Single-centre, parallel-group design, single-blind RCT. Analysis was per protocol as participants were excluded from analysis after randomisation due to not tolerating CPAP or bilevel NPPV. 2 participants in the CPAP group and 1 participant in the bilevel NPPV group did not tolerate therapy and were excluded from analysis. Informed consent obtained from the participant or their next-of-kin.
	Setting: Emergency Department
	Country: Giza, Egypt
	Funding: Not reported
	Study dates: May 2007 to November 2008
	Conflict of interest: not reported
Participants	66 participants analysed from 69 randomised. 3 participants did not tolerate NPPV and were excluded. Included 27 men and 39 women, with mean age 57.3 ± 5.6 (57 ± 5.3 in the control group, 58.4 ± 6.5 in the CPAP group, and 56.6 ± 5.1 in the bilevel group)
	Inclusion criteria: severe dyspnoea, bilateral rales on auscultation, and typical findings of congestion on chest radiography without evidence of pulmonary aspiration or pneumonia. Additional parameters: RR ? 30/min, PaO_2 ? 80 mmHg, $PaCO_2$? 45 mmHg
	Exclusion criteria: systolic BP ? 90 mmHg, requirement for percutaneous coronary intervention, COPD, life-threatening arrhythmia, acute MI or unstable angina, facial trauma, oesophageal or gastric surgery, gastrointestinal bleeding, pregnant
Interventions	CPAP group (N = 21): PEEP 10 cm H_2O
	BILEVEL group (N = 22). IPAP 15 cm H_2O and EPAP 10 cm H_2O
	Control group (N = 23): SMC + O_2 facemask (FiO_2 ? 50%)
	Co-intervention: supplemental oxygen up to 15 L per minute, nitroglycerine 0.4 mg SL if systolic BP > 100 mmHg, furosemide 40 mg IV repeated as required, morphine sulphate 2 mg IV repeated once if needed. Dopamine sulphate for hypotension if required
Outcomes	1. Primary endpoint: blood gases ($PaCO_2$, PaO_2, SaO_2, pH, bicarbonate concentration). Collected at entry, after 1 hour of therapy and 30 minutes of therapy discontinuation 2. Physiologic parameters (HR, RR, systolic BP, diastolic BP). Collected at entry, after 1 hour of therapy and 30 minutes of therapy discontinuation 3. Adverse events
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Did not describe the method of randomisation
Allocation concealment (selection bias)	Unclear risk	Used opaque envelopes which were concealed within another opaque envelope
Blinding of participants and personnel (performance bias)	High risk	Single-blinded, once enrolled impossible to mask treatment allocation
Blinding of outcome assessment (detection bias)	Low risk	Blinded laboratory investigators analysed samples.
Incomplete outcome data (attrition bias)	High risk	As-treated analysis performed, missing outcome data for exclusions after randomisation
Selective reporting (reporting bias)	Unclear risk	Study was not prospectively registered. Unclear if all expected outcomes were reported
Other bias	High risk	Figures do not provide a standard deviation, only a mean value

Frontin 2011

Methods	Single-centre, parallel-group, unblinded RCT, analysed using ITT approach. 2 participants (in the CPAP group) refused the ongoing use of their data once their condition stabilised and were not analysed. Informed consent was obtained from participants or their surrogates
	Setting: Pre-hospital care provided by "Service d'Aide Médicale Urgente" (SAMU) and continued in the ICU **Country:** Touslouse, France
	Funding: University Hospital of Toulouse
	Study dates: September 2006 to March 2008
	Conflict of interest: None
Participants	124 patients randomised, 122 analysed (52 men and 70 women), with mean age 79.4 ± 10.6 (79.3 ± 10.5 years in SMC group, 79.4 ± 10.7 in CPAP group)
	Inclusion criteria: 18 years or older with clinical symptoms of ACPE such as orthopnoea, diffuse crackles without evidence of pulmonary aspiration or infection, pulse oximetry (SpO_2) < 90% and a RR > 25 breaths a minute
	Exclusion criteria: Cardiovascular collapse or an impaired level of consciousness, AMI, or if they had an immediate need for intubation. People with a history of gastric surgery (< 8 days) and people vomiting
Interventions	CPAP group (N = 60): PEEP of 10 cm H_2O Control group (N = 62): SMC and oxygen facemask Co-intervention: furosemide 1mg/kg, morphine pre-hospital, isosorbide dinitrate infusion at 2 mg an hour (range, 3 - 5 mg an hour) in both groups
Outcomes	1. Primary outcome: treatment success defined, a priori, as all of RR < 25 breaths a minute and oxygen saturation > 90% at the end of the 1-hour study 2. Vital signs (RR, BP, HR) 3. Dyspnoea 4. Endotracheal intubation rate 5. Mortality at 5 and 30 days 6. Arterial blood gases (PaO_2, $PaCO_2$) 7. Adverse events 8. Length of hospital stay
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers determined the randomisation sequence
Allocation concealment (selection bias)	Low risk	Group assignments were sealed in opaque envelopes and opened sequentially by the SAMU dispatcher who then randomly assigned the participant to 1 of 2 treatment groups
Blinding of participants and personnel (performance bias)	High risk	Not blinded
Blinding of outcome assessment (detection bias)	Unclear risk	Investigator was blinded
Incomplete outcome data (attrition bias)	Low risk	All enrolled participants were accounted for
Selective reporting (reporting bias)	Low risk	Prospectively registered at ClinicalTrials.gov: NCT00439075. Outcomes that are of interest in the review have been reported in the prespecified manner
Other bias	Low risk	The study appears to be free of other sources of bias

Gray 2008

Methods	Multicentre, prospective, parallel-group, unblinded RCT. No ITT analysis, as participants not included despite being randomised. Included 3 treatment groups: standard oxygen therapy, CPAP, and bilevel NPPV. Participants were randomly assigned in a 1:1:1 ratio with the use of a 24-hour telephone randomisation service. The randomisation sequence was stratified according to centre, with variable block length. 87 participants were excluded after randomisation because of ineligibility or previous recruitment into the trial. Informed written or witnessed oral consent was obtained from the participant or relative
	Setting: Emergency Department
	Country: United Kingdom
	Funding: National Institute for Health Research
	Study dates: July 2003 to April 2007
	Conflict of interest: None
Participants	1069 participants, 56.9% female and mean age 77.7 ± 9.7 years (79 ± 9 years in SMC group), pulmonary oedema shown by a chest radiograph, RR > 20, and an arterial hydrogen ion concentration of > 45 nanomoles per litre (pH < 7.35)
	Exclusion criteria: requirement for emergency intervention, such as primary percutaneous coronary intervention; inability to give consent; or previous recruitment into the trial
Interventions	CPAP group (N = 346): PEEP = 10 ± 4 cm H_2O. Time = 2.2 ± 1.5 hours. CPAP was delivered using a face mask Bilevel NPPV group (N = 356): EPAP = 7 ± 3 cm H_2O and IPAP= 14 ± 5 cm H_2O. Time = 2.0 ± 1.3 hours. Bilevel NPPV was delivered using a face mask Control group (N = 367): SMC and O_2 mask with a reservoir Co-intervention: nitrates, diuretics and opioids
Outcomes	1. Primary outcome: 7-day mortality 2. Primary outcome: 7-day tracheal intubation rate 3. 30-day mortality 4. Arterial blood gases (PaO_2, $PaCO_2$, pH) 5. Vital signs (RR, BP, HR) 6. Incidence of acute myocardial infarction 7. Compliance of participants with NPPV 8. Side effects and complications 9. Length of hospital stay
Notes	Note: additional data were obtained from the authors through a personal communication on the following dates: 3 April 2018, 24 September 2018, 11 October 2018

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation sequence was generated by an independent statistician
Allocation concealment (selection bias)	Low risk	24-hour telephone randomisation service
Blinding of participants and personnel (performance bias)	High risk	Open study
Blinding of outcome assessment (detection bias)	High risk	Open study
Incomplete outcome data (attrition bias)	Low risk	All enrolled participants were accounted for
Selective reporting (reporting bias)	Low risk	Prospectively registered with ISRCTN: ISRCTN07448447. All of the prespecified outcomes have been reported adequately
Other bias	Low risk	The study appears to be free of other sources of bias

Hao 2002

Methods	Single-centre, parallel-group RCT. No details reported on ITT analysis, loss to follow-up, or informed consent **Setting:** not reported **Country**: China **Funding**: not reported **Study dates**: January 1991 to December 1995 **Conflict of interest**: not reported
Participants	51 participants. Mean age 68 ± 6 (CPAP arm 68 ± 7, control arm 67 ± 5) **Inclusion criteria:** ACPE defined by: 1) clinical signs of severe dyspnoea such as tripoding, intercostal muscle use, and sternal notch retraction; 2) RR > 25/min; 3) PaO_2 < 8.0 kPa on room air **Exclusion criteria**: 1) Change in level of consciousness; 2) Excessive airway secretions that cause airway obstruction; 3) COPD; 4) Severe shock, valvular stenosis, cardiopulmonary arrest; 5) Severe pulmonary infection
Interventions	CPAP group (N = 25): nasal mask with ventilator (Siemens 900 c ventilator). CPAP settings were 6 to 10 cm H_2O, FiO_2 45% Control group (N = 26): oxygen delivered by nasal prongs Co-intervention: IV diuretics (20 - 40 mg), morphine 2 mg, buccal nitroglycerin 0.5 mg or IV 1 mg (0.2 - 0.4 mg if no angina)
Outcomes	1. Treatment effectiveness rate (mix of dyspnoea, tripoding, intercostal muscle use, and resolution of sternal notch retraction, resolution of pulmonary adventitious sounds) 2. Vital signs (HR, BP, RR) 3. Arterial blood gas (pH, PaO_2, $PaCO_2$) monitored pre-treatment and after 30 minutes of therapy 4. Intubation rate
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias)	Unclear risk	No details provided
Blinding of outcome assessment (detection bias)	Unclear risk	No details provided
Incomplete outcome data (attrition bias)	Unclear risk	No details provided
Selective reporting (reporting bias)	Unclear risk	No details provided
Other bias	High risk	This study provides insufficient detail to evaluate the type of patients included, therapy provided, and efficacy of the therapy provided

Kelly 2002

Methods	Single-centre, parallel-group RCT. Used ITT analysis. No participants were lost to follow-up. Informed consent was obtained from participants.
	Setting: Emergency Department and continued in the high-dependency unit
	Country: United Kingdom
	Funding: San Diego Foundation
	Study dates: not reported
	Conflict of interest: not reported
Participants	58 participants (26 men and 32 women), with mean age 78 ± 2 (78 ± 2 years in the control group and 77 ± 2 in the CPAP group)
	Inclusion criteria: Acute onset of breathlessness, RR > 20 a minute, bilateral basal crackles or chest auscultation, presentation typical of pulmonary oedema. Causes: left ventricular systolic dysfunction and hypertensive crisis; the CPAP group had more severe disease with a slightly greater acidosis and hypercapnia
	Exclusion criteria: People with radiograph consistent with pneumonia or pneumothorax, or if they had received pre-hospital treatment with intervention other than oxygen, diuretics or opiates
Interventions	CPAP group (N = 27): PEEP = 7.5 cm H_2O. Time = minimum of 6 hours Control group (N = 31): SMC and oxygen full-face mask. (FiO_2 = 60%) Co-intervention: furosemide, morphine sulphate, nitrate
Outcomes	1. Primary outcome: Treatment failure 2. Mortality 3. Endotracheal intubation rate 4. Arterial blood gases (PaO_2, $PaCO_2$) 5. Vital signs (RR, BP, HR) 6. Incidence of acute myocardial infarction at admission 7. Side effects 8. Dropouts/withdrawals 9. Length of hospital stay
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes
Blinding of participants and personnel (performance bias)	Unclear risk	Not described
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Low risk	All enrolled participants were accounted for
Selective reporting (reporting bias)	Unclear risk	Trial protocol was not prospectively registered. Unclear if all expected outcomes are reported
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists. No power calculation to explain the sample size used for the trial

L'Her 2004

Bias	Authors' judgement	Support for judgement

Methods	Multicentre, parallel-group, unblinded RCT conducted in 3 teaching hospitals. Analsyis completed using ITT approach. No participants were lost to follow-up. Participants or their next of kin provided informed consent
	Setting: Emergency Department
	Country: France
	Funding: Technical support (material and ventilatory circuits) was provided by Allegiance SA (Paris, France)
	Study dates: not reported
	Conflict of interest: not reported
Participants	89 participants (37 men and 52 women), with mean age 84 ± 6 (84 ± 6 years in both SMC and CPAP groups)
	Inclusion criteria: Age similar or > 75 years, acute hypoxaemic respiratory failure (PaO_2/FiO_2 < 300 despite O_2 > 8 L a minute for 15 minutes), RR > 25, contraction of accessory muscles, clinical examination: systolic and/or diastolic hypertension, widespread crackles or wheezing; medical record: previous cardiomyopathy, and/or acute dyspnoea with progressive orthopnoea; electrocardiographic tracing (Q waves and/or abnormalities in the T wave and ST segment; left ventricular hypertrophy, bundle branch block, atrial fibrillation); and chest radiography (cardiac enlargement with a cardiothoracic ratio > 50%, and/or pulmonary congestion with Kerley B lines, alveolar filing, pleural effusions) compatible with a diagnosis of cardiogenic pulmonary oedema. Causes: tachyarrhythmia, acute IHD, hypertensive crises, respiratory tract infection, undiagnosed
	Exclusion criteria: GCS ? 7, SpO_2 ? 85% despite oxygen, haemodynamic instability, chronic respiratory insufficiency
Interventions	CPAP group (N = 43): PEEP = 7.5 cm H_2O. Time = 8 ± 6 hours Control group (N = 46): SMC with oxygen facemask Co-intervention: furosemide, nitroglycerin, glyceryl-trinitrate, morphine, isosorbide dinitrate
Outcomes	1. Primary outcome: 48-hour mortality 2. Endotracheal intubation rate 3. Arterial blood gases ($PaCO_2$, pH) 4. Vital signs (RR, BP, HR) 5. Treatment failure 6. Side effects 7. Droupouts/withdrawals 8. Length of hospital stay 9. Compliance of participant
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation protocol was computer-generated and equalised in groups of 10 participants
Allocation concealment (selection bias)	Low risk	Assigned using a phone call to a randomisation centre
Blinding of participants and personnel (performance bias)	High risk	Not possible
Blinding of outcome assessment (detection bias)	High risk	Not possible
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	Trial protocol was not prospectively registered. Unclear if all prespecified outcomes are reported
Other bias	High risk	Early termination after performing an interim analysis (not pre-specified) and detecting improved survival with CPAP.

Levitt 2001

Methods	Single-centre, parallel-group, RCT. No ITT analysis. 4 participants were lost to follow-up. Informed consent was obtained from the participants. **Setting**: Emergency Department **Country:** USA **Funding:** not reported **Study dates:** December 1995 to June 1997 **Conflict of interest:** not reported
Participants	38 participants. 42 people were randomised, but 4 did not meet inclusion criteria following randomisation. Therefore, at study entry 38 participants (13 men and 25 women), with mean age 67.9 ± 14.8 (68.5 ± 15 years in SMC group and 67.4 ± 15 in bilevel group) **Inclusion criteria**: Tachypnoea, RR > 30 breaths a minute, diaphoresis or accessory muscle use, pulmonary rales, distended neck veins, peripheral oedema, history of congestive heart failure and radiographic findings of pulmonary oedema. Causes: acute congestive heart failure. **Exclusion criteria**: People with a radiograph not consistent with congestive heart failure or required immediate intubation
Interventions	Bilevel group (N = 21): started with EPAP of 3 cm H_2O and IPAP of 8 cm H_2O. These pressures could be adjusted in 2 cm H_2O increments. Time = 2 hours. Bilevel NPPV was mostly delivered by facemask, but switching to nasal mask was permitted for participant comfort Control group (N = 17): SMC and oxygen nasal or facemask Co-intervention: morphine, furosemide, nitroglycerin
Outcomes	1. Primary outcome: endotracheal intubation rate 2. Mortality 3. Treatment failure 4. Incidence of acute myocardial infarction (follow-up) 5. Length of hospital stay 6. Vital signs (RR, BP, HR) 7. Pulse oximetry 8. Arterial blood gases ($PaCO_2$, pH)
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised from a previously computer-generated list
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias)	Unclear risk	Details not provided
Blinding of outcome assessment (detection bias)	Unclear risk	Details not provided
Incomplete outcome data (attrition bias)	Unclear risk	Insufficient information provided
Selective reporting (reporting bias)	Unclear risk	Trial protocol was not prospectively registered. Unclear if all expected outcomes were reported
Other bias	High risk	Early termination after author became aware of study by Mehta et al. and wanted to present preliminary findings: no increased rate in acute myocardial infarction rates.

Li 2005

Methods	Single-entre, parallel-group RCT. No details reported about ITT analysis, study location, loss to follow-up, or informed consent
	Setting: not reported
	Country: China
	Funding: not reported
	Study dates: January 2001 to October 2004
	Conflict of interest: not reported
Participants	42 participants. Mean age 71.7 (range 60 - 82) in the NPPV arm; and mean age was 69.9 (range 60 - 82) in the control therapy arm
	Inclusion criteria: acute cardiogenic pulmonary oedema. **Exclusion criteria**: not provided.
Interventions	CPAP group (N = 22): ventilator (Servo 300A or NPB 7200A) in PSV and PEEP ventilation mode. PSV at 10 cm H_2O and gradually increased to 15 - 18 cm H_2O within 15 minutes. PEEP was started at 2 to 3 cm H_2O, then gradually increased to between 5 and 8 cm H_2O. FiO_2 was 60%
	Control group: Oxygen delivered by mask
	Co-intervention: vasodilators, diuretics, cardiotonic, and sedative
Outcomes	1. Treatment efficacy (dyspnoea, difficulty breathing, lip cyanosis, adventitious sound reduction, or pinky frothy sputum reduction)
	2. Arterial blood gas indicators (pH, PaO_2, $PaCO_2$) monitored pre-treatment, 2 hours post-treatment, and 24 hours post-treatment
	3. Vital signs: HR and RR
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias)	Unclear risk	No details provided
Blinding of outcome assessment (detection bias)	Unclear risk	No details provided
Incomplete outcome data (attrition bias)	Unclear risk	No details provided
Selective reporting (reporting bias)	Unclear risk	No details provided
Other bias	High risk	This study provides insufficient detail to evaluate the type of participants included, therapy provided, and efficacy of therapy provided

Lin 1991

Methods	Single-centre, parallel-design, unblinded RCT. There was no ITT analysis of results. 15 participants in the CPAP group and 10 in the oxygen group were lost to follow-up. Informed consent was obtained
	Setting: ICU; Wash-out of 30 minutes
	Country: Taiwan
	Funding: not reported
	Study dates: January 1, 1985 to January 31, 1987
	Conflict of interest: not reported
Participants	55 participants. 80 people were randomised, but 25 did not meet inclusion criteria following randomisation. Therefore, at study entry 55 participants (50 men and 5 women), with mean age 73.8 ± 8.5 (74.1 ± 8.8 years in SMC group and 73.4 ± 8.2 in CPAP group)
	Inclusion criteria: Radiologic evidence of acute interstitial or alveolar oedema of cardiac origin, tachypnoea, RR > 22 a minute, intercostal or suprasternal retractions, $PaO_2/FiO_2 > 200$, P(A-a) $O_2 > 200$
	Causes: congestive heart failure, dilated cardiomyopathy, Ischaemic heart disease, hypertensive cardiovascular disease, acute myocardial infarction
	Exclusion criteria: People unresponsive to speech or unable to maintain a patent airway and who had cardiogenic shock, signs of lung infection, evidence of pulmonary embolism, chronic lung disease with carbon dioxide retention at rest
Interventions	CPAP group (N = 25): PEEP average 3.75 ± 1.76 cm H_2O in first hour (pressure was applied by connecting a serial CPAP valve of 2.5 cm H_2O, 5 cm H_2O, 7.5 cm H_2O, 10 cm H_2O, 12.5 cm H_2O - to the face mask at each 30-minute interval. Time = 6 hours Control group (N = 30): SMC and oxygen facemask Co-intervention: medical treatment of pulmonary oedema was not restricted
Outcomes	1. Primary outcome: endotracheal intubation rate 2. Mortality 3. Arterial blood gases (PaO_2, $PaCO_2$, pH) 4. Vital signs (RR, BP, HR) 5. Dropouts/withdrawals 6. Treatment failure
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method used was not reported
Allocation concealment (selection bias)	Unclear risk	The method used was not reported
Blinding of participants and personnel (performance bias)	High risk	Not possible
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	High risk	Proportion of missing outcome data, only 20 participants from each group of 40 completed the protocol, compared to the observed event risk is enough to induce clinically relevant bias in the intervention effect estimate. Did not adhere to ITT principle, used as-treated analysis
Selective reporting (reporting bias)	Unclear risk	Trial protocol was not prospectively registered. Unclear if all expected outcomes were reported
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists. No power calculation to explain the sample size used for the trial

Lin 1995

Methods	Single-centre, parallel-design, unblinded RCT. Analysed using an ITT approach. No losses to follow-up were reported. Informed consent not reported. 85% of participants were recruited from the ED and 15% were recruited from a hospital ward. After recruitment there was a 30-minute wash-out
	Setting: CCU
	Country: Taiwan
	Funding: not reported
	Study dates: January 1, 1986 to December 31, 1992
	Conflict of interest: not reported
Participants	100 participants (90 men and 10 women), with mean age 73 ± 9 (73 ± 9 in SMC group and 72 ± 8 in CPAP group)
	Inclusion criteria: dyspnoea and tachypnoea, RR > 22 breaths a minute, use of accessory respiratory muscles, PaO_2/FiO_2 between 200 and 400, $P(A-a)O_2 < 250$. Chest x-ray bilateral diffuse interstitial or alveolar oedema and most rales, and without history aspiration or infection
	Causes: congestive heart failure, dilated cardiomyopathy, ischaemic heart disease, hypertensive crisis, acute myocardial infarction
	Exclusion criteria: People unresponsive, unable to maintain a patent airway and who had cardiogenic shock, ventricular septal rupture, any severe stenotic valvular disease or chronic lung disease
Interventions	CPAP group (N = 50): PEEP average 3.75 ± 1.7 cm H_2O in first hour (pressure was applied by connecting a serial CPAP valve: 2.5 cm H_2O, 5 cm H_2O, 7.5 cm H_2O, 10 cm H_2O, 12.5 cm H_2O; to the facemask at each 30-minute interval. Time = 6 hours Control group (N = 50): SMC and oxygen facemask Co-intervention: Isosorbide dinitrate, morphine, furosemide, nitroprusside, nitroglycerin, dopamine
Outcomes	1. Primary outcome: mortality 2. Endotracheal intubation rate 3. Arterial blood gases (PaO_2, PCO_2, pH) 4. Vital signs (RR, BP, HR) 5. Dropouts or withdrawals 6. Length of hospital stay 7. Length of ICU stay 8. Treatment failure
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details are not provided
Allocation concealment (selection bias)	Unclear risk	Details are not provided
Blinding of participants and personnel (performance bias)	High risk	Not possible
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	Trial protocol was not prospectively registered. Unclear if all expected outcomes were reported
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists. No power calculation to explain the sample size used for the trial

Masip 2000

Methods	Single-centre, unblinded RCT, using ITT analysis. Participants or next-of-kin provided informed consent
	Setting: Recruited from ED or ward and transferred to the ICU
	Country: Barcelona, Spain
	Funding: Fondo de Investigación Sanitaria (FIS Grant 1996), Ministerio de Sanidad y Consumo
	Study dates: April 1996 to December 1998
	Conflict of interest: not reported
Participants	37 participants. 40 were randomised, but 3 were excluded from the analysis. At study entry 37 participants (19 men and 18 women), with mean age 76.9 ± 8.7 (78.5 ± 5 in the SMC group, 75.3 ± 11 years in the bilevel group)
	Inclusion criteria: dyspnoea of sudden onset with physical findings consistent with pulmonary oedema (widespread rales with or without 3rd heart sound) and typical findings of congestion on a chest radiograph. History: heart failure, acute myocardial infarction, hypertension, diabetes mellitus, COPD
	Causes: acute myocardial infarction, hypertensive crisis, hypervolaemia, unstable angina, tachyarrhythmia, respiratory tract infection, treatment non-compliance
	Exclusion criteria: cardiogenic shock (systolic BP < 90 mmHg), severe acute or chronic airflow obstruction without evidence of cardiogenic pulmonary oedema, severe chronic renal failure, neurological impairment, acute myocardial infarction necessitating thrombolysis, evidence of pneumonia, immediate need for intubation, and absence of pulmonary oedema on the first chest radiograph
Interventions	Bilevel group (N = 19): EPAP = 5 cm H_2O and IPAP average 15.2 ± 2.4 cm H_2O. Time= 254 ± 90 minutes Control group (N = 26): SMC and oxygen facemask (FiO_2 ? 50%) Co-intervention: morphine, furosemide, glyceryl trinitrate, digoxin
Outcomes	1. Primary outcome: endotracheal intubation rate 2. Mortality 3. Arterial blood gases (pH) 4. Vital signs (RR, BP, HR) 5. Incidence of acute myocardial infarction (follow-up) 6. Dropouts/withdrawals 7. Side effects 8. Length of hospital
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation sequence was generated by a table of random numbers
Allocation concealment (selection bias)	High risk	Assignments were placed in closed envelopes attached to rounding sheets
Blinding of participants and personnel (performance bias)	High risk	Not blinded
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	Trial protocol was not prospectively registered. Unclear if all expected outcomes were reported
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Moritz 2003

Methods	Single-centre randomised controlled trial, parallel-design, and per protocol analysis. Informed consent obtained in writing either from participant or relative. No participants were lost to follow-up **Setting**: Emergency Department **Country**: France **Funding**: Unclear **Study dates:** August 2000 to February 2001 **Conflict of interest**: not reported
Participants	52 consecutive patients with ACPE were considered for the study and 30 were enrolled. Mean study age was 81 ± 11. ACPE defined as 1) past history of cardiovascular disease, 2) auscultation with crepitations, 3) Chest x-ray consistent with pulmonary oedema (bilateral alveolar and interstitial opacities) **Inclusion eligibility:** ACPE and RR > 25 breaths a minute, pulse oximetry < 90% on room air. Intubation criteria: haemodynamic instability, cardiac or respiratory arrest, refractory and progressive hypoxaemia (SpO_2 < 80% on FiO_2 100%) **Exclusions**: history suggesting pneumonia or aspiration, fever > 38 °C, cardiogenic shock, altered mental status, COPD, acute myocardial infarction requiring primary angioplasty.
Interventions	CPAP group (N = 15): Boussignac-CPAP valve and oxygen with full facemask. PEEP 10 cm H_2O with average 9.3 ± 0.3 cm H_2O. FiO_2 65%. Applied for 30 minutes Control group (N = 15): full facemask and oxygen Co-intervention: furosemide 40 mg IV or twice normal dose (mean dose 115 ± 6.5 mg), nitroglycerin infusion 0.125 to 0.25 mcg/kg/min mean total furosemide dose (mean dose 18 ± 2 mg/min)
Outcomes	1. Tidal volume at baseline and 30 minutes 2. Accessory muscle use (Patrick's scale) 3. Arterial blood gases (PaO_2/FiO_2, $PaCO_2$, pH) at baseline and 30 minutes 4. Vitals (FiO_2, SpO_2, RR, HR, systolic BP, diastolic BP) at baseline and 30 minutes
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes
Blinding of participants and personnel (performance bias)	Unclear risk	No details provided
Blinding of outcome assessment (detection bias)	Unclear risk	No details provided
Incomplete outcome data (attrition bias)	Unclear risk	No details provided
Selective reporting (reporting bias)	Unclear risk	No details provided
Other bias	Unclear risk	Per protocol analysis was used. Data only at 0 and 30 minutes

Nava 2003

Methods	Multicentre, parallel-group RCT analysed using ITT approach. Randomisation using a block design for each centre. Balanced according to initial $PaCO_2$ above or below 45 mmHg. No participants were lost to follow-up. Informed consent from participant or next-of-kin
	Setting: ED
	Country: Italy
	Funding: not reported
	Study dates: not reported
	Conflict of interest: None
Participants	130 participants (101 men and 29 women), with mean age 72.6 ± 8.7 (73.1 ± 8.3 years in the SMC group and 72.1 ± 9.1 in the bilevel group)
	Inclusion criteria: Dyspnoea of sudden onset with RR > 30 breaths a minute, PaO_2/FiO_2 < 250 after being on >10 L a minute oxygen for at least 15 minutes. Congestion on chest radiograph and physical signs of pulmonary oedema (widespread rales) without a history suggesting pulmonary aspiration or infection
	Causes: Acute myocardial infarction, hypertension, hyperthermia (but not showing any signs of pulmonary infection), arrhythmia, aortic stenosis, mitral regurgitation
	Exclusion criteria: Immediate need for endotracheal intubation, severe sensorial impairment, shock, ventricular arrhythmias, life-threatening hypoxia (SpO_2 < 80%), acute myocardial infarction necessitating thrombolysis, severe chronic renal failure and pneumothorax
Interventions	Bilevel group (N = 65): Started on IPAP of 10 cm H_2O and EPAP of 5 cm H_2O and adjusted as tolerated. Mean settings: EPAP 6.1 ± 3.2 cmH_2O and IPAP = 14.5 ± 21.1 cm H_2O. Time = 11.4 ± 3.6 hours
	Control group (N = 65): SMC and oxygen full facemask (to maintain an SpO_2 > 90%)
	Co-intervention: morphine sulphate up to 4 mg, furosemide 40 mg IV or double home dose repeated if necessary, glyceryl trinitrate at initial rate 1.5 mg an hour and titrated if systolic BP > 180 mmHg
Outcomes	1. Primary outcome: endotracheal intubation rate 2. Mortality 3. Arterial blood gases (PaO_2, $PaCO_2$, pH) 4. Vital signs (RR, BP, HR) 5. Incidence of acute myocardial infarction (follow-up) 6. Compliance of participant 7. Side effects 8. Length of hospital stay
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block design for each centre, random numbers generated by an independent statistician, equal distribution below and above $PaCO_2 > 45$
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes
Blinding of participants and personnel (performance bias)	Unclear risk	Not described
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	Trial protocol was not prospectively registered. Unclear if all expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Park 2001

Methods	Single-centre, parallel-design, unblinded RCT. Analysis did not use an ITT approach. Loss to follow-up not reported. Participants or guardians provided informed consent **Setting**: not reported **Country:** Sao Paulo, Brazil **Funding:** not reported **Study dates:** May 1997 to October 1997 **Conflict of interest**: not reported
Participants	26 participants (10 men and 16 women), with mean age 69 ± 7 years **Inclusion criteria**: Dyspnoea of acute onset or worsening, RR ? 25 breaths a minute, diagnosis compatible with pulmonary congestion **Causes**: Acute myocardial infarction, hypertensive emergencies, acute ischaemic heart disease, infectious endocarditis or undetermined **Exclusion criteria**: Systolic BP < 90 mmHg, arrhythmias requiring electric cardioversion, decreased consciousness level, bradypnoea, lack of co-operation or agitation, repetitive vomiting, upper digestive haemorrhage, facial deformities or any other decompensated respiratory disease
Interventions	CPAP group (N = 9): PEEP = 7.5 cm H_2O. Average duration of treatment was 170 ± 90 minutes; closed face mask Bilevel group (N = 7): EPAP = 4 cm H_2O, IPAP = 12 cm H_2O. Average duration of treatment was 155 ± 38 minutes; nasal mask Control group (N = 10): SMC and oxygen mask (15 L a minute) Co-intervention: isosorbide dinitrate (5 mg) and standard medications
Outcomes	1. Primary outcome: endotracheal intubation rate 2. Mortality 3. Arterial blood gases (PaO_2, $PaCO_2$, pH) 4. Vital signs (RR, BP, HR) 5. Incidence of acute myocardial infarction (follow-up) 6. Compliance of participant 7. Dropouts and withdrawals
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias)	Unclear risk	No details provided
Blinding of outcome assessment (detection bias)	Unclear risk	Not details provided
Incomplete outcome data (attrition bias)	Unclear risk	No details provided
Selective reporting (reporting bias)	Unclear risk	Trial protocol was not prospectively registered. Unclear if all expected outcomes were reported
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists. No power calculation to explain the sample size used for the trial

Park 2004

Methods	Single-centre, parallel-group design RCT. Analysis was per protocol and not with ITT. Participants were excluded from analysis after randomisation due to identification of an alternative cause of respiratory failure. 2 participants in the Bilevel group and 1 participant in the oxygen group were lost to follow-up. Informed consent obtained from the participant's next-of-kin
	Setting: ED
	Country: Sao Paulo, Brazil
	Funding: not reported
	Study dates: January 1999 to August 2000
	Conflict of interest: not reported
Participants	80 participants. 83 people randomised, but 3 did not meet study inclusion criteria. Included 34 men and 46 women, with mean age 64.0 ± 15.3 (65 ± 15 in the control group, 61 ± 17 in the CPAP group, and 66 ± 14 in the Bilevel group)
	Inclusion criteria: Age > 16 years, acute onset of severe respiratory distress (RR > 25 breaths a minute), associated tachycardia, diaphoresis, and findings of pulmonary congestion on physical examination and chest x-ray 2 hours after randomisation
	Causes: Acute myocardial infarction, hypertensive emergency, progressive heart failure, hypervolaemia
	Exclusion criteria: Systolic BP < 90 mmHg, decreased level of consciousness, intractable vomiting, acute myocardial infarction with persistent ST segment elevation, pulmonary embolism, COPD, pneumonia or pneumothorax
Interventions	CPAP group (N = 27): Initial PEEP 10 cm H_2O. Average PEEP of 11 ± 2 cm H_2O. Average duration of therapy was 102 ± 41 minutes Bilevel group (N = 27). Initial IPAP 15 cm H_2O and initial EPAP 10 cm H_2O. Average EPAP was 11 ± 2 cm H_2O and average IPAP was 17 ± 2 cm H_2O. Duration of therapy was 124 ± 62 minutes Control group (N = 26): SMC and oxygen facemask (FiO$_2$? 50%) Co-intervention: isosorbide dinitrate, morphine, furosemide, nitroprusside, nitroglycerin
Outcomes	1. Primary endpoint: endotracheal intubation rate 2. Mortality at 15 days and 60 days. 3. Incidence of acute myocardial infarction (baseline) 4. Compliance of participant 5. Dropouts and withdrawals 6. Treatment failure 7. Side effects 8. Length of hospital stay 9. Vitals: RR, mean BP, HR 10. Arterial blood gases: PaO$_2$/FiO$_2$, PaCO$_2$, pH at baseline, 30 minutes, 60 minutes, 180 minutes, and 360 minutes
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes
Blinding of participants and personnel (performance bias)	Unclear risk	Not described
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	High risk	As-treated analysis performed, missing outcome data for exclusions after randomisation
Selective reporting (reporting bias)	Unclear risk	Trial protocol was not prospectively registered. Unclear if all expected outcomes were reported
Other bias	Unclear risk	Early termination during second interim analysis identified a significant difference in endotracheal intubation rates among groups. Insufficient information to assess whether an important risk of bias exists

Räsänen 1985

Methods	Single-centre, parallel-group RCT. Analysis performed using ITT approach. Loss to follow-up and informed consent not reported
	Setting: ICU
	Country: Helsinki, Finland
	Funding: not reported
	Study dates: not reported
	Conflict of interest: not reported
Participants	40 participants (13 men and 27 women), with mean age 74 ± 9 (73 ± 9 in the control group and 74 ± 9 in the CPAP group)
	Inclusion criteria: Respiratory failure with clinical and radiologic evidence of ACPE. Required evidence of dyspnoea, increased work of breathing (intercostal and suprasternal retractions or use of accessory respiratory muscles), RR > 25 breaths a minute or $PaO_2/FiO_2 < 200$
	Causes: Severe heart failure primarily after acute myocardial infarction, or acute exacerbation of chronic left ventricular dysfunction
	Exclusion criteria: People unresponsive to speech or unable to maintain patent airway, with lung infection, pulmonary embolism, chronic lung disease with carbon dioxide retention at rest
Interventions	CPAP group (N = 20): PEEP = 10 cm H_2O. Maximum length of treatment was 180 minutes
	Control group (N = 20): SMC and oxygen facemask (FiO_2 of 28% - 30%)
	Co-intervention: furosemide, morphine, diazepam, chlorpromazine, nitroglycerin, nitroprusside, digitalis, dopamine, and dobutamine
Outcomes	1. Mortality
	2. Endotracheal intubation rate
	3. Arterial blood gases at baseline, 10 minutes, 60 minutes, 180 minutes (PaO_2, $PaCO_2$, pH)
	4. Vital signs (RR, BP, HR)
	5. Incidence of acute myocardial infarction (baseline)
	6. Treatment failure
	7. Side effects
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Randomly assigned to 1 of 2 group by opening 1 of 40 sealed envelopes
Blinding of participants and personnel (performance bias)	Unclear risk	No details provided
Blinding of outcome assessment (detection bias)	Unclear risk	No details provided
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	Trial protocol was not prospectively registered. Unclear if all expected outcomes were reported.
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists. No power calculation to explain the sample size used for the trial

Takeda 1997

Methods	Single-centre, parallel-design RCT. Analysis completed using ITT approach. Loss to follow-up not reported. Informed consent from next-of-kin **Setting**: ICU **Country:** Tokyo, Japan **Funding:** not reported **Study dates:** not reported **Conflict of interest**: not reported
Participants	30 participants (22 men and 8 women), with mean age 66.5 ± 9.7 (64 ± 9 in the control group and 69 ± 10 in the CPAP group) **Inclusion criteria**: Dyspnoea of sudden onset, PaO_2 < 80 mmHg with FiO_2 ? 50%, typical findings on chest radiographs, and widespread rales **Causes**: Acute myocardial infarction, prior myocardial infarction, cardiomyopathy, mitral valve regurgitation **Exclusion criteria**: History suggesting infection or pulmonary aspiration
Interventions	CPAP group (N = 15): PEEP of 4 to 10 cm H_2O Control group (N = 15): SMC and nasal oxygen mask Co-intervention: furosemide, morphine, nitroglycerin, digitalis, dopamine, dobutamine, norepinephrine
Outcomes	1. Primary outcome: plasma endothelin-1 concentrations 2. Haemodynamics at baseline, 6 hours, 12 hours, 24 hours: mean pulmonary artery pressure, pulmonary artery wedge pressure, central venous pressure, cardiac index, and stroke volume index 3. Blood gases: PaO_2/FiO_2, $PaCO_2$ 4. Vitals: mean arterial pressure, HR, RR at baseline, 6 hours, 12 hours, 24 hours 5. Mortality 6. Endotracheal intubation rate 7. Length of ICU stay
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias)	Unclear risk	No details provided
Blinding of outcome assessment (detection bias)	Unclear risk	No details provided
Incomplete outcome data (attrition bias)	Unclear risk	Loss to follow-up was not reported
Selective reporting (reporting bias)	Unclear risk	Trial protocol was not prospectively registered. Unclear if all expected outcomes were reported
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists. No power calculation to explain the sample size used for the trial

Takeda 1998

Methods	Single-centre, parallel-group design, unblinded RCT. Analysis completed using ITT approach. No participants were lost after randomisation. Informed consent obtained from next of kin **Setting**: CCU **Country:** Tokyo, Japan **Funding:** not reported **Study dates:** not reported **Conflict of interest**: not reported
Participants	22 participants admitted to the CCU with acute myocardial infarction. 17 men and 5 women with mean age of 75 ± 10 (75 ± 10 in the SMC group and 74 ± 11 in the CPAP group) **Inclusion criteria:** Dyspnoea of sudden onset, $PaO_2 < 80$ mmHg on $FiO_2 = 50\%$, typical findings on chest radiograph, and widespread rales without a history suggesting pulmonary aspiration or infection. Acute myocardial infarction was diagnosed by typical chest pain lasting at least 30 minutes, CK at least twice the normal value, and ECG changes consistent with an acute myocardial infarction **Exclusion criteria**: Left ventricular free wall rupture, immediate need for endotracheal intubation, shock
Interventions	CPAP group (N = 11): PEEP of 4 to 10 cm H_2O Control group (N = 11): SMC and nasal oxygen mask Co-intervention: furosemide, morphine, nitroglycerin, dopamine, dobutamine, norepinephrine, epinephrine
Outcomes	1. Primary outcome: haemodynamics at baseline, 24 hours, 48 hours (mean arterial pressure, HR, RR, mean pulmonary artery pressure, pulmonary artery wedge pressure, cardiac index, stroke volume index) 2. Mortality 3. Endotracheal intubation rate 4. Arterial blood gases at baseline 24 hours, 48 hours (PaO_2/FiO_2)
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	2 groups by envelope method
Blinding of participants and personnel (performance bias)	Unclear risk	Not described
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	Trial protocol was not prospectively registered. Unclear if all expected outcomes were reported.
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists. No power calculation to explain the sample size used for the trial

Thys 2002

Methods	Single-centre, parallel design, and single- blinded RCT. Analysed using an ITT approach. No participants were lost to follow-up. Informed consent was obtained
	Setting: ED. After discharge from ED participants were transferred to the ICU
	Country: Belgium
	Funding: Fondation Saint-Luc
	Study dates: 2 year period 1999 to 2000
	Conflict of interest: not reported
Participants	People with either acute exacerbation of COPD or ACPE. Planned enrolment of 60 participants. 8 participants (5 mens and 3 women) had ACPE. Mean age was 77.5 ± 8.4 (77.6 ± 9.5 in SMC, 77.3 ± 8.0 in bilevel NPPV group)
	Inclusion criteria: ACPE with orthopnoea, bibasilar crackles, bilateral perihilar infiltrates on chest radiograph with cardiomegaly and a compatible clinical history; age > 18 years, acute onset of moderate-to-severe dyspnoea, RR > 30 breaths a minute or < 10 breaths a minute, hypoxaemia (PaO_2 < 55 mmHg) or need for O_2 supplementation, pH < 7.33. Evaluated by 2 investigators before inclusion
	Exclusion criteria: Immediate need for endotracheal intubation, major unrest, haemodynamic instability, facial or thoracic trauma, lack of co-operation, difficulty adapting to a face mask, suspicion of pulmonary embolism, retrosternal pain suggestive of an acute myocardial infarction even with a normal admission ECG
Interventions	Bilevel group (N = 3): EPAP 4 cm H_2O titrated as tolerated. IPAP 10 cm H_2O titrated as tolerated. The inspiratory pressure was increased by 2 cm H_2O steps until the person showed signs of discomfort, leaks were observed between the face mask and skin or a pressure of 20 cm H_20 was reached. Oxygen was delivered by nasal cannulae inside the mask and titrated until oxygen saturation of 90% was reached
	Control group (N = 5): SMC and oxygen with similar mask (placebo). A nasal catheter was used until an oxygen saturation of 90% was reached
	Co-intervention: furosemide IV 40 mg, isosorbide dinitrate (2 mg an hour). Participants failing placebo NPPV were put on active NPPV when the decision to use intubation and active ventilation by the attending physician was made
Outcomes	1. Primary outcome: endotracheal intubation rate
	2. Mortality
	3. Incidence of acute myocardial infarction (follow-up)
	4. Side effects
	5. Length of hospital stay
	6. Length of ICU stay
	7. ED length of stay
	8. Arterial blood gases: pH, $PaCO_2$, PaO_2, SaO_2, SpO_2. Measured before and after intervention
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Sealed, opaque envelopes, opened at time of inclusion in batches of 20 envelopes
Blinding of participants and personnel (performance bias)	High risk	Attempt made to use same machine with modifications for BPAP and control for participant, but physician not blinded
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Low risk	No missing outcomes data
Selective reporting (reporting bias)	Unclear risk	Trial protocol was not prospectively registered. Unclear if all expected outcomes were reported
Other bias	Unclear risk	Early termination during first interim analysis as the differences in treatment failure were significant. Insufficient information to assess whether an important risk of bias exists

Zokaei 2016

Methods	Single-centre, parallel-group RCT. Written informed consent was obtained
	Setting: CCU
	Country: Iran
	Funding: not reported
	Study dates: not reported
	Conflict of interest: not reported
Participants	120 participants with ACPE, age > 20 years, diagnosed by a cardiologist. Mean age was 71 (control group mean age 72 and bilevel group mean age 70)
	Exclusion criteria: reduced GCS ? 11, hypotensive systolic BP < 80 mmHg, bradycardia HR < 45, tachycardia HR > 120, ventricular arrhythmia, recent oesophageal, facial, cranial trauma, or surgery. Lack of co-operation, inability to clear secretions, tracheostomy, active gastrointestinal bleeding, need for emergent intubation, and severe organ dysfunction in addition to respiratory failure (respiratory rate > 35 breaths a minute and PaO_2 < 50 mmHg, $PaCO_2$ > 50 mmHg)
Interventions	Bilevel NPPV group (N = 60): Medical care used in control group and non-invasive pressure control inverse ratio ventilation through a face or nasal mask. IPAP of 10 cm H_2O and increased up to 20 cm H_2O to obtain a respiratory rate < 20 a minute. EPAP of 4 - 7 cm H_2O
	Control group (N = 60): Venturi mask with 10 L a minute oxygen. Both groups were given IV furosemide 40 - 320 mg to achieve satisfactory urine output, IV nitroglycerin 5 - 50 mcg/kg/min if systolic BP > 100 mmHg, morphine sulphate 5 - 10 mg, SC or IV heparin and ASA if ECG suggestive of ischaemia. Dopamine or dobutamine or adrenaline used if systolic BP < 60 mmHg, urine output < 0.5 mL/kg/h
Outcomes	1. Primary outcome: 7-day mortality, endotracheal intubation rate 2. Hospital mortality 3. Endotracheal intubation rate 4. CCU length of stay and recovery time 5. Arterial blood gas data at 15-minute intervals for 1 hour (pH, SaO_2, PaO_2, $PaCO_2$)
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Unclear risk	Not described
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Unclear risk	No details provided
Selective reporting (reporting bias)	High risk	Trial protocol was not prospectively registered. Expected outcomes such as adverse events are not described, mortality at 7 days (primary outcome) is not reported
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists. No power calculation to explain the sample size used for the trial

Footnotes

A-a: alveolar arterial; ACPE: acute cardiogenic pulmonary oedema; BP: blood pressure; CCU: coronary care unit; CK: creatinine kinase; CPAP: continuous positive airway pressure; DBP: diastolic blood pressure; ECG: electrocardiogram; EPAP: expiratory positive airway pressure; FiO_2: fraction of inspired oxygen; GCS: Glasgow Coma Scale; H_2O: water; HF: heart failure; HR: heart rate; ICU: intensive care unit; IHD: ischaemic heart disease; IPAP: inspiratory positive airway pressure; ITT: intention-to-treat; mmHg: millimetres of mercury; NPPV: non-invasive positive pressure ventilation; $PaCO_2$: arterial partial pressure of carbon dioxide; PaO_2: arterial partial pressure of oxygen; PEEP: positive end-expiratory pressure; RCT: randomised controlled trial; RICU: respiratory intensive care unit; RR: respiratory rate; SBP: systolic blood pressure; SMC: standard medical care

Characteristics of excluded studies

ACTRN12610000487011

Reason for exclusion	Proposed trial comparing continuous positive airway pressure to standard medical care in the pre-hospital setting for acute cardiogenic pulmonary oedema. The trial was not started and is currently suspended

ACTRN12610000528055

Reason for exclusion	Proposed trial comparing continuous positive airway pressure to standard medical care in acute cardiogenic pulmonary oedema. The trial was suspended prior to completing an ethics review

Baratz 1992

Reason for exclusion	Ineligible study type: no control arm, not a randomised controlled trial

Bautin 2005

Reason for exclusion	Ineligible population: post-cardiac surgery patients developing heart failure after extubation

Belenguer-Muncharaz 2017

Reason for exclusion	Ineligible intervention: continuous positive airway pressure compared to bilevel non-invasive positive pressure ventilation without a control arm

Bellone 2002

Reason for exclusion	Ineligible intervention: randomised cross-over study that compared continuous positive airway pressure and bilevel non-invasive positive pressure ventilation for reducing mitral regurgitation severity in acute exacerbation of heart failure. Did not have a standard therapy control arm

Bellone 2004

Reason for exclusion	Ineligible intervention: compared bilevel non-invasive positive pressure ventilation to continuous positive airway pressure in people with acute pulmonary oedema. Did not have a standard therapy control arm

Bellone 2005

Reason for exclusion	Ineligible intervention: compared bilevel noninvasive positive pressure ventilation to continuous positive airway pressure with acute pulmonary oedema. Did not have a standard therapy control arm

Bendjelid 2005

Reason for exclusion	Ineligible study type: observational study evaluating effect of continuous positive airway pressure on left ventricular function in cardiogenic pulmonary oedema

Bersten 1991

Reason for exclusion	Ineligible study type: quasi-randomised controlled trial comparing continuous positive airway pressure to standard medical therapy. Participants were allocated to a treatment group through the selection of a coloured cap

Blanco 2015

Reason for exclusion	Ineligible study type: not a randomised controlled trial, a summary of an article describing an observational study

Chadda 2002

Reason for exclusion	Ineligible study type: randomised cross-over study that compared continuous positive airway pressure to bilevel non-invasive positive pressure ventilation for acute cardiogenic pulmonary oedema

Craven 2000

Reason for exclusion	Ineligible study type: not a randomised controlled trial but a sequential trial comparing ambulances equipped with either bilevel non-invasive positive pressure ventilation or control therapy

Delclaux 2000

Reason for exclusion	Ineligible population: acute lung injury with hypoxaemic respiratory failure due to infection, direct lung injury, indirect lung injury, and cardiac causes

Dib 2012

Reason for exclusion	Ineligible study type: review article on the pre-hospital use of continuous positive airway pressure for acute heart failure

Ferrari 2007

Reason for exclusion	Ineligible intervention: continuous positive airway pressure compared to bilevel noninvasive positive pressure ventilation for people with acute cardiogenic pulmonary oedema. No control therapy arm

Ferrari 2010

Reason for exclusion	Ineligible intervention: continuous positive airway pressure compared to bilevel noninvasive positive pressure ventilation without additional standard medical care group in people with acute cardiogenic pulmonary oedema

Ferrer 2003

Reason for exclusion	Ineligible population, hypoxaemic respiratory failure, did not stratify by cause, included 30% cardiogenic pulmonary oedema

Fontanella 2010

Reason for exclusion	Ineligible intervention: continuous positive airway pressure compared to bilevel non-invasive positive pressure ventilation without additional standard medical care group

Foti 2009

Reason for exclusion	Ineligible study type: not a randomised controlled trial, all patients received continuous positive airway pressure in the pre-hospital setting with or without standard medical care

Gorbunova 2007

Reason for exclusion	Ineligible study type: not a randomised controlled trial. Evaluated patients with cardiogenic pulmonary oedema due to acute myocardial infarction and haemodynamics with use of continuous positive airway pressure

Hubble 2006

Reason for exclusion	Ineligible study type: not a randomised controlled trial. Compared 2 emergency medical services interventions control and continuous positive airway pressure

L'Her 2003

Reason for exclusion	Wrong study type: review article

Leman 2005

Reason for exclusion	Ineligible study type: no control arm. Compared continuous positive airway pressure delivery mechanisms in the management of acute pulmonary oedema

Liesching 2014

Reason for exclusion	Ineligible intervention: compared bilevel noninvasive positive pressure ventilation to continuous positive airway pressure in acute cardiogenic pulmonary oedema

Martin-Bermudez 2002

Reason for exclusion	Ineligible intervention: compared bilevel noninvasive positive pressure ventilation to continuous positive airway pressure in acute cardiogenic pulmonary oedema

Mehta 1997

Reason for exclusion	Ineligible intervention: continuous positive airway pressure compared to bilevel noninvasive positive pressure ventilation without a control treatment group

Minuto 2003

Reason for exclusion	Ineligible study type: cohort study comparing continuous positive airway pressure vs bilevel noninvasive positive pressure ventilation for people with acute cardiogenic pulmonary oedema that had failed medical therapy.

Moritz 2007

Reason for exclusion	Ineligible study type: quasi-randomised controlled trial, participants randomised to consecutive study numbers as either CPAP or bilevel NPPV. Ineligible intervention: compared continuous positive airway pressure to bilevel noninvasive positive pressure ventilation without a control group

NCT00375154

Reason for exclusion	Study withdrawn due to difficulties in training investigators in other centres

Nouira 2011

Reason for exclusion	Ineligibleg intervention: compared bilevel non-invasive positive pressure ventilation to continuous positive airway pressure

Oliver 2013

Reason for exclusion	Wrong study type: a review article.

Ozsancak 2013

Reason for exclusion	Ineligible intervention: compared total face mask or oronasal mask noninvasive ventilation

Pagano 2018

Reason for exclusion	Wrong study type: observational study of bilevel noninvasive positive pressure ventilation and continuous positive airway pressure for people with acute cardiogenic pulmonary oedema

Philip-Joet 1999

Reason for exclusion	Ineligible intervention: continuous positive airway pressure or bilevel noninvasive positive pressure ventilation without control group. Ineligible population: people with or without congestive heart failure. Ineligible study type: not a randomised controlled trial, a comparative cohort study

Plaisance 2007

Reason for exclusion	Ineligible study type: cross-over randomised controlled trial that compared continuous positive airway pressure starting at different times

Popova 2010

Reason for exclusion	Ineligible population: decompensated heart failure. Evaluated exercise effects, 6-minute walking distance, of non-invasive ventilation or standard care

Rusterholtz 1999

Reason for exclusion	Wrong study type: uncontrolled prospective study. Wrong intervention: no control group

Sharon 2000

Reason for exclusion	Ineligible study type: quasi-randomised controlled trial with randomisation performed by assigning consecutive patients to one or other treatment groups according to their numerical order on a list that had been predetermined by lot. Ineligible intervention: compared bilevel non-invasive positive pressure ventilation against high-dose intravenous nitrate standard medical therapy

Somauroo 2000

Reason for exclusion	Ineligible population: chronic congestive heart failure. Ineligible intervention: compared continuous positive airway pressure to bilevel non-invasive positive pressure ventilation

Uy 2004

Reason for exclusion	Ineligible intervention: compared continuous positive airway pressure to mechanical ventilation for people with acute cardiogenic pulmonary oedema

Vaisanen 1987

Reason for exclusion	Ineligible study type: cross-over study comparing participants randomised to the sequence of continuous positive airway pressure or standard medical therapy first followed by standard medical therapy or continuous positive airway pressure

Weitz 2007

Reason for exclusion	Ineligible study type: quasi-randomised controlled trial with randomisation by birth year. Compared non-invasive ventilation to standard medical therapy

Footnotes

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

Footnotes

Summary of findings tables

1 NPPV compared to SMC for cardiogenic pulmonary oedema

NPPV compared to standard medical care for cardiogenic pulmonary oedema
Patient or population: People with cardiogenic pulmonary oedema **Setting:** Pre-hospital intensive care, emergency department, coronary care unit, or intensive care unit **Intervention:** NPPV **Comparison:** Standard medical care (SMC)

Outcomes	Anticipated absolute effects[*] (95% CI)		Relative effect (95% CI)	[1] of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with SMC	Risk with NPPV				
HOSPITAL MORTALITY follow-up: median 13 days; range 1 day - 41 days	Study population		RR 0.65 (0.51 to 0.82)	2484 (21 RCTs)	???? LOW[a,b]	-
	176 per 1000	114 per 1000 (90 to 144)				

ETI RATE follow-up: median 1 day; range 0.1 day - 30 days	Study population		RR 0.49 (0.38 to 0.62)	2449 (20 RCTs)	???? MODERATE[c]	-
	154 per 1000	75 per 1000 (58 to 95)				
ACUTE MI INCIDENCE follow-up: median 3 days; range 1 day - 41 days	Study population		RR 1.03 (0.91 to 1.16)	1313 (5 RCTs)	???? MODERATE[d]	-
	421 per 1000	433 per 1000 (383 to 488)				
HOSPITAL LENGTH OF STAY	The mean HOSPITAL LENGTH OF STAY was 9.65 days	MD 0.31 days lower (1.23 lower to 0.61 higher)	-	1714 (11 RCTs)	???? VERY LOW[e,f,g]	-
ICU LENGTH OF STAY	This outcome could not be pooled due to high heterogeneity. There was no evidence of a difference between NPPV and SMC in 4 RCTs, and 2 RCTs reported a shorter length of stay for NPPV (1 day shorter (95% CI ?1.79 to ?0.21); n = 30; 4 days shorter (95% CI ?4.36 to ?3.64); n = 120)	-	-	587 (6 RCTs)	???? VERY LOW[h,i,j]	Data were not pooled due to high heterogeneity with an I^2 of 99%
INTOLERANCE TO ALLOCATED TREATMENT - not reported	-	-	-	-	-	Outcome was not reported
ADVERSE EVENTS	Reported adverse events included skin damage, pneumonia, gastrointestinal bleeding, gastric distention, vomiting, pneumothorax, sinusitis, mask discomfort, hypotension, arrhythmia, cardiorespiratory arrest, gastric aspiration, stroke, seizures, claustrophobia, and hypercapnia. There was no evidence of a difference between groups for most of these events. However, there was an increase in discomfort with mask reported with NPPV (35/658) compared with SMC (0/442); RR 12.59 (95% CI 2.39 to 66.28). One small study (n = 83) reported a higher incidence of gastric distention in the NPPV group (13/56 in NPPV group, 0/27 in SMC group; RR 13.26 (95% CI 0.82 to 215.12)), but the number of events was low and the confidence interval wide. There was also some weak evidence of a lower incidence of cardiorespiratory arrest in the NPPV group (24/836 (NPPV) vs 26/516 (SMC); RR 0.60 (95% CI 0.34 to 1.05)	-	-	2038 (11 RCTs)	???? LOW[k,l]	-

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Footnotes

[a]Downgraded by one level for risk of bias. Most trials providing hospital mortality evidence were at unclear or high risk of bias

for key domains, including: randomisation sequence, allocation concealment, selective reporting bias, and other significant bias.

[b]Downgraded by one level for imprecision. Most trials had few participants and few mortality events, with a confidence interval crossing a RR of 0.75.

[c]Downgraded by one level for risk of bias. Most trials providing ETI evidence were rated as having unclear or high risk of bias for key domains, which included randomisation sequence generation, allocation concealment, selective reporting bias, and other significant bias.

[d]Downgraded by one level for imprecision. Most trials had few participants and few acute MI events, with a confidence interval crossing a RR of 1.0. In addition, the definition of acute MI varied between trials, with some trials using creatinine kinase and others using troponin.

[e]Downgraded by one level for risk of bias. Most trials were at low or unclear risk of bias. Potential limitations from lack of blinding are likely to lower confidence in hospital length of stay.

[f]Downgraded by one level for inconsistency. Hospital length of stay was heterogeneous, with an I^2 of 58% and visually-evident heterogeneity.

[g]Downgraded by one level for imprecision. Most trials had few participants, with a confidence interval crossing a MD of 0.

[h]Downgraded by one level for risk of bias. Most information was from studies at low or unclear risk of bias. Potential limitations from lack of blinding are likely to lower confidence in ICU length of stay.

[i]Downgraded by one level for imprecision. Most trials had few participants, with a confidence interval crossing a MD of 0.

[j]Downgraded by one level for inconsistency. ICU length of stay was heterogeneous, with an I^2 of 99% and visually-evident heterogeneity.

[k]Downgraded by one level for risk of bias. Most studies had at least one domain at high or unclear risk of bias.

[l]Downgraded by one level for imprecision, as confidence intervals included both directions of effect for many of the adverse events.

Additional tables

1 NPPV intervention summary: EPAP, IPAP, and PEEP settings, duration of therapy.

Study	Mask type	IPAP level (cmH2O) ± SD	EPAP in bilevel NPPV (cmH2O) ± SD	PEEP in CPAP (cmH2O) ± SD	Time of bilevel NPPV (h) ± SD	Time of CPAP (h) ± SD
Agmy 2008	Face mask	NA	NA	NA	NA	NA
Austin 2013	Face mask	NA	NA	10	NA	0.583333
Crane 2004	Face mask	15	5	10	NA	NA
Ducros 2011	Face mask	NA	NA	10	NA	3
El-Refay 2016	Face mask	15	10	10	1	-
Frontin 2011	Face mask	NA	NA	10	NA	NA
Gray 2008	Face mask	14±5	7 ± 3	10 ± 4	2 ± 1.3	2.2 ± 1.5
Hao 2002	Face mask	NA	NA	6 to 10	NA	4.6 ± 2.8
Kelly 2002	Face mask	NA	NA	7.5	NA	NA
L'Her 2004	Face mask	NA	NA	7.5	NA	NA
Levitt 2001	Face mask selected for mouth breathers Nasal available	NA	NA	NA	2	2
Li 2005	Face mask	15 to 18	5 to 8	NA	2	NA
Lin 1991	Face mask	NA	NA	12.5	NA	6
Lin 1995	Face mask	NA	NA	12.5	NA	6
Masip 2000	Face mask	15.2 ± 2.4	5	NA	4.2 ± 1.5	NA
Moritz 2003	Face mask	NA	NA	9.3 ± 0.3	0.5	NA
Nava 2003	Face mask	14.5 ± 21.1	6.1 ± 3.2	NA	11.4 ± 3.6	NA
Park 2001	Nasal bilevel and face mask for CPAP	12	4	7.5	2.6 ± 0.6	2.8 ± 1.5
Park 2004	Face mask	17 ± 2	11 ± 2	11 ± 2	2.1 ± 1	1.7 ± 0.7
Räsänen 1985	Face mask	NA	NA	10	NA	NA
Takeda 1997	Nasal	NA	NA	4 to 10	11.9 ± 8.4	NA
Takeda 1998	Nasal	NA	NA	4 to 10	NA	NA
Thys 2002	Face mask	16.5 ± 3.3	6.1 ± 1.5	NA	1.3 ± 0.3	NA
Zokaei 2016	Face mask 1st, nasal 2nd	10 to 20	4 to 7	NA	1	NA

Footnotes

Not all papers provided a mean and standard deviation. Where unavailable, the range represents the IPAP/EPAP/CPAP settings described in the Methods. NA: not applicable

2 Standard medical therapy for each trial

Study	Lasix	Lasix dose	Nitrate	FiO$_2$ mask and %FiO$_2$	Other	Additional differences between SMC received in treatment group
Agmy 2008	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Austin 2013	yes	40 mg	Sublingual 400 - 1600 mcg q5min	Yes, 8 - 15 Lpm	Morphine 1 - 2 mg IV	None
Crane 2004	yes	Unclear	nitrates	Yes, 10 Lpm	diamorphine	None
Ducros 2011	yes	Lasix 40 mg - 120 mg IV or 1 - 3 mg bumetanide	nitroglycerin (1 mg per 3 min) and a continuous IV infusion unless systolic BP < 110 mmHg	15 Lpm	NA	None
El-Refay 2016	yes	Lasix 40 mg IV	nitroglycerin 0.4 mg sublingual	15 Lpm	Morphine 2 mg IV	None
Frontin 2011	yes	1 mg/kg IV	isosorbide dinitrate IV 2 mg if SBP > 180 mmHg	15 Lpm	NA	None
Gray 2008	yes	50 mg above usual dose to max 100 mg IV	Buccal nitrates 2 - 5 mg	15 Lpm	Opiates	None
Hao 2002	yes	20 - 40 mg IV	Buccal nitrates 0.5 mg to 1 mg IV	6 Lpm	Morphine 2 mg IV	None
Kelly 2002	yes	50 - 100 mg IV	buccal nitrate 5 mg if systolic BP > 90 mmHg	oxygen 60% by venturi mask	morphine IV 2.5 - 10 mg	None
Li 2005	yes	Unclear	nitroglycerin	Mask high concentration	Unclear	None
Levitt 2001	yes	Unclear	nitroglycerin IV	Mask high flow	Morphine	None
L'Her 2004	yes	80 mg IV	nitroglycerin IV infusion 1 mg/hour	8 Lpm	Morphine 2 - 10 mg IV	None
Lin 1991	Unclear	Unclear	Unclear	FiO$_2$ 100%	Unclear	Unclear
Lin 1995	yes	40 mg IV or double home dose	nitroglycerin sublingual 0.6 mg or isosorbide 10 - 20 mg, or nitro infusion 10 - 50 mcg/min	FiO$_2$ 100%	Morphine 2 - 10 mg IV	None
Masip 2000	yes	40 mg IV	IV glyceryl trinitrate 1mg if systolic BP > 180 mmHg	FiO$_2$ 50%	Morphine 4 mg IV	None
Moritz 2003	yes	40 mg IV or double home dose	IV nitroglycerin infusion 0.125 - 0.25 mcg/kg/min	FiO$_2$ 100%	Unclear	None
Nava 2003	yes	40 mg IV or double usual dose, repeated, if necessary, every 20 mins, up to 320 mg	continuous glyceryl trinitrate at an initial rate of 1.5 mg/hour. A bolus dose of 1 mg IV was added if systolic BP > 180 mmHg	10 Lpm	morphine sulphate up to 4 mg	None
Park 2001	Unclear	Unclear	5 mg isosorbide dinitrite if systolic BP > 100 mm Hg	15 Lpm	Unclear	Unclear
Park 2004	Unclear	Unclear	5 mg isosorbide dinitrate was given sublingually and if necessary titrated up to 15 mg	FiO$_2$ 50%	Unclear	Unclear
Räsänen 1985	yes	40 - 80 mg IV	Nitroprusside, nitroglycerine	FiO$_2$ 30%	Morphine	Unclear

Study	Lasix	Lasix dose	Nitrate	FiO$_2$ mask and %FiO$_2$	Other	Additional differences between SMC received in treatment group
Takeda 1997	yes	Unclear	Nitroglycerin infusion	FiO2 50%	Morphine	Unclear
Takeda 1998	yes	Unclear	Nitroglycerin infusion	FiO$_2$ 70%	Morphine	Unclear
Thys 2002	yes	40 mg IV	isosorbide dinitrate 2 mg/hour	Unclear	Unclear	Unclear
Zokaei 2016	yes	40 - 320 mg	IV nitroglycerin 5 - 50 mcg/kg/min	10 Lpm	morphine 5 - 10 mg	Unclear

Footnotes

BP: blood pressure; FiO$_2$: fraction of inspired oxygen; IV: intravenous; Lpm: litres per minute; NA: not available; mcg: micrograms; mcg/kg/min: micrograms per kilogram per minute; mg: milligrams; min: minutes; mmHg = millimetres of mercury

3 In-hospital mortality duration of follow-up

Study	Follow-up (days)
Agmy 2008	Unclear
Austin 2013	7.2[a]
Crane 2004	41[b]
Ducros 2011	> 7
El-Refay 2016	1
Frontin 2011	30
Gray 2008	30
Hao 2002	NA
Kelly 2002	15[a]
Li 2005	NA
Levitt 2001	38[b]
L'Her 2004	12[a]
Lin 1991	1
Lin 1995	9
Masip 2000	14[a]
Moritz 2003	NA
Nava 2003	5.4[a]
Park 2001	3[b]
Park 2004	15
Räsänen 1985	Unclear
Takeda 1997	7.7[a]
Takeda 1998	Unclear
Thys 2002	17.6[a]
Zokaei 2016	7

Footnotes

[a]Estimated based on longest reported mean hospital length of stay; [b]Based on latest death reported in trial

4 Intubation criteria for trials reporting endotracheal intubation rates

Study	Intubation Criteria
Agmy 2008	Unclear
Austin 2013	Unclear
Crane 2004	RR > 40, RR < 10, altered level of consciousness, arterial pH < 7.2
Ducros 2011	SpO_2 < 85% after 30 mins of 15 Lpm or FiO_2 60% CPAP, respiratory arrest, psychomotor agitation, SBP < 80 mmHg
El-Refay 2016	Unclear
Frontin 2011	Worsening SpO_2 despite effective treatment, loss of airway protective reflexes (cough, swallow), decreased level of consciousness, haemodynamic instability, intolerance/poor fit of face mask for the CPAP group, medical clinical impression of deterioration, or participant request
Gray 2008	At discretion of treating clinician
L'Her 2004	Cardiac or respiratory arrest, severe haemodynamic instability (SBP < 80), administration of epinephrine/norepinephrine, refractory hypoxaemia SaO_2 < 92% despite face mask, clinical signs of respiratory exhaustion (accessory muscle use with paradoxical abdominal motion), coma or seizures, agitation requiring sedation
Levitt 2001	Clinical or arterial blood gas findings. Severe respiratory distress, deterioration in mental status, or further deterioration in vital signs with increasing HR, RR, or a decrease in BP. Decrease in pO_2 < 60 or rise in pCO_2 > 50 along with signs of clinical deterioration warranted intubation
Lin 1991	Clinician discretion. Loss of consciousness or airway obstruction were indications for intubation
Lin 1995	Cardiopulmonary resuscitation or clinical deterioration with any 2 of the following: (1) a rise in arterial carbon dioxide tension to more than 55 mm Hg; (2) arterial blood oxygen partial pressure divided by fraction of inspired oxygen content less than 200 mm Hg; and (3) respiratory rate over 35 breaths/min.
Masip 2000	Patients were intubated when the criteria for treatment failure were met. Details not specified.
Nava 2003	Unclear
Park 2001	Clinical judgement
Park 2004	Clinical judgement
Räsänen 1985	Clinical judgement. Loss of consciousness or airway obstruction were indications for intubation at any time.
Takeda 1997	Clinical deterioration and either a decrease in the PaO_2/FiO_2 < 100 with an FIO_2 ? 70% or a increase in the $PaCO_2$ > 55 mmHg
Takeda 1998	Clinical deterioration and either a fall in PaO_2/FiO_2 < 100 with an FiO_2 of 70% or a rise in $PaCO_2$ to > 55 mmHg.
Thys 2002	Deterioration in clinical status including all of the following: dyspnoea, respiratory or heart frequency or both, sweating and agitation or deterioration in blood gases or in haemodynamic status or both
Zokaei 2016	RR after 1 hour of bilevel NPPV > 30, persistent hypoxaemia, haemodynamic instability (systolic BP < 70), agitation, or worsened neurologic status, inability to tolerate mask or aspiration of gastric content

Footnotes

BP: blood pressure; CPAP: continuous positive airway pressure; FiO_2: fraction of inspired oxygen; HR: heart rate; Lpm: litres per minute; $PaCO_2$: arterial partial pressure of carbon dioxide; PaO_2: arterial partial pressure of oxygen; RR: respiratory rate; SBP: systolic blood pressure

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Data and analyses

1 NPPV vs SMC

| Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 HOSPITAL MORTALITY	21	2484	Risk Ratio(M-H, Random, 95% CI)	0.65 [0.51, 0.82]
1.2 Hospital mortality - by NPPV	21	2484	Risk Ratio(M-H, Random, 95% CI)	0.71 [0.58, 0.87]
1.2.1 CPAP vs SMC	16	1454	Risk Ratio(M-H, Random, 95% CI)	0.65 [0.48, 0.88]
1.2.2 bilevel NPPV vs SMC	11	1030	Risk Ratio(M-H, Random, 95% CI)	0.72 [0.53, 0.98]
1.3 Hospital mortality - by location	21	2484	Risk Ratio(M-H, Random, 95% CI)	0.65 [0.51, 0.82]
1.3.1 ER	10	1596	Risk Ratio(M-H, Random, 95% CI)	0.66 [0.47, 0.93]
1.3.2 ICU	10	862	Risk Ratio(M-H, Random, 95% CI)	0.52 [0.35, 0.77]
1.3.3 unclear	1	26	Risk Ratio(M-H, Random, 95% CI)	1.94 [0.09, 43.50]
1.4 Hospital mortality - by baseline $PaCO_2$	21	2484	Risk Ratio(M-H, Random, 95% CI)	0.65 [0.51, 0.82]
1.4.1 PaCO2 <= 45mmHg	10	581	Risk Ratio(M-H, Random, 95% CI)	0.41 [0.27, 0.63]
1.4.2 PaCO2 > 45mmHg	11	1903	Risk Ratio(M-H, Random, 95% CI)	0.82 [0.65, 1.03]
1.5 Hospital mortality - sensitivity analysis (low risk of bias)	7	1505	Risk Ratio(M-H, Random, 95% CI)	0.81 [0.61, 1.06]
1.6 Hospital mortality - sensitivity analysis (missing data)	18	2283	Risk Ratio(M-H, Random, 95% CI)	0.68 [0.54, 0.86]
1.7 Hospital mortality - sensitivity analysis (fixed-effect)	21	2484	Risk Ratio(M-H, Fixed, 95% CI)	0.67 [0.55, 0.81]
1.8 ETI RATE	20	2449	Risk Ratio(M-H, Random, 95% CI)	0.49 [0.38, 0.62]
1.9 ETI rate - by NPPV	20	2449	Risk Ratio(M-H, Random, 95% CI)	0.49 [0.39, 0.63]
1.9.1 CPAP vs SMC	15	1413	Risk Ratio(M-H, Random, 95% CI)	0.46 [0.34, 0.62]
1.9.2 Bilevel NPPV vs SMC	11	1036	Risk Ratio(M-H, Random, 95% CI)	0.50 [0.31, 0.81]
1.10 ETI rate - by location	20	2449	Risk Ratio(M-H, Random, 95% CI)	0.49 [0.38, 0.62]
1.10.1 ER	9	1561	Risk Ratio(M-H, Random, 95% CI)	0.60 [0.37, 0.96]
1.10.2 ICU	10	862	Risk Ratio(M-H, Random, 95% CI)	0.40 [0.29, 0.56]
1.10.3 unclear	1	26	Risk Ratio(M-H, Random, 95% CI)	0.47 [0.13, 1.67]
1.11 ETI rate - by baseline $PaCO_2$	20	2449	Risk Ratio(M-H, Random, 95% CI)	0.49 [0.38, 0.62]
1.11.1 PaCO2 <= 45mmHg	9	523	Risk Ratio(M-H, Random, 95% CI)	0.37 [0.26, 0.52]
1.11.2 PaCO2 > 45mmHg	11	1926	Risk Ratio(M-H, Random, 95% CI)	0.64 [0.46, 0.91]
1.12 ETI rate - sensitivity analysis (low risk of bias)	6	1491	Risk Ratio(M-H, Random, 95% CI)	0.85 [0.55, 1.32]
1.13 ETI rate - sensitivity analysis (missing data)	17	2248	Risk Ratio(M-H, Random, 95% CI)	0.52 [0.40, 0.69]

1.14 ETI rate - by face mask type	20	2449	Risk Ratio(M-H, Random, 95% CI)	0.49 [0.38, 0.62]
1.14.1 Exclusive full face mask use	15	2213	Risk Ratio(M-H, Random, 95% CI)	0.52 [0.40, 0.69]
1.14.2 Exclusive or permissive nasal mask use	5	236	Risk Ratio(M-H, Random, 95% CI)	0.35 [0.20, 0.62]
1.15 ACUTE MI INCIDENCE	5	1313	Risk Ratio(M-H, Random, 95% CI)	1.03 [0.91, 1.16]
1.16 Acute MI incidence - by NPPV	5	1313	Risk Ratio(M-H, Random, 95% CI)	1.03 [0.91, 1.16]
1.16.1 CPAP vs SMC	3	569	Risk Ratio(M-H, Random, 95% CI)	0.96 [0.80, 1.14]
1.16.2 bilevel NPPV vs SMC	5	744	Risk Ratio(M-H, Random, 95% CI)	1.09 [0.92, 1.29]
1.17 HOSPITAL LENGTH OF STAY	11	1714	Mean Difference(IV, Random, 95% CI)	-0.31 [-1.23, 0.61]
1.18 Hospital length of stay - by NPPV	11	1714	Mean Difference(IV, Random, 95% CI)	-0.19 [-1.02, 0.64]
1.18.1 CPAP vs SMC	7	943	Mean Difference(IV, Random, 95% CI)	-0.52 [-1.77, 0.72]
1.18.2 bilevel NPPV vs SMC	6	771	Mean Difference(IV, Random, 95% CI)	0.39 [-0.35, 1.13]
1.19 Hospital length of stay - by location	11	1714	Mean Difference(IV, Random, 95% CI)	-0.30 [-1.21, 0.61]
1.19.1 ER	8	1455	Mean Difference(IV, Random, 95% CI)	-0.38 [-1.70, 0.93]
1.19.2 ICU	3	259	Mean Difference(IV, Random, 95% CI)	-0.21 [-1.30, 0.89]
1.20 Hospital length of stay - by baseline PaCO$_2$	11	1714	Mean Difference(IV, Random, 95% CI)	-0.30 [-1.21, 0.61]
1.20.1 PaCO2 <= 45mmHg	5	397	Mean Difference(IV, Random, 95% CI)	-1.18 [-2.33, -0.04]
1.20.2 PaCO2 > 45mmHg	6	1317	Mean Difference(IV, Random, 95% CI)	0.60 [-0.15, 1.34]
1.21 ICU LENGTH OF STAY	6		Mean Difference(IV, Random, 95% CI)	No totals
1.22 SYSTOLIC BP AFTER ONE HOUR	7	1408	Mean Difference(IV, Random, 95% CI)	-1.72 [-5.03, 1.58]
1.23 Systolic BP after one hour - by NPPV	7	1408	Mean Difference(IV, Random, 95% CI)	-1.72 [-5.03, 1.59]
1.23.1 CPAP vs SMC	7	866	Mean Difference(IV, Random, 95% CI)	-1.65 [-5.58, 2.28]
1.23.2 bilevel NPPV vs SMC	3	542	Mean Difference(IV, Random, 95% CI)	-1.89 [-8.01, 4.23]
1.24 DIASTOLIC BP AFTER ONE HOUR	6	1361	Mean Difference(IV, Random, 95% CI)	1.46 [-1.86, 4.78]
1.25 Diastolic BP after one hour - by NPPV	6	1361	Mean Difference(IV, Random, 95% CI)	1.05 [-2.15, 4.25]
1.25.1 CPAP vs SMC	6	823	Mean Difference(IV, Random, 95% CI)	0.92 [-3.92, 5.75]
1.25.2 bilevel NPPV vs SMC	3	538	Mean Difference(IV, Random, 95% CI)	1.08 [-2.88, 5.04]
1.26 MEAN BP AFTER ONE HOUR	3	251	Mean Difference(IV, Random, 95% CI)	-2.50 [-8.29, 3.30]
1.27 RESPIRATORY RATE AFTER ONE HOUR	10	1636	Mean Difference(IV, Random, 95% CI)	-1.87 [-2.70, -1.03]
1.28 Respiratory rate after one hour - by NPPV	10	1636	Mean Difference(IV, Random, 95% CI)	-1.58 [-2.22, -0.94]
1.28.1 CPAP vs SMC	10	1107	Mean Difference(IV, Random, 95% CI)	-1.64 [-2.41, -0.87]
1.28.2 bilevel NPPV vs SMC	3	529	Mean Difference(IV, Random, 95% CI)	-2.17 [-4.69, 0.35]

|				
1.29 PaO$_2$ (mmHg) AFTER ONE HOUR	10	1428	Mean Difference(IV, Random, 95% CI)	16.19 [3.54, 28.84]
1.30 PaO$_2$ (mmHg) after one hour - by NPPV	10	1428	Mean Difference(IV, Random, 95% CI)	13.74 [2.72, 24.76]
1.30.1 CPAP vs SMC	8	761	Mean Difference(IV, Random, 95% CI)	9.55 [-9.10, 28.19]
1.30.2 bilevel NPPV vs SMC	6	667	Mean Difference(IV, Random, 95% CI)	19.50 [4.29, 34.71]
1.31 ADVERSE EVENTS	11	9570	Risk Ratio(M-H, Random, 95% CI)	1.04 [0.73, 1.50]
1.31.1 Skin damage	2	190	Risk Ratio(M-H, Random, 95% CI)	9.09 [0.74, 111.09]
1.31.2 Pneumonia	1	130	Risk Ratio(M-H, Random, 95% CI)	0.50 [0.05, 5.38]
1.31.3 Gastrointestinal bleeding	2	170	Risk Ratio(M-H, Random, 95% CI)	2.32 [0.35, 15.42]
1.31.4 Gastric distention	1	83	Risk Ratio(M-H, Random, 95% CI)	13.26 [0.82, 215.12]
1.31.5 Vomiting	5	1467	Risk Ratio(M-H, Random, 95% CI)	1.03 [0.49, 2.17]
1.31.6 Pneumothorax	2	1165	Risk Ratio(M-H, Random, 95% CI)	0.72 [0.08, 6.89]
1.31.7 Sinusitis	1	130	Risk Ratio(M-H, Random, 95% CI)	3.00 [0.12, 72.31]
1.31.8 Discomfort with mask	3	1100	Risk Ratio(M-H, Random, 95% CI)	12.59 [2.39, 66.28]
1.31.9 Hypotension	1	1030	Risk Ratio(M-H, Random, 95% CI)	0.82 [0.58, 1.16]
1.31.10 Arrhythmia	1	1027	Risk Ratio(M-H, Random, 95% CI)	0.83 [0.50, 1.38]
1.31.11 Cardiorespiratory arrest	4	1352	Risk Ratio(M-H, Random, 95% CI)	0.60 [0.34, 1.05]
1.31.12 Gastric aspiration	1	1037	Risk Ratio(M-H, Random, 95% CI)	1.58 [0.06, 38.61]
1.31.13 Stroke	1	130	Risk Ratio(M-H, Random, 95% CI)	0.20 [0.01, 4.09]
1.31.14 Seizures	1	130	Risk Ratio(M-H, Random, 95% CI)	0.33 [0.01, 8.03]
1.31.15 Claustrophobia	1	130	Risk Ratio(M-H, Random, 95% CI)	3.00 [0.12, 72.31]
1.31.16 Hypercapnia	3	299	Risk Ratio(M-H, Random, 95% CI)	0.76 [0.16, 3.62]

Figures

Figure 1
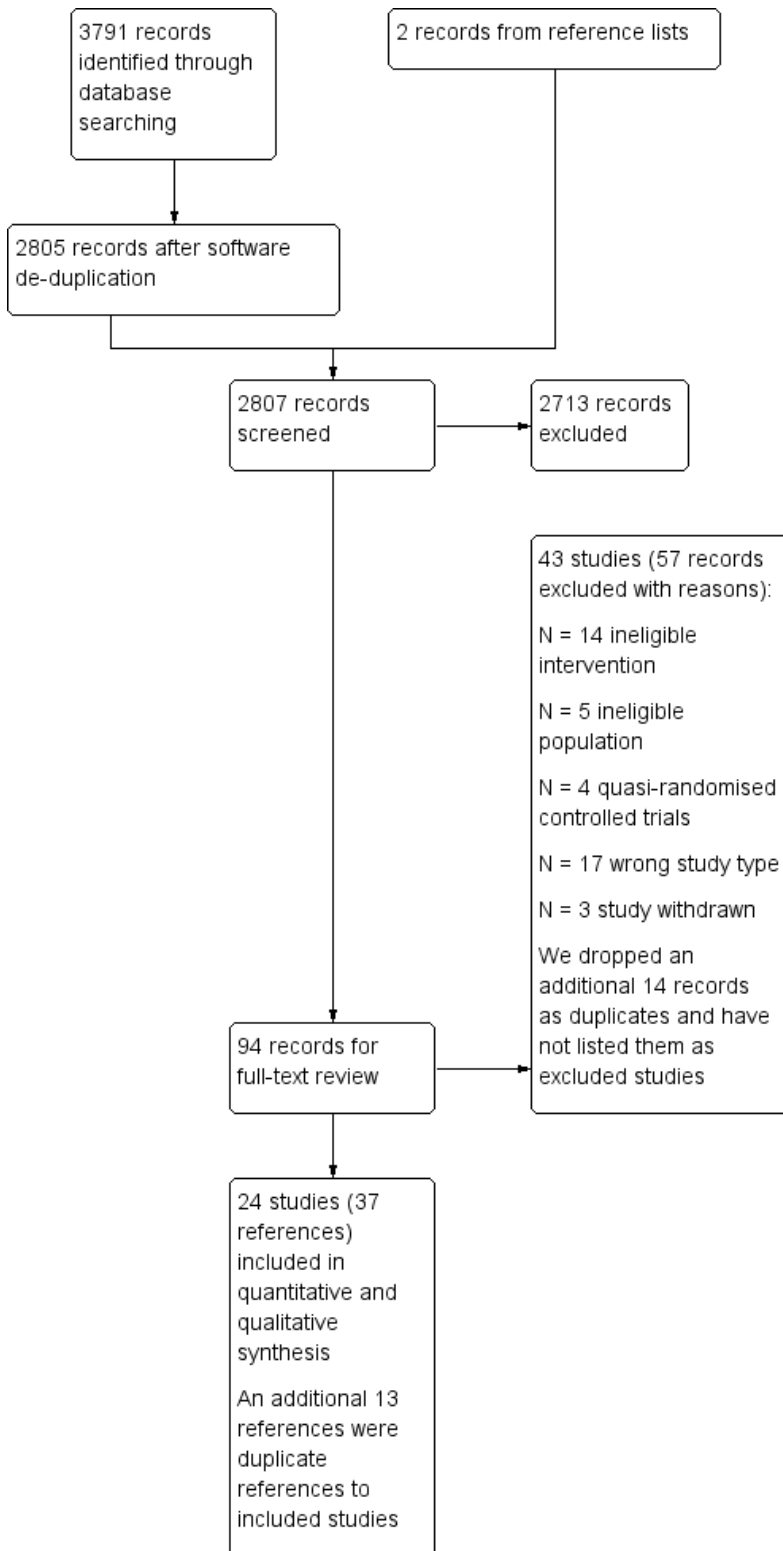
Caption

PRISMA statement flow diagram for 2019 review update.

Figure 2
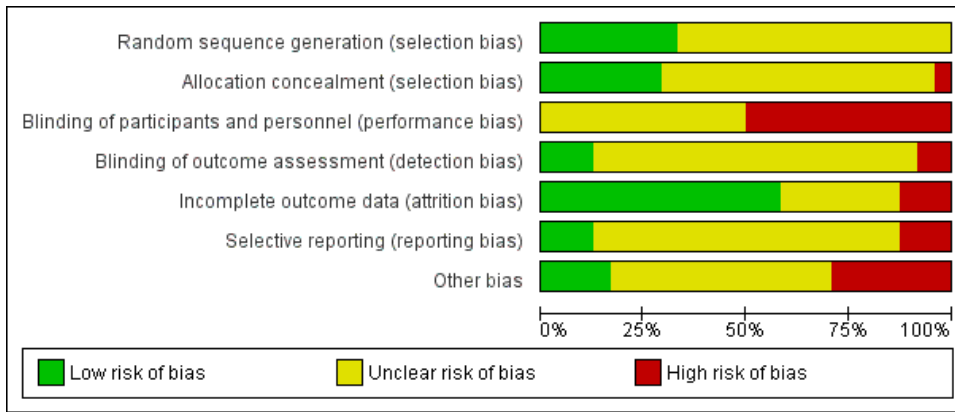
Caption

Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.
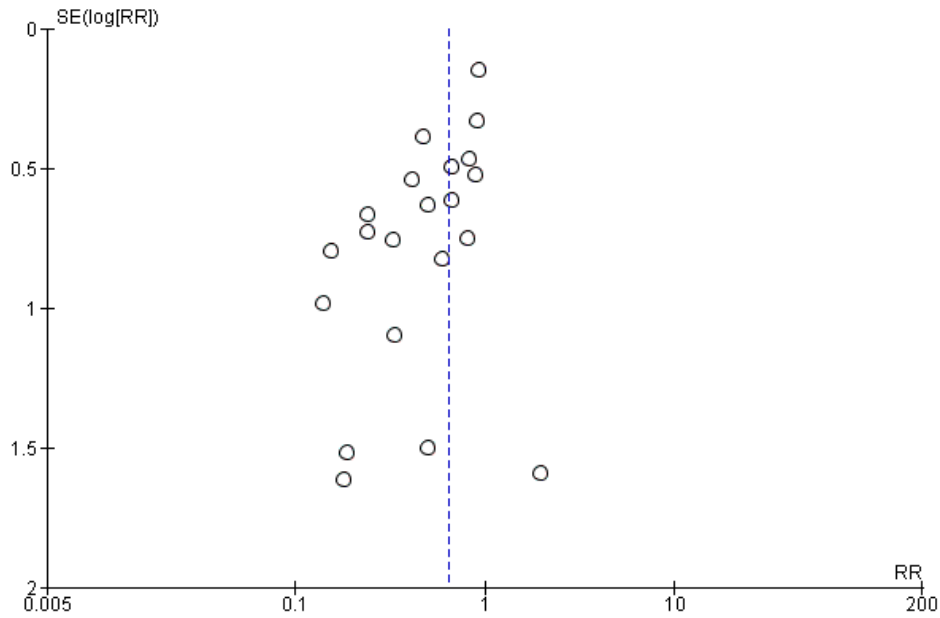
Figure 3

Caption

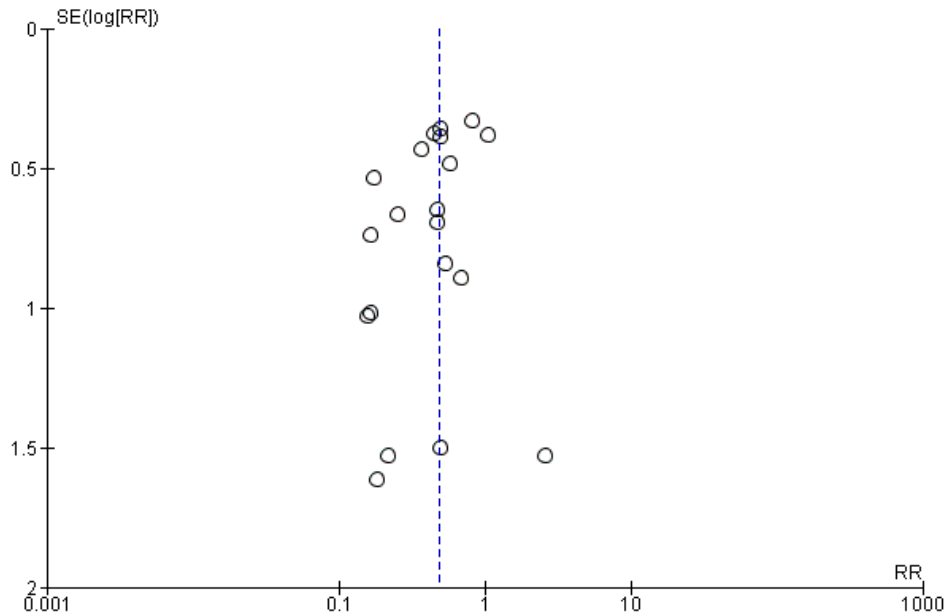Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Figure 4 (Analysis 1.1)

Caption

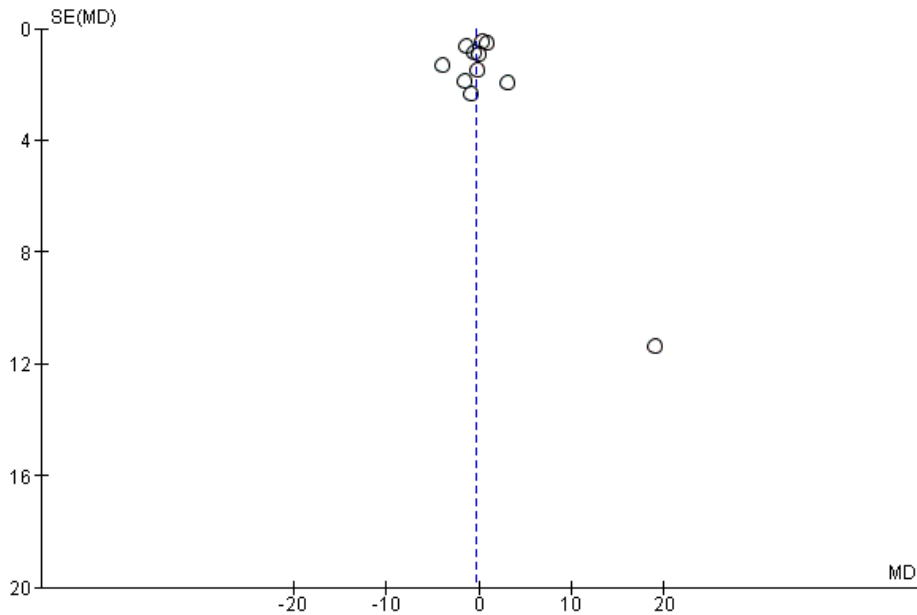Funnel plot of comparison: 1 NPPV vs SMC, outcome: 1.1 HOSPITAL MORTALITY.

Figure 5 (Analysis 1.8)

Caption

Funnel plot of comparison: 1 NPPV vs SMC, outcome: 1.8 ETI RATE.

Figure 6 (Analysis 1.17)

Caption

Funnel plot of comparison: 1 NPPV vs SMC, outcome: 1.17 HOSPITAL LENGTH OF STAY.

Sources of support

Internal sources

- No sources of support provided

External sources

- This project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Heart Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health, UK

Feedback

Appendices

1 Search strategy 2018

CENTRAL & DARE

#1 MeSH descriptor: [Heart Failure] explode all trees

#2 MeSH descriptor: [Myocardial Infarction] explode all trees

#3 myocardial next infarction

#4 (cardiogenic near/6 edema)

#5 (cardiogenic near/6 oedema)

#6 (pulmonary near/6 edema)

#7 (pulmonary near/6 oedema)

#8 heart next failure

#9 cardiac next failure

#10 cardiac next insufficiency

#11 heart next insufficiency

#12 left next ventricular next insufficiency

#13 left next ventricular next dysfunction

#14 wet next lung

#15 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14

#16 MeSH descriptor: [Ventilators, Mechanical] explode all trees

#17 MeSH descriptor: [Respiration, Artificial] explode all trees

#18 mechanical next ventilation

#19 artificial next ventilation

#20 assisted next ventilation

#21 artificial next respiration

#22 (positive near/6 pressure near/6 ventilation)

#23 (respirator or respirators)

#24 pulmonary next ventilat*

#25 non next invasive next ventilation

#26 noninvasive next ventilation

#27 non-invasive next ventilation

#28 positive next airway next pressure

#29 positive next pressure next respiration

#30 pressure next support next ventilation

#31 mask next ventilation

#32 bipap

#33 nippv

#34 nppv

#35 niv

#36 cpap

#37 niav

#38 aprv

#39 ippb

#40 ippv

#41 peep

#42 positive next end next expiratory next pressure

#43 (#16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26)

#44 (#27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36)

#45 (#37 or #38 or #39 or #40 or #41 or #42)

#46 #43 or #44 or #45

#47 #15 and #46

MEDLINE Ovid

1. exp Heart Failure/

2. exp Myocardial Infarction/

3. cardiogenic edema$.tw.

4. cardiogenic oedema$.tw.

5. pulmonary oedema.tw.

6. pulmonary edema.tw.

7. cardiac failure.tw.

8. heart failure.tw.

9. cardiac insufficiency.tw.

10. Pulmonary Edema/

11. heart insufficiency.tw.

12. Ventricular Dysfunction, Left/

13. wet lung.tw.

14. or/1-13

15. exp Respiration, Artificial/

16. exp Ventilators, Mechanical/

17. mechanical ventilation.tw.

18. artificial ventilation.tw.

19. assisted ventilation.tw.

20. artificial respiration.tw.

21. (respirator or respirators).tw.

22. bipap.tw.

23. nippv.tw.

24. nppv.tw.

25. niv.tw.

26. niav.tw.

27. cpap.tw.

28. aprv.tw.

29. ippb.tw.

30. ippv.tw.

31. peep.tw.

32. positive pressure ventilation.tw.

33. pulmonary ventilation.tw.

34. non invasive ventilation.tw.

35. noninvasive ventilation.tw.

36. pressure support ventilation.tw.

37. positive end expiratory pressure.tw.

38. bi-level positive airway pressure.tw.

39. bilevel positive airway pressure.tw.

40. or/15-39

41. 14 and 40

42. randomized controlled trial.pt.

43. controlled clinical trial.pt.

44. randomized.ab.

45. placebo.ab.

46. drug therapy.fs.

47. randomly.ab.

48. trial.ab.

49. groups.ab.

50. 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49

51. exp animals/ not humans.sh.

52. 50 not 51

53. 41 and 52

Embase Ovid

1. exp Congestive Heart Failure/

2. exp Heart Infarction/

3. cardiogenic oedema$.tw.

4. cardiogenic edema$.tw.

5. pulmonary oedema.tw.

6. pulmonary edema.tw.

7. cardiac failure.tw.

8. heart failure.tw.

9. cardiac insufficiency.tw.

10. Lung Edema/

11. heart insufficiency.tw.

12. heart left ventricle function/

13. wet lung.tw.

14. or/1-13

15. exp Ventilator/

16. exp Artificial Ventilation/

17. mechanical ventilation.tw.

18. artificial ventilation.tw.

19. assisted ventilation.tw.

20. artificial respiration.tw.

21. (respirator or respirators).tw.

22. bipap.tw.

23. nippv.tw.

24. nppv.tw.

25. niv.tw.

26. niav.tw.

27. cpap.tw.

28. aprv.tw.

29. ippb.tw.

30. ippv.tw.

31. peep.tw.

32. positive pressure ventilation.tw.

33. pulmonary ventilation.tw.

34. non invasive ventilation.tw.

35. noninvasive ventilation.tw.

36. pressure support ventilation.tw.

37. positive end expiratory pressure.tw.

38. bi-level positive airway pressure.tw.

39. bilevel positive airway pressure.tw.

40. or/15-39

41. 14 and 40

42. random$.tw.

43. factorial$.tw.

44. crossover$.tw.

45. cross over$.tw.

46. cross-over$.tw.

47. placebo$.tw.

48. (doubl$ adj blind$).tw.

49. (singl$ adj blind$).tw.

50. assign$.tw.

51. allocat$.tw.

52. volunteer$.tw.

53. crossover procedure/

54. double blind procedure/

55. randomized controlled trial/

56. single blind procedure/

57. 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56

58. (animal/ or nonhuman/) not human/

59. 57 not 58

60. 41 and 59

61. limit 60 to embase

CINAHL

S43 S14 and S39 and S42

S42 S40 or S41

S41 TI (random* or trial or clinical study or group* or placebo*) or AB (random* or trial or clinical study or group* or placebo*)

S40 (MH "Clinical Trials+")

S39 S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38

S38 TI (bi-level positive airway pressure) or AB (bi-level positive airway pressure)

S37 TI (positive end expiratory pressure) or AB (positive end expiratory pressure)

S36 TI (pressure support ventilation) or AB (pressure support ventilation)

S35 TI (noninvasive ventilation) or AB (noninvasive ventilation)

S34 TI (non invasive ventilation) or AB (non invasive ventilation)

S33 TI (pulmonary ventilation) or AB (pulmonary ventilation)

S32 TI (positive pressure ventilation) or AB (positive pressure ventilation)

S31 TI (peep) or AB (peep)

S30 TI (ippv) or AB (ippv)

S29 TI (ippb) or AB (ippb)

S28 TI (aprv) or AB (aprv)

S27 TI (cpap) or AB (cpap)

S26 TI (niav) or AB (niav)

S25 TI (niv) or AB (niv)

S24 TI (nppv) or AB (nppv)

S23 TI (nippv) or AB (nippv)

S22 TI (bipap) or AB (bipap)

S21 TI (respirator or respirators) or AB (respirator or respirators)

S20 TI (artificial respiration) or AB (artificial respiration)

S19 TI (assisted ventilation) or AB (assisted ventilation)

S18 TI (artificial ventilation) or AB (artificial ventilation)

S17 TI (mechanical ventilation) or AB (mechanical ventilation)

S16 (MH "Ventilation, Mechanical, Differentiated")

S15 (MH "Ventilators, Mechanical")

S14 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13

S13 TI (wet lung) or AB (wet lung)

S12 (MH "Ventricular Dysfunction, Left")

S11 TI (heart insufficiency) or AB (heart insufficiency)

S10 (MH "Pulmonary Edema")

S9 TI (cardiac insufficiency) or AB (cardiac insufficiency)

S8 TI (heart failure) or AB (heart failure)

S7 TI (cardiac failure) or AB (cardiac failure)

S6 TI (pulmonary edema*) or AB (pulmonary edema*)

S5 TI (pulmonary oedema*) or AB (pulmonary oedema*)

S4 TI (cardiogenic edema*) or AB (cardiogenic edema*)

S3 TI (cardiogenic oedema*) or AB (cardiogenic oedema*)

S2 (MH "Myocardial Infarction+")

S1 (MH "Heart Failure, Congestive+")

LILACS

("congestive heart failure" OR "cardiogenic edema" OR "cardiogenic oedema" OR "cardiac insufficiency" OR "heart insufficiency" OR "left ventricular dysfunction" OR "myocardial infarction" OR "heart failure" OR "pulmonary edema" OR "left ventricular dysfunction" OR "wet lungs") [Words] and ("artificial ventilation" OR "assisted ventilation" OR "mechanical ventilation" OR "artificial respiration" OR "positive pressure ventilation" OR "respirator or respirators" OR "pulmonary ventilator" OR "positive end expiratory pressure" OR "non invasive ventilation" OR "noninvasive ventilation" OR "bi-level positive airway pressure" OR "bilevel positive airway pressure" OR "positive airway pressure" OR "positive pressure respiration" OR "pressure support ventilation" OR "mask ventilation" OR "peep" OR "cpap" OR "nppv" OR "nippv" OR "niv" OR "niav" OR "aprv" OR "ippb" OR "ippv") [Words]

WHO database

Condition: congestive heart failure or cardiogenic oedema or cardiac insufficiency or heart insufficiency or left ventricular dysfunction or myocardial infarction or heart failure or pulmonary oedema or left ventricular dysfunction or wet lungs

Intervention: artificial ventilation or assisted ventilation or mechanical ventilation or positive pressure ventilation or positive end expiratory pressure or noninvasive ventilation or cpap or nppv or bilevel or niv

Clinicaltrials.gov

Condition: congestive heart failure OR cardiogenic edema OR cardiac insufficiency OR heart insufficiency OR left ventricular dysfunction OR myocardial infarction OR heart failure OR pulmonary oedema OR wet lungs

Intervention: (artificial OR assisted OR mechanical OR positive pressure OR noninvasive) AND ventilation OR positive end expiratory pressure OR cpap OR nppv OR bilevel OR niv