Ontario
Health Quality Ontario
Qualité des services de santé Ontario

Noninvasive Positive Pressure Ventilation for Acute Respiratory Failure Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis

BR McCurdy

March 2012

Ontario Health Technology Assessment Series; Vol. 12: No. 8, pp. 1–102, March 2012

Suggested Citation

This report should be cited as follows:

McCurdy BR. Noninvasive positive pressure ventilation for acute respiratory failure in patients with chronic obstructive pulmonary disease (COPD): an evidence-based analysis. Ont Health Technol Assess Ser [Internet]. 2012 March; 12(8):1-102. Available from:
www.hqontario.ca/en/mas/tech/pdfs/2012/rev_COPD_Ventilation_Acute_March.pdf

Indexing

The *Ontario Health Technology Assessment Series* is currently indexed in Excerpta Medica/EMBASE and the Center for Reviews and Dissemination database.

Permission Requests

All inquiries regarding permission to reproduce any content in the *Ontario Health Technology Assessment Series* should be directed to: MASinfo@hqontario.ca.

How to Obtain Issues in the *Ontario Health Technology Assessment Series*

All reports in the *Ontario Health Technology Assessment Series* are freely available in PDF format at the following URL: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

Conflict of Interest Statement

All analyses in the *Ontario Health Technology Assessment Series* are impartial and subject to a systematic evidence-based assessment process. There are no competing interests or conflicts of interest to declare.

Peer Review

All analyses in the *Ontario Health Technology Assessment Series* are subject to external expert peer review. Additionally, the public consultation process is also available to individuals wishing to comment on an analysis prior to finalization. For more information, please visit:
http://www.hqontario.ca/en/mas/ohtac_public_engage_overview.html.

About the Medical Advisory Secretariat

Effective April 5, 2011, the Medical Advisory Secretariat (MAS) became a part of Health Quality Ontario (HQO), an independent body funded by the Ministry of Health and Long-Term Care. The mandate of MAS is to provide evidence-based recommendations on the coordinated uptake of health services and health technologies in Ontario to the Ministry of Health and Long-Term Care and to the health care system. This mandate helps to ensure that residents of Ontario have access to the best available and most appropriate health services and technologies to improve patient outcomes.

To fulfill its mandate, MAS conducts systematic reviews of evidence and consults with experts in the health care services community. The resulting evidence-based analyses are reviewed by the Ontario Health Technology Advisory Committee—to which MAS also provides a secretariat function—and published in the *Ontario Health Technology Assessment Series*.

About the *Ontario Health Technology Assessment Series*

To conduct its comprehensive analyses, MAS systematically reviews the available scientific literature, making every effort to consider all relevant national and international research; collaborates with partners across relevant government branches; consults with clinical and other external experts and developers of new health technologies; and solicits any necessary supplemental information.

In addition, the Secretariat collects and analyzes information about how a new technology fits within current practice and existing treatment alternatives. Details about the technology's diffusion into current health care practices add an important dimension to the review of the provision and delivery of the health technology in Ontario. Information concerning the health benefits; economic and human resources; and ethical, regulatory, social and legal issues relating to the technology assist decision-makers in making timely and relevant decisions to optimize patient outcomes.

The public consultation process is available to individuals wishing to comment on an analysis prior to publication. For more information, please visit: http://www.hqontario.ca/en/mas/ohtac_public_engage_overview.html.

Disclaimer

This evidence-based analysis was prepared by MAS for the *Ontario Health Technology Advisory Committee* and developed from analysis, interpretation, and comparison of scientific research and/or technology assessments conducted by other organizations. It also incorporates, when available, Ontario data and information provided by experts and applicants to MAS to inform the analysis. While every effort has been made to reflect all scientific research available, this document may not fully do so. Additionally, other relevant scientific findings may have been reported since completion of the review. This evidence-based analysis is current to the date of the literature review specified in the methods section. This analysis may be superseded by an updated publication on the same topic. Please check the MAS website for a list of all evidence-based analyses: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

Table of Contents

TABLE OF CONTENTS 4

LIST OF TABLES 6

LIST OF FIGURES 7

LIST OF ABBREVIATIONS 8

EXECUTIVE SUMMARY 9

Objective 10

Clinical Need and Target Population 10

Acute Hypercapnic Respiratory Failure 10

Technology 10

Research Questions 11

Research Methods 11

Literature Search 11

Statistical Methods 12

Quality of Evidence 12

Summary of Findings 13

NPPV for the Treatment of ARF due to Acute Exacerbations of COPD 13

NPPV for Weaning COPD Patients From IMV 15

NPPV After Extubation of COPD Patients From IMV 16

Conclusions 16

NPPV Plus UMC Versus UMC Alone for First Line Treatment of ARF due to Acute Exacerbations of COPD 16

NPPV Versus IMV for the Treatment of ARF in Patients Who Have Failed UMC 16

NPPV for Weaning COPD Patients From IMV 17

NPPV for the Treatment of ARF in COPD Patients After Extubation From IMV 17

BACKGROUND 18

Objective of Analysis 19

Clinical Need and Target Population 19

Acute Hypercapnic Respiratory Failure 19

Technology 19

NPPV to Wean COPD Patients From IMV 20

NPPV to Prevent or Treat Recurrent ARF After Extubation From IMV 20

EVIDENCE-BASED ANALYSIS 21

Research Questions 21

Research Methods 21

Literature Search 21

Statistical Analysis 22

Quality of Evidence 23

Results of Evidence-Based Analysis 24

NPPV for the Treatment of Acute Respiratory Failure due to Acute Exacerbations of COPD 25

Systematic Reviews 26

Randomized Controlled Trials 26

NPPV for Weaning COPD Patients From IMV 42

Systematic Reviews 42

Randomized Controlled Trials 42

NPPV After Extubation From IMV in COPD Patients 45
Systematic Reviews 45
Randomized Controlled Trials 46
ECONOMIC ANALYSIS 48
CONCLUSIONS 49
GLOSSARY 50
ACKNOWLEDGEMENTS 53
APPENDICES 55
Appendix 1: Literature Search Strategies 55
Appendix 2: Details About Included Systematic Reviews 58
NPPV for the Treatment of Acute Respiratory Failure due to Acute Exacerbations of COPD: Systematic Reviews 58
NPPV for Weaning COPD Patients From Invasive Mechanical Ventilation: Systematic Reviews 66
NPPV for Acute Respiratory Failure After Extubation From Invasive Mechanical Ventilation: Systematic Reviews 70
Appendix 3: Detailed Study Descriptions 71
NPPV for the Treatment of ARF due to Acute Exacerbations of COPD: NPPV Plus UMC Versus UMC Alone 71
NPPV for the Treatment of Acute Respiratory Failure due to Acute Exacerbations of COPD: NPPV Versus IMV 80
NPPV for Weaning COPD Patients from Invasive Mechanical Ventilation 83
Appendix 4: Summary Tables of Study Methodological Quality and GRADE Quality of Evidence 87
NPPV for the Treatment of ARF due to Acute Exacerbations of COPD: NPPV for ARF 87
NPPV for Weaning COPD Patients from IMV: NPPV Versus IMV 91
NPPV for ARF After Extubation From IMV: NPPV Plus UMC Versus UMC Alone 93
Appendix 5: Subgroup Analyses 94
REFERENCES 96

List of Tables

Table 1: Body of Evidence Examined According to Study Design* 25
Table 2: Duration of NPPV (NPPV Plus UMC Versus UMC Alone Comparison)* 27
Table 3: Mean Hospital Length of Stay (NPPV Plus UMC Versus UMC Alone)* 32
Table 4: Dyspnea Results (NPPV Plus UMC Versus UMC Alone Comparison)* 35
Table 5: NPPV Tolerance (NPPV Plus UMC Versus UMC Alone Comparison)* 36
Table 6: Reported Complications by Study Group (NPPV Plus UMC Versus UMC Alone Comparison)* 37
Table 7: Summary of Results (NPPV Versus IMV Comparison)* 40
Table 8: Complications (NPPV Versus IMV Comparison)* 41
Table 9: Summary of Findings by Research Question* 49
Table A1: Comparison of Systematic Reviews Published Since 2000 and MAS Evidence-Based Reviews* 58
Table A2: Summary of the Systematic Reviews' Methods* 61
Table A3: Summary of the Systematic Reviews' Results* 64
Table A4: Comparison of Systematic Reviews Published Since 2000 (NPPV for Weaning)* 66
Table A5: Summary of the Systematic Reviews' Methods (NPPV for Weaning)* 67
Table A6: Summary of the Systematic Reviews' Results (NPPV for Weaning)* 69
Table A7: Comparison of Systematic Reviews Published Since 2000 (NPPV Postextubation from IMV)* 70
Table A8: General Study Characteristics (NPPV Plus UMC Versus UMC Alone)* 71
Table A9: General Study Characteristics – Intervention and Control Group Details (NPPV Plus UMC Versus UMC Alone)* 75
Table A10: Characteristics of the Patients in the Included Studies (NPPV Plus UMC Versus UMC Alone)* 78
Table A11: General Study Characteristics (NPPV Versus IMV)* 80
Table A12: General Study Characteristics – Intervention and Control Group Details (NPPV Versus IMV)* 81
Table A13: Characteristics of the Patients in the Included Studies (NPPV Versus IMV)* 82
Table A14: General Study Characteristics (NPPV Versus IMV for Weaning)* 83
Table A15: General Study Characteristics – Intervention and Control Group Details (NPPV Versus IMV for Weaning)* 85
Table A16: Characteristics of the Patients in the Included Studies (NPPV Versus IMV for Weaning)* 86
Table A17: Summary of Study Methodological Characteristics That Impact Study Quality (NPPV Plus UMC Versus UMC Alone or IMV)* 87
Table A18: GRADE Quality of Evidence (NPPV Plus UMC Versus UMC Alone)* 89
Table A19: GRADE Quality of Evidence (NPPV Versus IMV)* 90
Table A20: GRADE Quality of Evidence (NPPV Versus IMV for Weaning)* 91
Table A21: Summary of Study Methodological Characteristics That Impact Study Quality (NPPV Versus IMV for Weaning)* 92
Table A22: Summary of Study Methodological Characteristics That Impact Study Quality (NPPV Versus UMC After Extubation)* 93
Table A23: GRADE Quality of Evidence (NPPV Versus UMC After Extubation)* 93

List of Figures

Figure 1: Citation Flow Chart 24
Figure 2: Pooled Results for the Need for Endotracheal Intubation (NPPV Plus UMC Versus UMC Alone)* 28
Figure 3: Pooled Results for the Need for Endotracheal Intubation Stratified by Severity of ARF (NPPV Plus UMC Versus UMC Alone Comparison)* 29
Figure 4: Pooled Results for Inhospital Mortality (NPPV Plus UMC Versus UMC Alone Comparison)* 30
Figure 5: Pooled Results for Inhospital Mortality Stratified by Severity of ARF (NPPV Plus UMC Versus UMC Alone Comparison)* 31
Figure 6: Pooled Results for Mean Hospital Length of Stay (NPPV Plus UMC Versus UMC Alone Comparison)* 33
Figure 7: Pooled Mean Hospital Length of Stay Stratified by Severity of ARF (NPPV Plus UMC Versus UMC Alone)* 34
Figure 8: Pooled Mortality Results (NPPV Versus IMV for Weaning Comparison)* 43
Figure 9: Pooled ICU Length of Stay Results (NPPV Versus IMV for Weaning Comparison)* 43
Figure 10: Pooled Duration of Mechanical Ventilation (NPPV Versus IMV for Weaning Comparison)* 44
Figure 11: Pooled Incidence of Nosocomial Pneumonia (NPPV Versus IMV for Weaning Comparison)* 44
Figure A1: Pooled Results for the Need for Endotracheal Intubation by Hospital Ward or ICU (NPPV Plus UMC Versus UMC Alone)* 94
Figure A2: Pooled Results for the Need for Endotracheal Intubation by Presence of A Priori Intubation Criteria (NPPV Plus UMC Versus UMC Alone)* 95

List of Abbreviations

ARF	Acute Respiratory Failure
BiPAP	Bilevel positive airway pressure
CI	Confidence interval(s)
cm H_2O	Centimetres of water
COPD	Chronic obstructive pulmonary disease
FEV_1	Forced expiratory volume in 1 second
FiO_2	Fraction of inspired oxygen
HRQOL	Health-related quality of life
ICU	Intensive care unit
IMV	Invasive mechanical ventilation
LOS	Length of stay
MAS	Medical Advisory Secretariat
NPPV	Noninvasive positive pressure ventilation
$PaCO_2$	Partial pressure of carbon dioxide in the arterial blood
PaO_2	Partial pressure of oxygen in the arterial blood
RCT	Randomized controlled trial
RR	Relative risk
SD	Standard deviation
UMC	Usual medical care
VAP	Ventilator-associated pneumonia
WMD	Weighted mean difference

Executive Summary

In July 2010, the Medical Advisory Secretariat (MAS) began work on a Chronic Obstructive Pulmonary Disease (COPD) evidentiary framework, an evidence-based review of the literature surrounding treatment strategies for patients with COPD. This project emerged from a request by the Health System Strategy Division of the Ministry of Health and Long-Term Care that MAS provide them with an evidentiary platform on the effectiveness and cost-effectiveness of COPD interventions.

After an initial review of health technology assessments and systematic reviews of COPD literature, and consultation with experts, MAS identified the following topics for analysis: vaccinations (influenza and pneumococcal), smoking cessation, multidisciplinary care, pulmonary rehabilitation, long-term oxygen therapy, noninvasive positive pressure ventilation for acute and chronic respiratory failure, hospital-at-home for acute exacerbations of COPD, and telehealth (including telemonitoring and telephone support). Evidence-based analyses were prepared for each of these topics. For each technology, an economic analysis was also completed where appropriate. In addition, a review of the qualitative literature on patient, caregiver, and provider perspectives on living and dying with COPD was conducted, as were reviews of the qualitative literature on each of the technologies included in these analyses.

The Chronic Obstructive Pulmonary Disease Mega-Analysis series is made up of the following reports, which can be publicly accessed at the MAS website at: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

- Chronic Obstructive Pulmonary Disease (COPD) Evidentiary Framework
- Influenza and Pneumococcal Vaccinations for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Smoking Cessation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Community-Based Multidisciplinary Care for Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Pulmonary Rehabilitation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Long-term Oxygen Therapy for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Acute Respiratory Failure Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Chronic Respiratory Failure Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Hospital-at-Home Programs for Patients With Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Home Telehealth for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Cost-Effectiveness of Interventions for Chronic Obstructive Pulmonary Disease Using an Ontario Policy Model
- Experiences of Living and Dying With COPD: A Systematic Review and Synthesis of the Qualitative Empirical Literature

For more information on the qualitative review, please contact Mita Giacomini at: http://fhs.mcmaster.ca/ceb/faculty_member_giacomini.htm.

For more information on the economic analysis, please visit the PATH website: http://www.path-hta.ca/About-Us/Contact-Us.aspx.

The Toronto Health Economics and Technology Assessment (THETA) collaborative has produced an associated report on patient preference for mechanical ventilation. For more information, please visit the THETA website: http://theta.utoronto.ca/static/contact.

Objective

The objective of this evidence-based analysis was to examine the effectiveness, safety, and cost-effectiveness of noninvasive positive pressure ventilation (NPPV) in the following patient populations: patients with acute respiratory failure (ARF) due to acute exacerbations of chronic obstructive pulmonary disease (COPD); weaning of COPD patients from invasive mechanical ventilation (IMV); and prevention of or treatment of recurrent respiratory failure in COPD patients after extubation from IMV.

Clinical Need and Target Population

Acute Hypercapnic Respiratory Failure

Respiratory failure occurs when the respiratory system cannot oxygenate the blood and/or remove carbon dioxide from the blood. It can be either acute or chronic and is classified as either hypoxemic (type I) or hypercapnic (type II) respiratory failure. Acute hypercapnic respiratory failure frequently occurs in COPD patients experiencing acute exacerbations of COPD, so this is the focus of this evidence-based analysis. Hypercapnic respiratory failure occurs due to a decrease in the drive to breathe, typically due to increased work to breathe in COPD patients.

Technology

There are several treatment options for ARF. Usual medical care (UMC) attempts to facilitate adequate oxygenation and treat the cause of the exacerbation, and typically consists of supplemental oxygen, and a variety of medications such as bronchodilators, corticosteroids, and antibiotics. The failure rate of UMC is high and has been estimated to occur in 10% to 50% of cases.

The alternative is mechanical ventilation, either invasive or noninvasive. Invasive mechanical ventilation involves sedating the patient, creating an artificial airway through endotracheal intubation, and attaching the patient to a ventilator. While this provides airway protection and direct access to drain sputum, it can lead to substantial morbidity, including tracheal injuries and ventilator-associated pneumonia (VAP).

While both positive and negative pressure noninvasive ventilation exists, noninvasive negative pressure ventilation such as the iron lung is no longer in use in Ontario. Noninvasive positive pressure ventilation provides ventilatory support through a facial or nasal mask and reduces inspiratory work. Noninvasive positive pressure ventilation can often be used intermittently for short periods of time to treat respiratory failure, which allows patients to continue to eat, drink, talk, and participate in their own treatment decisions. In addition, patients do not require sedation, airway defence mechanisms and swallowing functions are maintained, trauma to the trachea and larynx are avoided, and the risk for VAP is reduced. Common complications are damage to facial and nasal skin, higher incidence of gastric distension with aspiration risk, sleeping disorders, and conjunctivitis. In addition, NPPV does not allow direct access to the airway to drain secretions and requires patients to cooperate, and due to potential discomfort, compliance and tolerance may be low.

In addition to treating ARF, NPPV can be used to wean patients from IMV through the gradual removal of ventilation support until the patient can breathe spontaneously. Five to 30% of patients have difficultly weaning. Tapering levels of ventilatory support to wean patients from IMV can be achieved using IMV or NPPV. The use of NPPV helps to reduce the risk of VAP by shortening the time the patient is intubated.

Following extubation from IMV, ARF may recur, leading to extubation failure and the need for reintubation, which has been associated with increased risk of nosocomial pneumonia and mortality. To

avoid these complications, NPPV has been proposed to help prevent ARF recurrence and/or to treat respiratory failure when it recurs, thereby preventing the need for reintubation.

Research Questions

1. What is the effectiveness, cost-effectiveness, and safety of NPPV for the treatment of acute hypercapnic respiratory failure due to acute exacerbations of COPD compared with
   a. usual medical care, and
   b. invasive mechanical ventilation?
2. What is the effectiveness, cost-effectiveness, and safety of NPPV compared with IMV in COPD patients after IMV for the following purposes:
   a. weaning COPD patients from IMV,
   b. preventing ARF in COPD patients after extubation from IMV, and
   c. treating ARF in COPD patients after extubation from IMV?

Research Methods

Literature Search

A literature search was performed on December 3, 2010 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, the Cumulative Index to Nursing & Allied Health Literature (CINAHL), Wiley Cochrane, and the Centre for Reviews and Dissemination/International Agency for Health Technology Assessment (INAHTA) for studies published from January 1, 2004 until December 3, 2010. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search.

Since there were numerous studies that examined the effectiveness of NPPV for the treatment of ARF due to exacerbations of COPD published before 2004, pre-2004 trials which met the inclusion/exclusion criteria for this evidence-based review were identified by hand-searching reference lists of included studies and systematic reviews.

Inclusion Criteria

- English language full-reports;
- health technology assessments, systematic reviews, meta-analyses, and randomized controlled trials (RCTs);
- studies performed exclusively in patients with a diagnosis of COPD or studies performed with patients with a mix of conditions if results are reported for COPD patients separately;
- patient population: (Question 1) patients with acute hypercapnic respiratory failure due to an exacerbation of COPD; (Question 2a) COPD patients being weaned from IMV; (Questions 2b and 2c) COPD patients who have been extubated from IMV.

Exclusion Criteria

- < 18 years of age
- animal studies

- duplicate publications
- grey literature
- studies examining noninvasive negative pressure ventilation
- studies comparing modes of ventilation
- studies comparing patient-ventilation interfaces
- studies examining outcomes not listed below, such as physiologic effects including heart rate, arterial blood gases, and blood pressure

Outcomes of Interest

- mortality
- intubation rates
- length of stay (intensive care unit [ICU] and hospital)
- health-related quality of life
- breathlessness
- duration of mechanical ventilation
- weaning failure
- complications
- NPPV tolerance and compliance

Statistical Methods

When possible, results were pooled using Review Manager 5 Version 5.1, otherwise, the results were summarized descriptively. Dichotomous data were pooled into relative risks using random effects models and continuous data were pooled using weighted mean differences with a random effects model. Analyses using data from RCTs were done using intention-to-treat protocols; P values < 0.05 were considered significant. A priori subgroup analyses were planned for severity of respiratory failure, location of treatment (ICU or hospital ward), and mode of ventilation with additional subgroups as needed based on the literature. Post hoc sample size calculations were performed using STATA 10.1.

Quality of Evidence

The quality of each included study was assessed taking into consideration allocation concealment, randomization, blinding, power/sample size, withdrawals/dropouts, and intention-to-treat analyses.

The quality of the body of evidence was assessed as high, moderate, low, or very low according to the GRADE Working Group criteria. The following definitions of quality were used in grading the quality of the evidence:

High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain.

Summary of Findings

NPPV for the Treatment of ARF due to Acute Exacerbations of COPD

NPPV Plus Usual Medical Care Versus Usual Medical Care Alone for First Line Treatment

A total of 1,000 participants were included in 11 RCTs[1]; the sample size ranged from 23 to 342. The mean age of the participants ranged from approximately 60 to 72 years of age. Based on either the Global Initiative for Chronic Obstructive Lung Disease (GOLD) COPD stage criteria or the mean percent predicted forced expiratory volume in 1 second (FEV_1), 4 of the studies included people with severe COPD, and there was inadequate information to classify the remaining 7 studies by COPD severity. The severity of the respiratory failure was classified into 4 categories using the study population mean pH level as follows: mild ($pH \geq 7.35$), moderate ($7.30 \leq pH < 7.35$), severe ($7.25 \leq pH < 7.30$), and very severe ($pH < 7.25$). Based on these categories, 3 studies included patients with a mild respiratory failure, 3 with moderate respiratory failure, 4 with severe respiratory failure, and 1 with very severe respiratory failure.

The studies were conducted either in the ICU (3 of 11 studies) or general or respiratory wards (8 of 11 studies) in hospitals, with patients in the NPPV group receiving bilevel positive airway pressure (BiPAP) ventilatory support, except in 2 studies, which used pressure support ventilation and volume cycled ventilation, respectively. Patients received ventilation through nasal, facial, or oronasal masks. All studies specified a protocol or schedule for NPPV delivery, but this varied substantially across the studies. For example, some studies restricted the amount of ventilation per day (e.g., 6 hours per day) and the number of days it was offered (e.g., maximum of 3 days); whereas, other studies provided patients with ventilation for as long as they could tolerate it and recommended it for much longer periods of time (e.g., 7 to 10 days). These differences are an important source of clinical heterogeneity between the studies. In addition to NPPV, all patients in the NPPV group also received UMC. Usual medical care varied between the studies, but common medications included supplemental oxygen, bronchodilators, corticosteroids, antibiotics, diuretics, and respiratory stimulators.

The individual quality of the studies ranged. Common methodological issues included lack of blinding and allocation concealment, and small sample sizes.

Need for Endotracheal Intubation

Eleven studies reported the need for endotracheal intubation as an outcome. The pooled results showed a significant reduction in the need for endotracheal intubation in the NPPV plus UMC group compared with the UMC alone group (relative risk [RR], 0.38; 95% confidence interval [CI], 0.28–0.50). When subgrouped by severity of respiratory failure, the results remained significant for the mild, severe, and very severe respiratory failure groups.
GRADE: moderate

Inhospital Mortality

Nine studies reported inhospital mortality as an outcome. The pooled results showed a significant reduction in inhospital mortality in the NPPV plus UMC group compared with the UMC group (RR, 0.53; 95% CI, 0.35–0.81). When subgrouped by severity of respiratory failure, the results remained significant for the moderate and severe respiratory failure groups.
GRADE: moderate

Hospital Length of Stay

Eleven studies reported hospital length of stay (LOS) as an outcome. The pooled results showed a significant decrease in the mean length of stay for the NPPV plus UMC group compared with the UMC

[1] Two of the RCTs reported results from the same study, so these papers were treated as 1 publication.

alone group (weighted mean difference [WMD], −2.68 days; 95% CI, −4.41 to −0.94 days). When subgrouped by severity of respiratory failure, the results remained significant for the mild, severe, and very severe respiratory failure groups.
GRADE: moderate

Complications
Five studies reported complications. Common complications in the NPPV plus UMC group included pneumonia, gastrointestinal disorders or bleeds, skin abrasions, eye irritation, gastric insufflation, and sepsis. Similar complications were observed in the UMC group including pneumonia, sepsis, gastrointestinal disorders or bleeds, pneumothorax, and complicated endotracheal intubations. Many of the more serious complications in both groups occurred in those patients who required endotracheal intubation. Three of the studies compared complications in the NPPV plus UMC and UMC groups. While the data could not be pooled, overall, the NPPV plus UMC group experienced fewer complications than the UMC group.
GRADE: low

Tolerance/Compliance
Eight studies reported patient tolerance or compliance with NPPV as an outcome. NPPV intolerance ranged from 5% to 29%. NPPV tolerance was generally higher for patients with more severe respiratory failure. Compliance with the NPPV protocol was reported by 2 studies, which showed compliance decreases over time, even over short periods such as 3 days.

NPPV Versus IMV for the Treatment of Patients Who Failed Usual Medical Care
A total of 205 participants were included in 2 studies; the sample sizes of these studies were 49 and 156. The mean age of the patients was 71 to 73 years of age in 1 study, and the median age was 54 to 58 years of age in the second study. Based on either the GOLD COPD stage criteria or the mean percent predicted FEV_1, patients in 1 study had very severe COPD. The COPD severity could not be classified in the second study. Both studies had study populations with a mean pH less than 7.23, which was classified as very severe respiratory failure in this analysis. One study enrolled patients with ARF due to acute exacerbations of COPD who had failed medical therapy. The patient population was not clearly defined in the second study, and it was not clear whether they had to have failed medical therapy before entry into the study.

Both studies were conducted in the ICU. Patients in the NPPV group received BiPAP ventilatory support through nasal or full facial masks. Patients in the IMV group received pressure support ventilation.

Common methodological issues included small sample size, lack of blinding, and unclear methods of randomization and allocation concealment. Due to the uncertainty about whether both studies included the same patient population and substantial differences in the direction and significance of the results, the results of the studies were not pooled.

Mortality
Both studies reported ICU mortality. Neither study showed a significant difference in ICU mortality between the NPPV and IMV groups, but 1 study showed a higher mortality rate in the NPPV group (21.7% vs. 11.5%) while the other study showed a lower mortality rate in the NPPV group (5.1% vs. 6.4%). One study reported 1-year mortality and showed a nonsignificant reduction in mortality in the NPPV group compared with the IMV group (26.1% vs. 46.1%).
GRADE: low to very low

Intensive Care Unit Length of Stay
Both studies reported LOS in the ICU. The results were inconsistent. One study showed a statistically significant shorter LOS in the NPPV group compared with the IMV group (5 ± 1.35 days vs. 9.29 ± 3

days; $P < 0.001$); whereas, the other study showed a nonsignificantly longer LOS in the NPPV group compared with the IMV group (22 ± 19 days vs. 21 ± 20 days; $P = 0.86$).
GRADE: very low

Duration of Mechanical Ventilation
Both studies reported the duration of mechanical ventilation (including both invasive and noninvasive ventilation). The results were inconsistent. One study showed a statistically significant shorter duration of mechanical ventilation in the NPPV group compared with the IMV group (3.92 ± 1.08 days vs. 7.17 ± 2.22 days; $P < 0.001$); whereas, the other study showed a nonsignificantly longer duration of mechanical ventilation in the NPPV group compared with the IMV group (16 ± 19 days vs. 15 ± 21 days; $P = 0.86$).
GRADE: very low

Complications
Both studies reported ventilator-associated pneumonia and tracheotomies. Both showed a reduction in ventilator-associated pneumonia in the NPPV group compared with the IMV group, but the results were only significant in 1 study (13% vs. 34.6%, $P = 0.07$; and 6.4% vs. 37.2%, $P < 0.001$, respectively). Similarly, both studies showed a reduction in tracheotomies in the NPPV group compared with the IMV group, but the results were only significant in 1 study (13% vs. 23.1%, $P = 0.29$; and 6.4% vs. 34.6%; $P < 0.001$).
GRADE: very low

Other Outcomes
One of the studies followed patients for 12 months. At the end of follow-up, patients in the NPPV group had a significantly lower rate of needing de novo oxygen supplementation at home. In addition, the IMV group experienced significant increases in functional limitations due to COPD, while no increase was seen in the NPPV group. Finally, no significant differences were observed for hospital readmissions, ICU readmissions, and patients with an open tracheotomy, between the NPPV and IMV groups.

NPPV for Weaning COPD Patients From IMV

A total of 80 participants were included in the 2 RCTs; the sample sizes of the studies were 30 and 50 patients. The mean age of the participants ranged from 58 to 69 years of age. Based on either the GOLD COPD stage criteria or the mean percent predicted FEV_1, both studies included patients with very severe COPD. Both studies also included patients with very severe respiratory failure (mean pH of the study populations was less than 7.23). Chronic obstructive pulmonary disease patients receiving IMV were enrolled in the study if they failed a T-piece weaning trial (spontaneous breathing test), so they could not be directly extubated from IMV.

Both studies were conducted in the ICU. Patients in the NPPV group received weaning using either BiPAP or pressure support ventilation NPPV through a face mask, and patients in the IMV weaning group received pressure support ventilation. In both cases, weaning was achieved by tapering the ventilation level.

The individual quality of the studies ranged. Common methodological problems included unclear randomization methods and allocation concealment, lack of blinding, and small sample size.

Mortality
Both studies reported mortality as an outcome. The pooled results showed a significant reduction in ICU mortality in the NPPV group compared with the IMV group (RR, 0.47; 95% CI, 0.23–0.97; $P = 0.04$).
GRADE: moderate

Intensive Care Unit Length of Stay
Both studies reported ICU LOS as an outcome. The pooled results showed a nonsignificant reduction in ICU LOS in the NPPV group compared with the IMV group (WMD, −5.21 days; 95% CI, −11.60 to 1.18 days).
GRADE: low

Duration of Mechanical Ventilation
Both studies reported duration of mechanical ventilation (including both invasive and noninvasive ventilation) as an outcome. The pooled results showed a nonsignificant reduction in duration of mechanical ventilation (WMD, −3.55 days; 95% CI, −8.55 to 1.44 days).
GRADE: low

Nosocomial Pneumonia
Both studies reported nosocominal pneumonia as an outcome. The pooled results showed a significant reduction in nosocomial pneumonia in the NPPV group compared with the IMV group (RR, 0.14; 95% CI, 0.03–0.71; $P = 0.02$).
GRADE: moderate

Weaning Failure
One study reported a significant reduction in weaning failure in the NPPV group compared with the IMV group, but the results were not reported in the publication. In this study, 1 of 25 patients in the NPPV group and 2 of 25 patients in the IMV group could not be weaned after 60 days in the ICU.

NPPV After Extubation of COPD Patients From IMV

The literature was reviewed to identify studies examining the effectiveness of NPPV compared with UMC in preventing recurrence of ARF after extubation from IMV or treating acute ARF which has recurred after extubation from IMV. No studies that included only COPD patients or reported results for COPD patients separately were identified for the prevention of ARF postextubation.

One study was identified for the treatment of ARF in COPD patients that recurred within 48 hours of extubation from IMV. This study included 221 patients, of whom 23 had COPD. A post hoc subgroup analysis was conducted examining the rate of reintubation in the COPD patients only. A nonsignificant reduction in the rate of reintubation was observed in the NPPV group compared with the UMC group (7 of 14 patients vs. 6 of 9 patients, $P = 0.67$). *GRADE: low*

Conclusions

NPPV Plus UMC Versus UMC Alone for First Line Treatment of ARF due to Acute Exacerbations of COPD

- Moderate quality of evidence showed that compared with UMC, NPPV plus UMC significantly reduced the need for endotracheal intubation, inhospital mortality, and the mean length of hospital stay.
- Low quality of evidence showed a lower rate of complications in the NPPV plus UMC group compared with the UMC group.

NPPV Versus IMV for the Treatment of ARF in Patients Who Have Failed UMC

- Due to inconsistent and low to very low quality of evidence, there was insufficient evidence to draw conclusions on the comparison of NPPV versus IMV for patients who failed UMC.

NPPV for Weaning COPD Patients From IMV

- Moderate quality of evidence showed that weaning COPD patients from IMV using NPPV results in significant reductions in mortality, nosocomial pneumonia, and weaning failure compared with weaning with IMV.
- Low quality of evidence showed a nonsignificant reduction in the mean LOS and mean duration of mechanical ventilation in the NPPV group compared with the IMV group.

NPPV for the Treatment of ARF in COPD Patients After Extubation From IMV

- Low quality of evidence showed a nonsignificant reduction in the rate of reintubation in the NPPV group compared with the UMC group; however, there was inadequate evidence to draw conclusions on the effectiveness of NPPV for the treatment of ARF in COPD patients after extubation from IMV.

Background

In July 2010, the Medical Advisory Secretariat (MAS) began work on a Chronic Obstructive Pulmonary Disease (COPD) evidentiary framework, an evidence-based review of the literature surrounding treatment strategies for patients with COPD. This project emerged from a request by the Health System Strategy Division of the Ministry of Health and Long-Term Care that MAS provide them with an evidentiary platform on the effectiveness and cost-effectiveness of COPD interventions.

After an initial review of health technology assessments and systematic reviews of COPD literature, and consultation with experts, MAS identified the following topics for analysis: vaccinations (influenza and pneumococcal), smoking cessation, multidisciplinary care, pulmonary rehabilitation, long-term oxygen therapy, noninvasive positive pressure ventilation for acute and chronic respiratory failure, hospital-at-home for acute exacerbations of COPD, and telehealth (including telemonitoring and telephone support). Evidence-based analyses were prepared for each of these topics. For each technology, an economic analysis was also completed where appropriate. In addition, a review of the qualitative literature on patient, caregiver, and provider perspectives on living and dying with COPD was conducted, as were reviews of the qualitative literature on each of the technologies included in these analyses.

The Chronic Obstructive Pulmonary Disease Mega-Analysis series is made up of the following reports, which can be publicly accessed at the MAS website at: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

- Chronic Obstructive Pulmonary Disease (COPD) Evidentiary Framework
- Influenza and Pneumococcal Vaccinations for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Smoking Cessation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Community-Based Multidisciplinary Care for Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Pulmonary Rehabilitation for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Long-term Oxygen Therapy for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Acute Respiratory Failure Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Noninvasive Positive Pressure Ventilation for Chronic Respiratory Failure Patients With Stable Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Hospital-at-Home Programs for Patients With Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Home Telehealth for Patients With Chronic Obstructive Pulmonary Disease (COPD): An Evidence-Based Analysis
- Cost-Effectiveness of Interventions for Chronic Obstructive Pulmonary Disease Using an Ontario Policy Model
- Experiences of Living and Dying With COPD: A Systematic Review and Synthesis of the Qualitative Empirical Literature

For more information on the qualitative review, please contact Mita Giacomini at: http://fhs.mcmaster.ca/ceb/faculty_member_giacomini.htm.

For more information on the economic analysis, please visit the PATH website: http://www.path-hta.ca/About-Us/Contact-Us.aspx.

The Toronto Health Economics and Technology Assessment (THETA) collaborative has produced an associated report on patient preference for mechanical ventilation. For more information, please visit the THETA website: http://theta.utoronto.ca/static/contact.

Objective of Analysis

The objective of this evidence-based analysis was to examine the effectiveness, safety, and cost-effectiveness of noninvasive positive pressure ventilation (NPPV) in the following patient populations: patients with acute respiratory failure (ARF) due to acute exacerbations of chronic obstructive pulmonary disease (COPD); weaning of COPD patients from invasive mechanical ventilation (IMV); and prevention of or treatment of recurrent respiratory failure in COPD patients after extubation from IMV.

Clinical Need and Target Population

Acute Hypercapnic Respiratory Failure

Acute respiratory failure can lead to life-threatening changes in the arterial blood gases and acid-base status and develops quickly. (1) Respiratory failure occurs when the respiratory system cannot oxygenate the blood and/or remove carbon dioxide from the blood. It can be either acute or chronic and is classified as either hypoxemic (type I) or hypercapnic (type II) respiratory failure. Acute hypercapnic respiratory failure frequently occurs in COPD patients experiencing acute exacerbations of COPD, so this is the focus of this evidence-based analysis.

Hypercapnic respiratory failure occurs due to a decrease in the drive to breathe, typically due to increased work to breathe in COPD patients. (2) Chronic obstructive pulmonary disease patients typically have impaired oxygenation due to loss of alveolar volume and impaired ventilation from dead space and poor respiratory mechanics. This puts COPD patients at high risk of developing respiratory failure when faced with additional pulmonary challenges such as an acute exacerbation. (3)

Technology

There are several treatment options for ARF. Usual medical care (UMC) attempts to facilitate adequate oxygenation and treat the cause of the exacerbation, and typically consists of supplemental oxygen, and a variety of medications such as bronchodilators, corticosteroids, and antibiotics. (4) The failure rate of UMC is high and has been estimated to occur in 10% to 50% of cases. (5)

The alternative treatment for ARF is mechanical ventilation, either invasive or noninvasive. Traditionally, IMV was the primary alternative, which involves sedating the patient, creating an artificial airway through endotracheal intubation, and attaching the patient to a ventilator. This provides airway protection and direct access to drain sputum. However, there are a number of common complications that may cause substantial morbidity and risk in patients receiving IMV, including tracheal injuries sustained during the intubation procedure as well as complications during the course of IMV, such as ventilator-associated pneumonia (VAP) and sinusitis. (4;6;7) Ventilator-associated pneumonia is associated with mortality rates of 30% or higher in the intensive care unit (ICU). (6)

Noninvasive ventilation is an alternative to IMV. While both positive and negative pressure noninvasive ventilation exists, noninvasive negative pressure ventilation such as the iron lung is no longer in use in Ontario. Noninvasive positive pressure ventilation provides ventilatory support through a facial or nasal mask attached to a flow generator or regular ventilator. (4) It reduces inspiratory work, recruits collapsed and poorly ventilated portions of the lung, and improves alveolar ventilation, enabling more efficient gas exchange. While there are different modes of NPPV possible, bilevel positive airway pressure ventilation (BiPAP) is the most common. Bilevel positive airway pressure ventilation uses alternating pressures, inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP), to enable improved ventilation and recruitment, respectively. (8)

There are numerous benefits to NPPV compared with IMV. Noninvasive positive pressure ventilation can often be used intermittently for short periods of time to treat respiratory failure, which allows patients to continue to eat, drink, talk, and participate in their own treatment decisions. (4) In addition, patients do not require sedation, airway defence mechanisms and swallowing functions are maintained, trauma to the trachea and larynx are avoided, and the risk of VAP is reduced. (9) Common complications associated with NPPV are damage to facial and nasal skin, higher incidence of gastric distension with aspiration risk, sleeping disorders, and conjunctivitis. (7) In addition, NPPV does not allow direct access to the airway to drain secretions and requires patients to cooperate, and due to potential discomfort, compliance and tolerance may be low. (4;7;9) Furthermore, there are various contraindications to NPPV: coma, shock, cardiorespiratory arrest, swallowing disorders, mental immaturity, face deformations, and an unstable respiratory centre. (7)

NPPV to Wean COPD Patients From IMV

In addition to treating ARF, NPPV can be used to wean patients from IMV. Approximately one third of the time patients spend on mechanical ventilation is spent weaning the patient from IMV through the gradual removal of ventilation support until the patient can breathe spontaneously. (10) Many patients are weaned without difficultly, but 5% to 30% have difficultly weaning, a problem which can be common in COPD patients. (10) Tapering levels of ventilatory support to wean patients from IMV can be achieved using IMV or NPPV. The use of NPPV helps to reduce the risk of VAP by shortening the time the patient is intubated.

NPPV to Prevent or Treat Recurrent ARF After Extubation From IMV

Following extubation from IMV, ARF may recur leading to extubation failure and the need for reintubation. Extubation failure has been associated with an increased risk of nosocomial pneumonia and mortality. (11) To avoid these complications, NPPV has been proposed to help prevent ARF recurrence and/or to treat respiratory failure when it recurs, thereby preventing the need for reintubation.

Evidence-Based Analysis

Research Questions

1. What is the effectiveness, cost-effectiveness, and safety of NPPV for the treatment of acute hypercapnic respiratory failure due to acute exacerbations of COPD compared with
   a. usual medical care, and
   b. invasive mechanical ventilation?
2. What is the effectiveness, cost-effectiveness, and safety of NPPV compared with IMV in COPD patients after IMV for the following purposes:
   a. weaning COPD patients from IMV,
   b. preventing ARF in COPD patients after extubation from IMV, and
   c. treating ARF in COPD patients after extubation from IMV?

Research Methods

Literature Search

Search Strategy

A literature search was performed on December 3, 2010 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, the Cumulative Index to Nursing & Allied Health Literature (CINAHL), Wiley Cochrane, and the Centre for Reviews and Dissemination/International Agency for Health Technology Assessment (INAHTA) for studies published from January 1, 2004 until December 3, 2010. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search.

Since there were numerous studies that examined the effectiveness of NPPV for the treatment of ARF due to exacerbations of COPD published before 2004, pre-2004 trials which met the inclusion/exclusion criteria for this evidence-based review were identified by hand-searching reference lists of included studies and systematic reviews.

Inclusion Criteria

- English language full-reports;
- health technology assessments, systematic reviews, meta-analyses, and randomized controlled trials (RCTs);
- studies performed exclusively in patients with a diagnosis of COPD or studies performed with patients with a mix of conditions if results are reported for COPD patients separately;
- patient population: (Question 1) patients with acute hypercapnic respiratory failure due to an exacerbation of COPD; (Question 2a) COPD patients being weaned from IMV; (Questions 2b and 2c) COPD patients who have been extubated from IMV.

Exclusion Criteria

- < 18 years of age
- animal studies
- duplicate publications
- grey literature
- studies examining noninvasive negative pressure ventilation
- studies comparing modes of ventilation
- studies comparing patient-ventilation interfaces
- studies examining outcomes not listed below such as physiologic effects including heart rate, arterial blood gases, and blood pressure

Outcomes of Interest

- mortality
- intubation rates
- length of stay (intensive care unit [ICU] and hospital)
- health-related quality of life (HRQOL)
- breathlessness
- duration of mechanical ventilation
- weaning failure
- complications
- NPPV tolerance and compliance

Statistical Analysis

When possible, results were pooled using Review Manager 5 Version 5.1 (12), otherwise, the results were summarized descriptively. Dichotomous data were pooled into relative risks using random effects models and continuous data were pooled using weighted mean differences with a random effects model. Analyses using data from RCTs were done using intention-to-treat protocols; *P* values < 0.05 were considered significant. Post hoc sample size calculations were performed using STATA 10.1.

A priori subgroup analyses were planned for the severity of respiratory failure, location of treatment (ICU or hospital ward), and mode of ventilation, with additional subgroups as needed based on the identified literature. For the severity of respiratory failure subgroups, the mean pH level was used to classify a study as mild ($pH \geq 7.35$), moderate ($7.30 \leq pH < 7.35$), severe ($7.25 \leq pH < 7.30$), and very severe ($pH < 7.25$) respiratory failure. For those studies that presented the mean pH for each study group separately, and the mean pH of the 2 arms fell into separate categories, the higher category was used.

Quality of Evidence

The quality of each included study was assessed taking into consideration the following 7 study design characteristics:

- adequate allocation concealment,
- randomization (study must include a description of the randomization procedure used and must be a proper method),
- power/sample size (adequate sample size based on a priori calculations; underpowered studies were identified, when possible, using post hoc sample size power calculations),
- blinding (if double blinding is not possible, a single blind study with unbiased assessment of outcomes was considered adequate for this criterion),
- < 20% withdrawals/dropouts,
- intention-to-treat analysis conducted and done properly (withdrawals/dropouts considered in analysis), and
- other criteria as appropriate for the particular research question and study design

To evaluate the quality of the weaning trials, several additional quality factors were identified based on the quality assessments conducted in previous systematic reviews on this topic by Burns et al (13;14):

- daily screening to identify patients capable of unassisted breathing,
- predefined criteria to identify weaning candidates,
- use of weaning protocols or guidelines (in both groups),
- predefined criteria for failure of a prerandomization spontaneous breathing trial,
- predefined criteria for discontinuation of mechanical ventilation (in both groups), and
- predefined criteria for reintubation after weaning failure.

The quality of the body of evidence was assessed as high, moderate, low, or very low according to the GRADE Working Group criteria (15) as presented below.

- Quality refers to the criteria such as the adequacy of allocation concealment, blinding, and follow-up.
- Consistency refers to the similarity of estimates of effect across studies. If there are important and unexplained inconsistencies in the results, our confidence in the estimate of effect for that outcome decreases. Differences in the direction of effect, the magnitude of the difference in effect, and the significance of the differences guide the decision about whether important inconsistency exists.
- Directness refers to the extent to which the interventions and outcome measures are similar to those of interest.

As stated by the GRADE Working Group, the following definitions of quality were used in grading the quality of the evidence:

High Further research is very unlikely to change confidence in the estimate of effect.

Moderate Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.

Low Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.

Very Low Any estimate of effect is very uncertain.

Results of Evidence-Based Analysis

The database search yielded 2,585 citations published between January 1, 2004, and December 3, 2010 (with duplicates removed). Articles were excluded based on information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment. Figure 1 shows the breakdown of when and for what reason citations were excluded in the analysis.

Nineteen studies (11 systematic reviews and 8 RCTs) met the inclusion criteria. The references lists of the included studies and identified systematic reviews were hand searched to identify any additional potentially relevant studies, and 12 additional citations (3 systematic reviews and 9 RCTs) which were published *before the 2004 search* date were included for a total of 31 included citations.

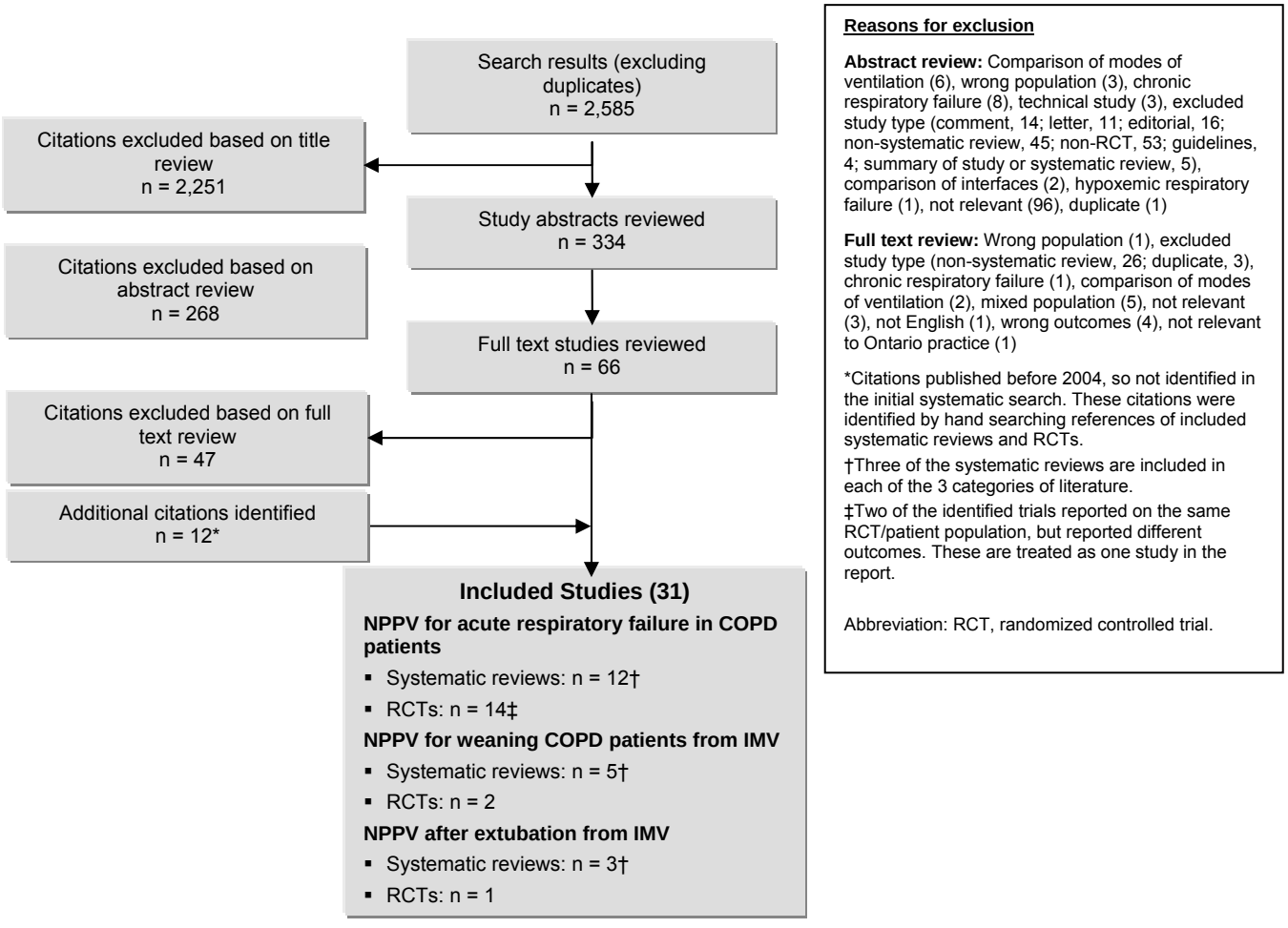

Figure 1: Citation Flow Chart

For each included study, the study design was identified and is summarized below in Table 1, which is a modified version of a hierarchy of study design by Goodman. (16)

Table 1: Body of Evidence Examined According to Study Design*

Study Design	Number of Eligible Studies
RCT Studies	
Systematic review of RCTs	14
Large RCT†	5‡
Small RCT	12§
Observational Studies	
Systematic review of non-RCTs with contemporaneous controls	0
Non-RCT with contemporaneous controls	0
Systematic review of non-RCTs with historical controls	0
Non-RCT with historical controls	0
Database, registry, or cross-sectional study	0
Case series	0
Retrospective review, modelling	0
Studies presented at an international conference or other sources of grey literature	0
Expert opinion	n/a
Total	31

*Abbreviation: RCT, randomized controlled trial.
†Large RCT refers to a study with at least 100 patients.
‡Two of the large RCTs report different outcomes for the same patient population.
§One study had more than 100 patients, but fewer than 100 COPD patients.

The results of this evidence-based analysis are divided into 3 sections:

- NPPV for the treatment of ARF due to acute exacerbations of COPD,
- NPPV for weaning COPD patients from IMV, and
- NPPV after extubation from IMV in COPD patients.

Each section addresses 1 or 2 of the research questions.

NPPV for the Treatment of Acute Respiratory Failure due to Acute Exacerbations of COPD

This section of the evidence-based review addresses the first research question: what is the effectiveness, cost-effectiveness, and safety of NPPV for the treatment of acute hypercapnic respiratory failure due to acute exacerbations of COPD?

Systematic Reviews

Twelve systematic reviews were identified that examined the published literature on the use of NPPV for the treatment of ARF due to exacerbations of COPD. (2-4;8;17-24) Seven of the reviews provide a narrative review of the evidence and discuss only a few of the key studies in the area or the findings and conclusions from other reviews/meta-analyses. (2;3;8;19;21;23;24) The remaining 5 reviews are more detailed and include statistical analyses such as meta-analyses. A main difference across the systematic reviews is the number of included studies. Common reasons for the variation in the studies included in these reviews are differences in language restrictions, inclusion or exclusion of unpublished (abstract) data, and inclusion or exclusion of studies with mixed patient populations.

Full details about the systematic reviews including a comparison of the included studies, and the methods and main findings can be found in Appendix 2. Overall, the systematic reviews found that NPPV plus UMC compared with UMC alone resulted in reduced mortality, intubation rates, and ICU or hospital lengths of stay.

Randomized Controlled Trials

Thirteen[1] RCTs evaluating the effectiveness of NPPV for the treatment of ARF due to acute exacerbations of COPD were identified. The following comparisons were examined:

- NPPV plus UMC versus UMC alone (11 RCTs)
- NPPV versus IMV (2 RCTs)

NPPV Plus UMC Compared With UMC Alone

For the 11 studies comparing NPPV plus UMC and UMC alone, the general study characteristics including inclusion and exclusion criteria, length of follow-up, outcomes, details about the intervention and UMC, and details on the patient populations included in each study are shown in Tables A1, A2, and A3 in Appendix 2.

The majority of the studies were conducted in either the ICU or respiratory wards in hospitals, with patients in the NPPV plus UMC group receiving BiPAP ventilatory support. All studies specified a protocol or schedule for NPPV delivery, but this varied substantially across the studies (Table A9). For example, some studies restricted the amount of ventilation per day (e.g., 6 hours per day) and the number of days it was offered (e.g., maximum of 3 days); whereas other studies provided patients with ventilation for as long as they could tolerate it and recommended it for much longer periods of time (e.g., 7 to 10 days). These differences are an important source of clinical heterogeneity between the studies.

Usual medical care varied between studies, but common medications included supplemental oxygen, bronchodilators, corticosteroids, antibiotics, diuretics, and respiratory stimulators. Patients had very severe COPD and ARF of varying severities from mild (mean pH $\geq$ 7.35) to very severe (mean pH $\leq$ 7.25).

Duration of NPPV

Given the differences in the ventilation protocols, the actual duration of NPPV, defined as either the number of hours of NPPV per day or the total number of days on NPPV, varied widely across studies (Table 2).

[1] Fourteen papers were identified; however 2 of the trials reported results for 1, study but different outcomes. These 2 papers have been treated as 1 study.

Table 2: Duration of NPPV (NPPV Plus UMC Versus UMC Alone Comparison)*

Author, Year	Duration NPPV, Mean Days (SD)	Duration NPPV, Mean Hours per Day (SD)	Duration of MV After Intubation, Days	
			NPPV	UMC
Barbe et al, 1996 (25)	Total: 3†	6 †	NR	NR
Bott et al, 1993 (26)	6 (range, 2–9)‡	7.63 (range, 1–23) per day‡	NR	NR
Brochard et al, 1995 (27)	4 (4) §	NR	25 (17)	17 (21)
Carrera et al, 2009 (28)	Total: 3	NPPV group Day 1: 13 (4) Day 2: 12 (4) Day 3: 11 (4) Sham group Day1 : 14 (5) Day 2: 13 (5) Day 3: 14 (5)	NR	NR
Dhamija et al, 2005 (29)	Total duration: 3 †	6 †	NR	NR
Dikensoy et al, 2002 (5)	Range, 6–36 hours	Mean total duration: 11.2 (9.5) (range, 6–36)	NR	NR
Keenan et al, 2005 (30)	Range, 0-3	For those compliant with therapy (>1 hour on day) Day 1: 6.2 (3.1) (range, 1–9), n = 22; Day 2: 5.7 (1.1) (range, 3–7), n = 17; Day 3: 4.2 (0.3) (range, 4–5), n = 12	NR	NR
Khilnani et al, 2010 (31)	NR	≤ 16/day†	NR	NR
Kramer et al, 1995 (9)	Mean (NPPV + IMV): 6.4 (2.4)	NR‖	NR	Mean (NPPV + IMV): 7.6 (3.6)
Plant et al, 2000/2001 (32)	Median, 3 (range, 0–26)	Day 1: median, 8 Day 2: median, 7 Day 3: median, 5	NR	NR
Wang et al, 2005 (33)	10 (7)	11 (5)	NR	NR

*Abbreviations: d, day; hr, hour; IMV, invasive mechanical ventilation; MV, mechanical ventilation; NPPV, noninvasive positive pressure ventilation; NR, not reported; SD, standard deviation; UMC, usual medical care.

†Based on study protocol, actual days or duration per day were not reported.

‡Results for the 26 patients who were compliant with NPPV therapy only

§n = 32, excludes those patients who received intubation and IMV

‖In all patients, including those without COPD, average daily use for the first 2 days was 14.4 ± 2.2 hours (range, 0.33–22 hours) throughout the day and night. Most patients were weaned entirely off NPPV after 3 to 4 days.

Need for Endotracheal Intubation

All 11 studies reported the need for endotracheal intubation as an outcome. (5;9;25-34) In some studies, the patients who were judged to need intubation for the delivery of IMV were not all intubated. Instead of intubation in these studies, patients may have been offered alternative treatment options or refused intubation. For example, patients in the UMC alone group may have been given the option of a trial of NPPV, the patients in the UMC or NPPV group may have refused the option of IMV and may have continued receiving NPPV or medical therapy, and/or the type of ventilator, ventilator mode, or interface may have been changed for the NPPV group. For the purposes of this analysis, all patients who failed their treatment and were judged to require intubation are included as events regardless of whether or not they were actually intubated.

When the results of all studies were pooled (Figure 2), there was a 62% reduction in the risk of the need for endotracheal intubation in the NPPV plus UMC group compared with the UMC alone group, and this reduction was statistically significant (RR, 0.38; 95% CI, 0.28–0.50; $P < 0.001$).

	NPPV		UMC			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Barbe 1996	0	10	0	14		Not estimable	
Bott 1993	0	30	5	30	1.0%	0.09 [0.01, 1.57]	
Brochard 1995	11	43	31	42	27.9%	0.35 [0.20, 0.60]	
Carrera 2009	5	37	13	38	9.5%	0.40 [0.16, 1.00]	
Dhamija 2005	0	14	1	15	0.8%	0.36 [0.02, 8.07]	
Dikensoy 2002	2	17	7	17	4.0%	0.29 [0.07, 1.18]	
Keenan 2005	2	25	5	27	3.4%	0.43 [0.09, 2.03]	
Khilnani 2010	3	20	12	20	6.7%	0.25 [0.08, 0.75]	
Kramer 1995	1	11	8	12	2.2%	0.14 [0.02, 0.92]	
Plant 2000	18	118	32	118	30.4%	0.56 [0.34, 0.94]	
Wang 2005	8	171	26	171	14.0%	0.31 [0.14, 0.66]	
Total (95% CI)		**496**		**504**	**100.0%**	**0.38 [0.28, 0.50]**	
Total events	50		140				

Heterogeneity: Tau² = 0.00; Chi² = 5.49, df = 9 (P = 0.79); I² = 0%
Test for overall effect: Z = 6.68 (P < 0.00001)

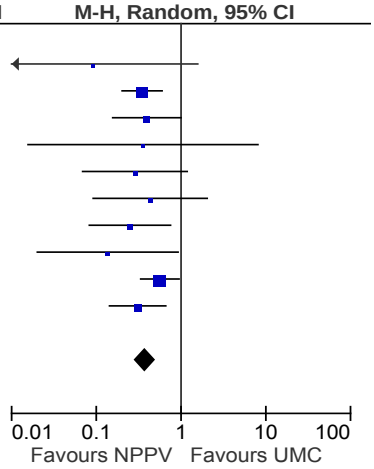

Figure 2: Pooled Results for the Need for Endotracheal Intubation (NPPV Plus UMC Versus UMC Alone)*

*Abbreviations: CI, confidence interval; M–H, Mantel–Haenszel; NPPV, noninvasive positive pressure ventilation; UMC, usual medical care.

When the results are subgrouped by severity of respiratory failure, the significant reduction is maintained in the mild, severe, and very severe groups, but the reduction in endotracheal intubation in the NPPV group with moderate respiratory failure is not statistically significant ($P = 0.21$) (Figure 3). Similarly, there is a significant reduction in the risk of the need for endotracheal intubation in the NPPV group for those patients treated in general or respiratory hospital wards ($P < 0.001$), patients treated in the ICU ($P < 0.00001$), studies which had a priori intubation criteria ($P < 0.001$), and studies which did not have a priori intubation criteria ($P = 0.02$) (Appendix 5).

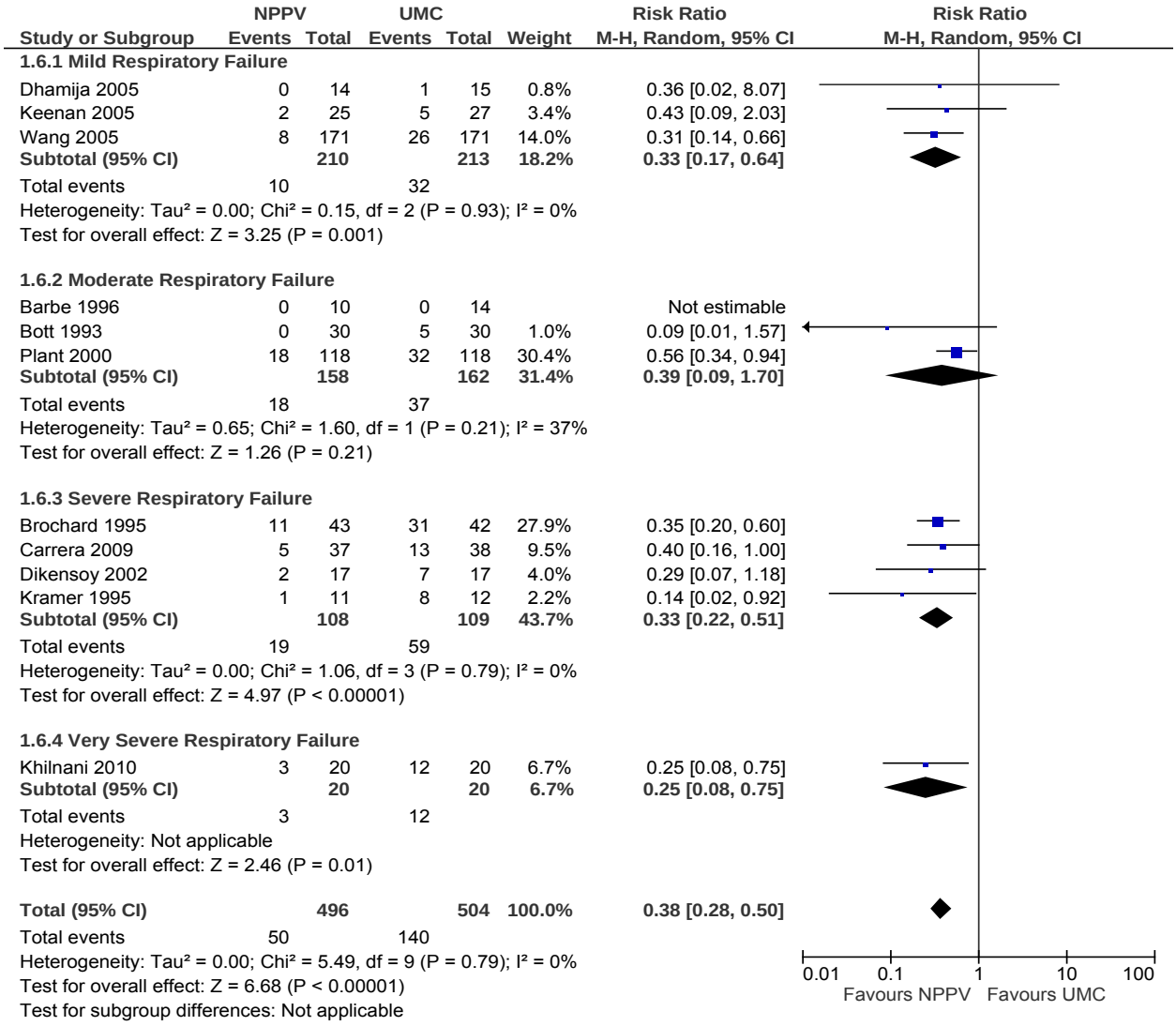

Figure 3: Pooled Results for the Need for Endotracheal Intubation Stratified by Severity of ARF (NPPV Plus UMC Versus UMC Alone Comparison)*

*Abbreviations: ARF, acute respiratory failure; CI, confidence interval; M–H, Mantel–Haenszel; NPPV, noninvasive positive pressure ventilation; UMC, usual medical care.

Mortality

All of the studies included mortality as an outcome. (5;9;25-34)[2] Inhospital mortality was most commonly reported, although Bott et al (26) reported 30-day mortality, and Plant et al (34) reported long-term survival (study follow-up ranged from 3 to 26 months).

Inhospital Mortality

When the results of all studies were pooled (Figure 4), there was a 47% reduction in the risk of death in the NPPV plus UMC group compared with the UMC alone group, and this reduction was statistically significant (RR, 0.53; 95% CI, 0.35–0.81, $P = 0.003$).

[2] The inhospital mortality results for Carrera et al (28) were obtained from the authors of the study.

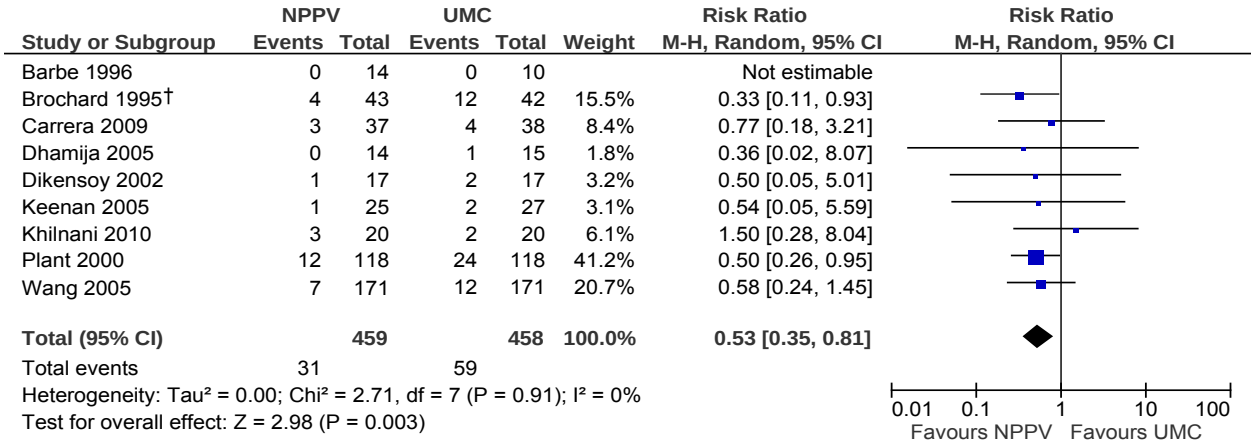

Figure 4: Pooled Results for Inhospital Mortality (NPPV Plus UMC Versus UMC Alone Comparison)*

*Abbreviations: CI, confidence interval; M–H, Mantel–Haenszel; NPPV, noninvasive positive pressure ventilation; UMC, usual medical care.

†While there was a significant difference in the inhospital mortality between the NPPV and UMC groups in Brochard et al (27), 3 of the 4 deaths in the NPPV group and 10 of the 12 deaths in the UMC alone group occurred in those patients who failed treatment and were intubated and mechanically ventilated. When the mortality rates were compared after adjustment for intubation, the difference was no longer significant. This indicates that the number of patients requiring intubation was the main factor influencing mortality. (27)

Note: the mortality data from Kramer et al (9) have been excluded from the pooled analysis because the results were for the entire study population and not presented separately for COPD patients only.

When the results are subgrouped by severity of respiratory failure, the significant reduction is maintained in the moderate and severe subgroups only. There is a nonsignificant reduction in the risk of death in the mild respiratory failure subgroup ($P = 0.16$). There is a nonsignificant increase in the risk of mortality in the NPPV group compared with the UMC alone group in the very severe respiratory failure subgroup, but this result is based on only 1 study with a small sample size ($P = 0.64$) (Figure 5).

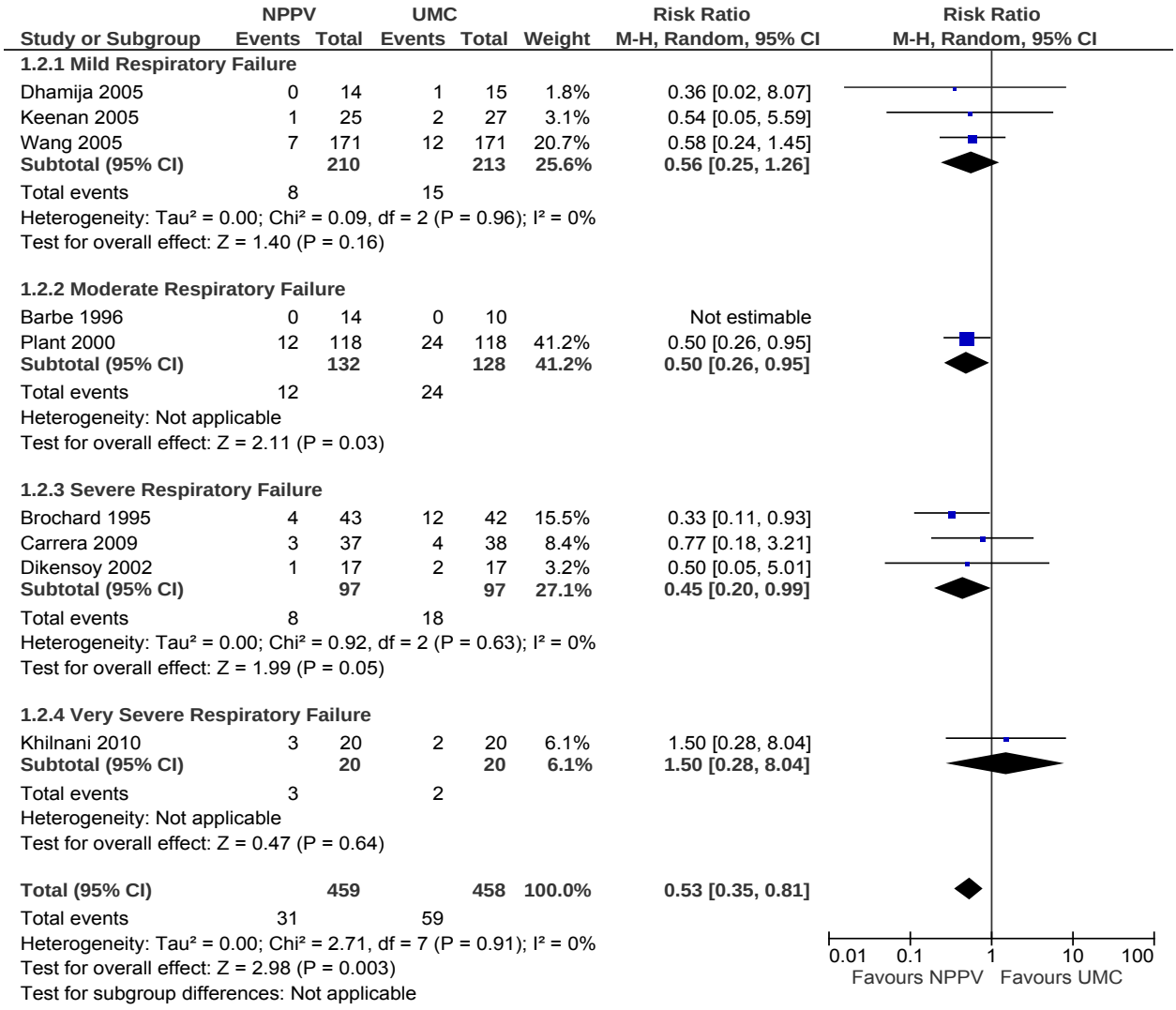

Figure 5: Pooled Results for Inhospital Mortality Stratified by Severity of ARF (NPPV Plus UMC Versus UMC Alone Comparison)*

*Abbreviations: ARF, acute respiratory failure; CI, confidence interval; M–H, Mantel–Haenszel; NPPV, noninvasive positive pressure ventilation; UMC, usual medical care.
Note: the mortality data from Kramer et al (9) have been excluded from the pooled analysis because the results were for the entire study population and not presented separately for COPD patients only.

Thirty-Day Mortality

Bott et al (26) found a nonsignificant reduction in the risk of death in the NPPV plus UMC group compared with the UMC alone group at 30 days (3 deaths vs. 9 deaths, $P = 0.07$). However, there was a significant difference in survival between the 3 centres involved in this study: 0 deaths among those patients enrolled at centre C, 5 among those at centre B, and 7 among those at centre A (centre C vs. centre A and B: Fisher's exact test, $P = 0.005$). (26)

Long-Term Survival

The second publication from Plant et al (34) followed patients for 3 to 26 months after enrolment to assess long-term survival. There was no significant difference ($P = 0.12$) in the median survival between the NPPV plus UMC and the UMC alone groups (16.8 months vs. 13.4 months, respectively). The 1-year survival in the NPPV plus UMC group was 61.6% compared with 53.9% in the UMC alone group. (34)

Hospital Length of Stay

All 11 studies reported hospital length of stay (LOS) (Table 3). The mean hospital LOS was 2.68 days shorter in the NPPV plus UMC group compared with the UMC alone group (mean difference, −2.68; 95% CI, −4.41 to −0.94; *P* = 0.002) (Figure 6).

Table 3: Mean Hospital Length of Stay (NPPV Plus UMC Versus UMC Alone)*

	Hospital Length of Stay, Mean (SD), Days		
Author, Year	**NPPV + UMC**	**UMC**	***P* Value**
Barbe et al, 1996 (25)	10.6 (9)	11.3 (1.3)	> 0.05
Bott et al, 1993 (26)	9 (5.25)† Median, 9 (range, 1–22)	9 (9.5)† Median, 9 (range, 1–39)	NR
Brochard et al, 1995 (27)	23 (17)‡	35 ± 33‡	0.02
Carrera et al, 2009 (28)	10 (5)§ Median, 8.5 (IQ range, 6.75–11)	12 (6)§ Median, 10.5 (IQ range, 7–15)	0.06 Median, 0.65
Dhamija et al, 2005 (29)	9.77 (3.32)	10.20 (5.64)	> 0.05
Dikensoy et al, 2002 (5)	8 (2.1) (range, 5–15)	12.3 (3.3) (range, 5–21)	< 0.05
Keenan et al, 2005 (30)	6.5 (5.6) (range, 2–31)‖ Median, 5	9.1 (7.3) (range, 2–36) Median, 7	Mean, 0.18‖ Median, 0.07‖
Khilnani et al, 2010 (31)	9.4 (4.3)	17.8 (2.6)	0.001
Kramer et al, 1995 (9)	14.9 (3.3)	17.3 (3.0)	NR
Plant et al, 2000 (32;34)	10 (22.167)† Median, 10 (range, 4–137)	10 (19.5)† Median, 10 (range, 2–119)	Median, 0.27
Wang et al 2005 (33)	16 (9)	18 (11)	0.15

*Abbreviations: IQ, interquartile; LOS, length of stay; NPPV, noninvasive positive pressure ventilation; NR, not reported; SD, standard deviation; UMC, usual medical care.

†Mean calculated using the median and range based on methods from Hozo et al. (35)

‡In Brochard et al (27), the total LOS was not reported; however, 7 patients (18%) in the NPPV group stayed in hospital for more than 28 days compared with 13 (47%) in the UMC alone group (*P* = 0.004).

§Mean reported in abstract, median in results

‖One patient in the NPPV group was identified as an outlier as the patient's LOS was 374 days, while all other patients in both groups had a mean LOS of less than 37 days, and was excluded from the mean and range for the NPPV group and *P* value reported in the table. Including the outlier patient, the mean ± SD (range) for the NPPV group was: 21.2 ± 73.7 (2–374) and the *P* value comparing the mean LOS with that in the UMC alone group was 0.397 and comparing the median LOS was 0.136. (30)

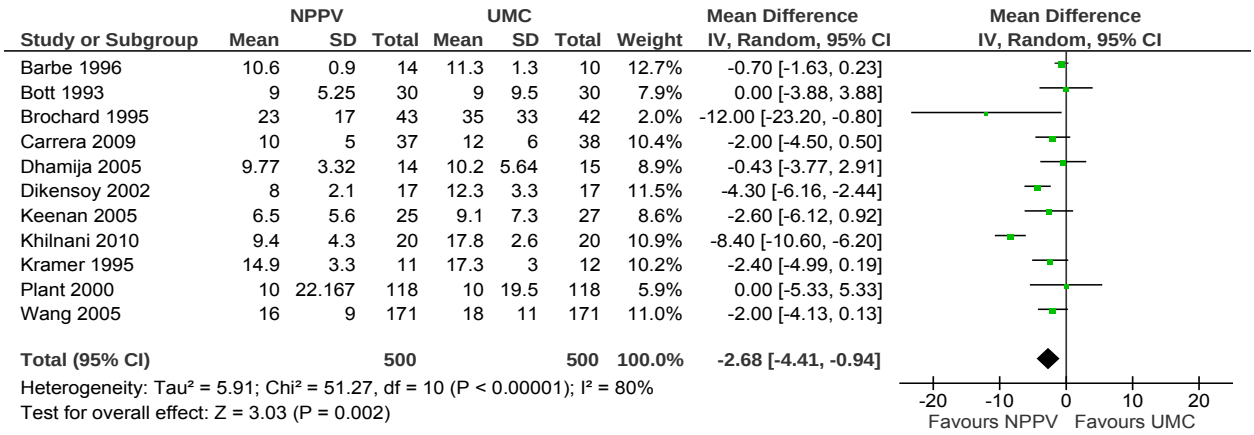

Figure 6: Pooled Results for Mean Hospital Length of Stay (NPPV Plus UMC Versus UMC Alone Comparison)[3]*

*Abbreviations: CI, confidence interval; NPPV, noninvasive positive pressure ventilation; SD, standard deviation; UMC, usual medical care.

Similarly, when the results are stratified by respiratory failure severity (Figure 7), the significant reduction in mean hospital LOS in the NPPV plus UMC group is maintained for the mild ($P = 0.03$), severe ($P < 0.001$), and very severe ($P < 0.001$) respiratory failure groups, with the benefit increasing as the disease severity increases.

[3] Bott et al (26) and Plant et al (32;34) reported median length of stay and range. These data were used to calculate approximate means and standard deviations for these 2 studies based on methods by Hozo et al (35). The resulting means and standard deviations were used to include these 2 studies in the pooled analysis.

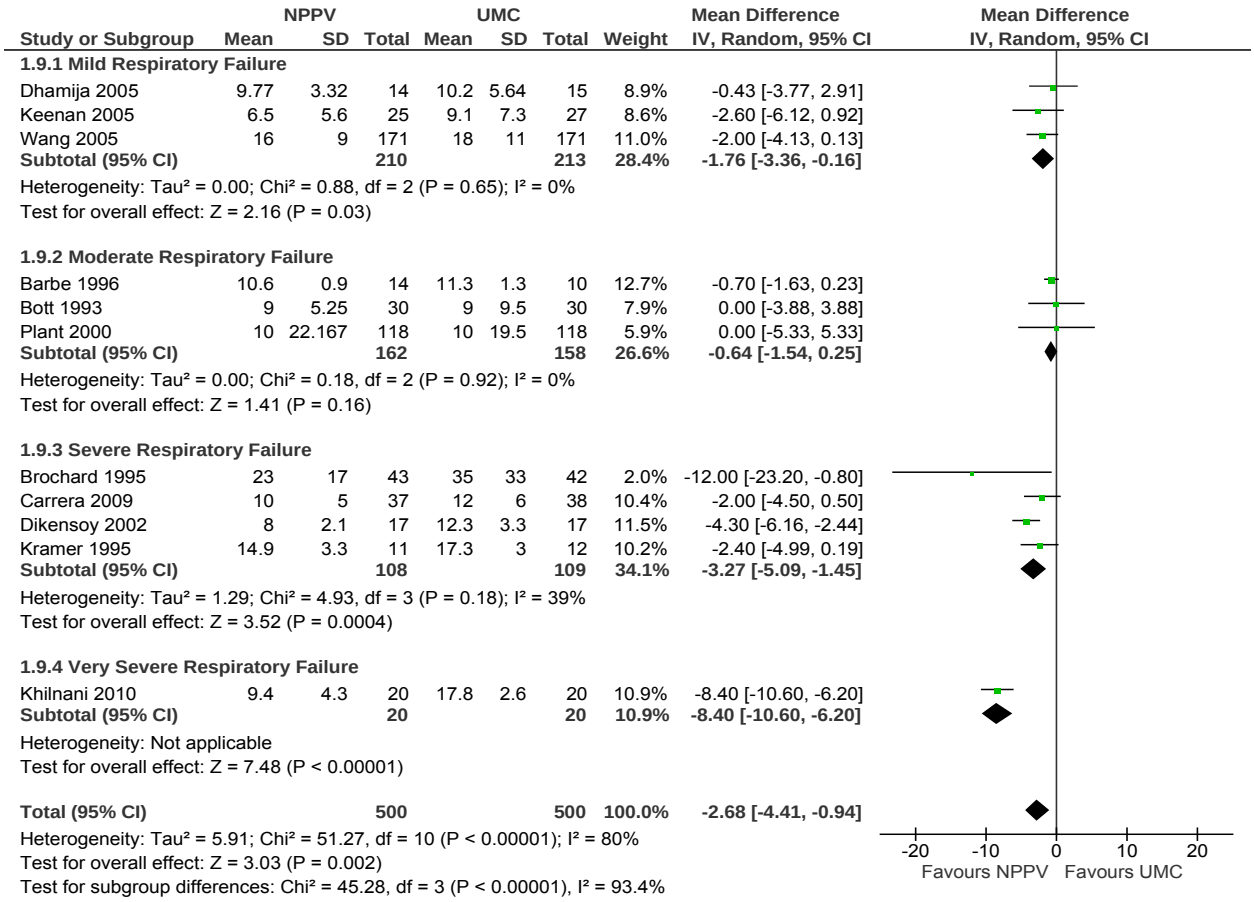

Figure 7: Pooled Mean Hospital Length of Stay Stratified by Severity of ARF (NPPV Plus UMC Versus UMC Alone)*

*Abbreviations: ARF, acute respiratory failure; CI, confidence interval; NPPV, noninvasive positive pressure ventilation; SD, standard deviation; UMC, usual medical care.

Dyspnea

Eight of the studies reported some measure of dyspnea as an outcome, but due to differences in reporting, the results could not be pooled. Individual study findings are listed in Table 4. The results are inconsistent: some studies reported a statistically significant decline in dyspnea in the NPPV plus UMC group compared with the UMC alone group, or a faster decline in dyspnea in the NPPV plus UMC group (results are shown in italics in Table 4), while other studies found no significant differences between the 2 groups.

Table 4: Dyspnea Results (NPPV Plus UMC Versus UMC Alone Comparison)*

Author, year	Breathlessness Measure	Results
Barbe et al, 1996 (25)	Borg Index	Significant decrease in dyspnea during hospitalization ($P < 0.001$) at 72 hours, 80 hours, and discharge in both NPPV plus UMC and UMC alone groups, but no significant difference between groups.
Bott et al, 1993 (26)	Visual analogue scale	*Over the first 3 days, there was a significantly lower score for dyspnea for the NPPV plus UMC group (median, 2.3 cm; range, 0.1–5.5 cm) than the UMC alone group (median, 4.5 cm; range, 0.9–8.8), P < 0.03.* This difference was no longer significant at 7 days and discharge.
Carrera et al, 2009 (28)	Borg scale	No significant change in dyspnea status during study period in either group. At discharge, there was no significant difference between the Borg scores (4 ± 2 in both groups).
Dhamija et al, 2005 (29)	Borg scale	Both groups reported a significant improvement in Borg scale within 1 hour of therapy.
Keenan et al, 2005 (30)	Borg scale	*Borg index at 1 hr and on day 2 were significantly better in NPPV plus UMC compared with the UMC alone group (P = 0.004 and P = 0.03, respectively).†*
Kramer et al, 1995 (9)	NR‡	n/a
Plant et al, 2000 (32)	5 point verbal rating score	*NPPV plus UMC group had a more rapid relief of breathlessness (P = 0.03).* Median time to relief of breathlessness was 4 days in the NPPV group compared with 7 days in UMC alone group.
Wang et al, 2005 (33)	Dyspnea score (4 point scale)	No significant reduction in dyspnea score between baseline and 24 hours in both groups. NPPV plus UMC: baseline, 3.6 ± 0.7; 24 hr, 3.3 ± 0.8 hr UMC alone: baseline, 3.6 ± 0.7; 24 hr, 3.3 ± 0.8 hr

*Abbreviations: hr, hour; n/a, not applicable; NPPV, noninvasive positive pressure ventilation; NR, not reported; SD, standard deviation; UMC, usual medical care.

†Borg scores were available for 80-90% of patients at each time point, but the number of patients with data for consecutive measurements fell off over time, with only 60% of patients having data out to day 3. Therefore the analysis was only done until day 3, so the repeated measures analysis was only done to day 3. (30)

‡Results were not reported for the COPD patients only. For the entire population including non-COPD patients, scores decreased in both groups and tended to be lower in the NPPV group compared with control throughout study. The decline from baseline was significantly greater among NPPV than control at 6 hours. (9)

Noninvasive Positive Pressure Ventilation Tolerance and Compliance

Patient tolerance or compliance with NPPV was reported in 8 studies (Table 5). In these studies, NPPV intolerance ranged from 5% to 29%. Factors that might contribute to this range include severity of respiratory failure, with more severe patients having increased tolerance compared with less severe patients, and the interface used to deliver NPPV.

Table 5: NPPV Tolerance (NPPV Plus UMC Versus UMC Alone Comparison)*

Author, Year	Number of Patients Who Could Not Tolerate NPPV (%)	Reason: n
Barbe et al, 1996 (25)	4 (29)	• Claustrophobia: 3 • Anxiety: 1
Bott et al, 1993 (26)	4 (13)	• Could not breathe through nose: 1 • Too confused to use NPPV: 2 • Withdrew from active treatment: 1
Dhamija et al, 2005 (29)	1 (7)	• Could not tolerate mask: 1
Dikensoy et al, 2002 (5)	2 (12)	• Discomfort: 2
Keenan et al, 2005 (30)	3† (12)	NR
Khilnani et al, 2010 (31)	1 (5)	• Could not tolerate mask: 1
Kramer et al, 1995 (9)	NR‡	–

*Abbreviations: n, number of patients; NPPV, noninvasive positive pressure ventilation; NR, not reported; UMC, usual medical care.

†Patients refused NPPV after its initial application, so they received less than 1 hour of NPPV. (30)

‡Data on tolerance/compliance were not reported for the COPD patients only. For the entire NPPV group including those without COPD, 4 patients did not tolerate NPPV. The reasons for the lack of tolerance in the 4 patients were not reported. (9)

Plant et al (32) and Keenan et al (30) reported compliance with NPPV. In Keenan et al (30), NPPV was provided to patients over 3 days. Out of 25 patients, 88% were compliant on day 1, 68% on day 2, and 48% on day 3. (30) Similarly, in Plant et al (32), 92.8% of patients were compliant on day 1, 76.4% on day 2, and 67.7% on day 3. In this study, patients who were not compliant with NPPV included those who could not tolerate NPPV, those who failed NPPV and were invasively ventilated, and those who self-weaned because they thought they no longer needed NPPV. (32) Both of these studies suggest that compliance decreases over time, even over short periods of time such as 3 days.

Plant et al (32) also reported mask comfort using a 5-point verbal rating score. The median comfort score during the first 3 days of NPPV was 2, which translates to mildly uncomfortable.

Complications

Five studies reported complications, although most reported complications associated with the NPPV procedure only. (5;27;30;31;33) While Kramer et al (9) also reported complications, they were not presented for the COPD group separately, so the study is not included in the results.

In Brochard et al (27), the proportion of patients with 1 or more complications was reported. Patients in the UMC alone group reported a significantly higher proportion of complications than patients in the NPPV plus UMC group (20 of 42 vs. 7 of 43; $P = 0.001$). In total, 232 complications were reported in the UMC alone group and 9 in the NPPV plus UMC group. The breakdown of the complications is shown in Table 6.

Table 6: Reported Complications by Study Group (NPPV Plus UMC Versus UMC Alone Comparison)*

Complication	Number of Complications	
	NPPV + UMC	UMC
Pneumonia	2	7
Sepsis	2	3
Gastrointestinal tract disorders	1	2
Myocardial infarction	1	2
Multiple pneumothoraxes	0	1
Difficult or complicated endotracheal intubation	0	4
Pulmomary embolism	0	1
Cerebral hemorrhage	1	0
Cardiac or respiratory problems when weaning	1	1
Cardiac arrest after weaning	0	2
Facial-skin necrosis	1	0

*Abbreviations: NPPV, noninvasive positive pressure ventilation; UMC, usual medical care.
Source: Brochard et al, 1995. (27)

In Dikensoy et al (5) complications were reported in 7 patients in the NPPV plus UMC group: nasal bridge ulceration (n = 2), eye irritation (n = 3), conjunctivitis (n = 2), and gastric insufflation (n = 2). Only complications related to NPPV were reported. (5)

Keenan et al (30) reported no nosocomial complications in the NPPV plus UMC group. Two nosocomial complications were reported in the UMC alone group: 1 patient who failed medical treatment and was intubated and invasively ventilated developed ventilator-associated pneumonia, and 1 patient developed hospital-acquired pneumonia and a urinary tract infection (this patient was not intubated). (30)

In Khilnani et al (31) 4 patients in the NPPV plus UMC group and 10 patients in the UMC alone group developed complications. In the NPPV plus UMC group, complications were aspiration pneumonia (n = 1), abdominal bloating sensation and irritation in the eyes (n = 2), and upper gastrointestinal bleed (n = 1). Complications in the UMC alone group were nosocomial pneumonia (n = 4), upper gastrointestinal bleed (n = 3), pneumothorax (n = 2), and paroxysmal supraventricular tachycardia (n = 1). (31)

Finally, in Wang et al (33), the following complications associated with NPPV were reported: gastric insufflation (n = 40), local facial skin abrasion (n = 27), sinusitis (n = 3), and aspiration pneumonia (n = 2). As well, mask leaks causing insufficient ventilation occurred in 51 of 171 patients.

Of the 3 studies that reported complications in both groups, each study reported fewer complications in the NPPV plus UMC group compared with the UMC alone group. It was not appropriate to pool these data because each reported different information.

Other Results

Many of the studies also reported changes in arterial blood gases, pulmonary function, heart rate, blood pressure, and respiratory rate; these outcomes, however, were out of scope of this review and are not reported in this analysis.

Bott et al (26) was the only study to report some measure of health-related quality of life (HRQOL). A visual analogue score was used to assess quality of sleep and general well-being; no significant differences were found between the scores for the NPPV plus UMC and UMC alone groups. (26)

While most studies did not report information on the number of patients in the NPPV plus UMC group who were successfully weaned from NPPV after resolution of the respiratory failure, most of the study protocols called for NPPV for a set number of days, so it was unlikely that patients continued on NPPV after the study. In Bott et al (26), however, 1 patient continued on NPPV after discharge from the hospital.

Comments on the Studies

One of the challenges of pooling the data from the studies for any of the outcomes is that many of the studies had very different ventilation protocols, both in terms of the total duration of NPPV (e.g., some studies called for NPPV for 7 to 10 days or as long as clinically necessary, but others only allowed for NPPV for a maximum of 3 days) and the number of hours per day of NPPV (e.g., some studies encouraged NPPV for as long as the patient could tolerate and some capped NPPV at 6 hours per day). These differences limit the generalizability of the studies and may provide a reason for the high statistical heterogeneity (measured by the I^2) observed in some of the pooled analyses such as mean hospital LOS. Given the limited reporting on total duration of NPPV and hours per day in some studies, and the variability across each study, it was not possible to create clear subgroups based on NPPV protocol or actual duration of NNPV to further explore this clinical heterogeneity.

Due to differences in the severity of respiratory failure of the patients in the included studies, stratified analyses were conducted for mild ($pH \geq 7.35$), moderate ($7.30 \leq pH < 7.35$), severe ($7.25 \leq pH < 7.30$), and very severe ($pH < 7.25$) respiratory failure. Studies were classified based on the mean pH of the patients included in the study; however, this does not account for the fact that some studies may have included some patients with substantially different pH levels from that of the mean. For example, in Wang et al (33), a subgroup analysis within the study shows that 151 patients (44%) had a pH greater than or equal to 7.35, but 118 patients (35%) had a more moderate respiratory failure ($7.30 \leq pH < 7.35$) and 73 patients (21%) had severe respiratory failure ($pH < 7.30$). Similarly, while the mean pH of the NPPV plus UMC and UMC alone groups in Bott et al (26) classifies the study as moderate respiratory failure, the mean pH of patients enrolled at centre C was 7.369, which indicates the patients at this centre had mild respiratory failure.

Different ventilators, pressure settings, ventilation modes, and interfaces were used across the studies. These factors may play a role in the effectiveness of the NPPV due to their impact on achieving adequate ventilation and patient tolerance, so these differences may also contribute to some of the heterogeneity across the studies.

In the studies by Barbe et al (25), Keenan et al (30), and Wang et al (33), initiation of noninvasive ventilation in the NPPV plus UMC group was not immediate, but delayed between 12 and 48 hours after the patients presented to the emergency department. This delay may have reduced the effectiveness of NPPV and therefore bias the results against NPPV.

A common theme identified by many of the study authors was the need for patients on NPPV to be closely monitored by trained clinicians. In some studies, NPPV use was commonplace before the study, but in others (especially those conducted in hospital wards), NPPV was not used before the study was initiated. Skill level and familiarity or comfort with NPPV may impact the study results because

physicians who are less comfortable with NPPV may be more likely to switch patients to intubation and IMV, especially in those studies which did not have a priori objective intubation criteria.

Quality of Evidence

The analysis was based on RCT evidence, but the majority of the trials had serious methodological issues based on the information available in the published papers[4]. Common methodological problems included lack of allocation concealment, unclear methods used for randomization, lack of blinding without adequate objective outcome assessment, and inadequate sample sizes to eliminate type II error (based on post hoc sample size calculations when possible) (summarized in Table A17 in Appendix 4).

The GRADE system was used to evaluate the quality of the overall body of evidence for NPPV plus UMC compared with UMC alone for the treatment of ARF due to acute exacerbations of COPD. The GRADE ranged from moderate to low. Detailed information on the GRADE by outcome is available in Table A18 in Appendix 4.

Summary of Findings

Based on moderate quality of evidence:

- Compared with the UMC alone group, there is a significant reduction in the risk of the need for endotracheal intubation and IMV in the NPPV plus UMC group.
- Compared with the UMC alone group, there is a significant reduction in the risk of inhospital mortality in the NPPV plus UMC group.
- Compared with the UMC alone group, there is a significant reduction in the mean length of hospital stay in the NPPV plus UMC group.

Based on low quality of evidence, complications are lower in the NPPV plus UMC group compared with the UMC alone group.

Due to limited and inconsistent data, conclusions on the effectiveness of NPPV plus UMC in reducing dyspnea compared with UMC alone could not be made.

NPPV Compared with Invasive Mechanical Ventilation

The remaining 2 studies that examined the use of NPPV for the treatment of ARF due to acute exacerbations of COPD compared the use of NPPV and IMV. (7;36) For these studies, the general study characteristics and details on the patient populations included in each study are shown in Tables A11, A12, and A13 in Appendix 3.

The Conti et al (36) trial enrolled patients who had failed usual medical treatment and required ventilatory support, but failed medical treatment was not a requirement for enrolment in Jurjevic et al (7) (based on the availability of information in the published paper). Therefore, it is uncertain whether the 2 studies have enrolled similar patient populations. For this reason, the results of the 2 studies were not pooled.

Mortality

Overall, there were no statistically significant differences between the NPPV and IMV groups in terms of ICU mortality, inhospital mortality, and 1-year mortality (Table 7). The results of ICU mortality are inconsistent between the 2 studies: Conti et al (36) observed a nonsignificant increase in mortality in the NPPV group; Jurjevic et al (7) observed a nonsignificant decrease in mortality in the NPPV group.

[4] It is possible that some of the methodological flaws which were identified in these studies were not actual flaws but the result of incomplete reporting in the published methods.

Table 7: Summary of Results (NPPV Versus IMV Comparison)*

Author, Year	NPPV	IMV	*P* value
ICU Mortality	**n/N (%)**	**n/N (%)**	
Conti et al, 2002 (36)	5/23 (21.7)	3/26 (11.5)	NR
Jurjevic et al, 2009 (7)	4/78 (5.1)	5/78 (6.4)	0.93
Inhospital Mortality	**n/N (%)**	**n/N (%)**	
Conti et al, 2002 (36)	6/23 (26.1)	4/26 (15.4)	NR
Jurjevic et al, 2009 (7)	NR	NR	n/a
1-year Mortality	**n/N (%)**	**n/N (%)**	
Conti et al, 2002 (36)	6/23 (26.1)	12/26 (46.1)	0.24
Jurjevic et al, 2009 (7)	NR	NR	n/a
Successful Treatment	**n/N (%)**	**n/N (%)**	
Conti et al, 2002 (36)	NR	NR	n/a
Jurjevic et al, 2009 (7)	48/78 (61)	38/78 (49)	0.32
ICU LOS	**LOS, Mean (SD), Days**	**LOS, Mean (SD), Days**	
Conti et al, 2002 (36)	22 (19)	21 (20)	NR
Jurjevic et al, 2009 (7)	5 (1.35)* Median: 5	9.29 (3)* Median: 9.29	Mean: NR Median: < 0.001
Duration of MV	**Mean (SD), Days**	**Mean (SD), Days**	
Conti et al, 2002 (36)	16 (19)	15 (21)	0.21
Jurjevic et al, 2009 (7)	3.92 (1.08) Median: 3.92†	7.17 (2.22) Median: 7.17†	Mean: NR Median: < 0.001

*Abbreviations: d, days; ICU, intensive care unit; IMV, invasive mechanical ventilation; MV, mechanical ventilation; N, sample size of group; n, number; n/a, not applicable; NPPV, noninvasive positive pressure ventilation; NR, not reported; LOS, length of stay; SD, standard deviation.

†The published reports provided only the median LOS and duration of mechanical ventilation. The median and range information provided in the report were used to calculate the mean and standard deviation according to the methods by Hozo et al. (35)

Intensive Care Unit Length of Stay

The ICU LOS results (Table 7) are inconsistent between the 2 studies. The mean LOS was slightly longer in the NPPV group compared with the IMV group in Conti et al, (36) although this difference was not significant. In Jurjevic et al (7) however, the mean LOS[5] was significantly shorter in the NPPV group compared with the IMV group. Furthermore, the mean LOS in the ICU was substantially longer in both groups (21 to 22 days) in the Conti et al (36) study compared with the Jurjevic et al (7) study (5 to 10 days).

Successful Treatment

Jurjevic et al (7) reported mechanical ventilation treatment success for both groups, which was defined as patients who remained in spontaneous respiration for at least 48 hours after the withdrawal of ventilation. Based on this definition, 48 patients (61%) in the NPPV group and 38 patients (49%) in the IMV group were treated successfully with mechanical ventilation during their stay in the ICU (Table 7). (7)

[5] The published results by Jurjevic et al only report the median ICU length of stay. The median length of stay and range were converted into the mean length of stay and standard deviation using the methods outlined by Hozo et al. (35) Median LOS (range): NPPV, 5 days (3.6–11.7 days); invasive mechanical ventilation: 9.29 days (6–24 days). (7)

Duration of Mechanical Ventilation

The results of duration of mechanical ventilation (including both noninvasive and invasive ventilation) are also inconsistent between the 2 studies (Table 7). The mean duration of mechanical ventilation was slightly longer (but this was not significant) in the NPPV group compared with the IMV group in Conti et al (36); however, the mean duration of mechanical ventilation[6] was significantly shorter in the NPPV group compared with the IMV group in the Jurjevic et al study. (7) In addition, the mean duration of mechanical ventilation was substantially longer in both groups (15 to 16 days) in the Conti et al (36) study compared with the Jurjevic et al (7) study (4 to 7 days).

Tolerance

Tolerance was only reported in 1 study. Conti et al (36) reported that 3 patients in the NPPV group required intubation and mechanical ventilation due to mask intolerance.

Complications

In Conti et al (36), the proportion of patients who developed at least 1 complication was not significantly different between the NPPV and IMV groups (6 patients vs. 11 patients, $P = 0.37$). The breakdown of complications were: septic shock (5 vs. 4, $P = 0.41$), sepsis or severe sepsis (1 vs. 9, $P = 0.009$), ventilator-associated pneumonia (3 vs. 9, $P = 0.07$), tracheotomy (3 vs. 6, $P = 0.29$), acute renal failure (1 vs. 0, $P = 0.46$), pneumothorax (1 vs. 0, $P = 0.46$), urinary tract infection (0 vs. 2, $P = 0.27$), gastrointestinal bleeding (0 vs. 1, $P = 0.58$), and other (1 vs. 2, $P = 0.54$). All of the complications in the NPPV group occurred in patients who failed NPPV and were intubated and mechanically ventilated. (36)

Both studies reported a reduction in the number of cases of VAP and tracheotomies in the NPPV groups compared with the IMV groups, although these reductions were only significant in the Jurjevic et al (7) study ($P < 0.001$) (Table 8).

Table 8: Complications (NPPV Versus IMV Comparison)*

Author, Year	NPPV	IMV	*P* value
Ventilator-associated Pneumonia	**n/N (%)**	**n/N (%)**	
Conti et al, 2002 (36)	3/23 (13.0)	9/26 (34.6)	0.07
Jurjevic et al, 2009 (7)	5/78 (6.4)	29/78 (37.2)	< 0.001
Tracheotomies	**n/N (%)**	**n/N (%)**	
Conti et al, 2002 (36)	3/23 (13.0)	6/26 (23.1)	0.29
Jurjevic et al, 2009 (7)	5/78 (6.4)	27/78 (34.6)	< 0.001

*Abbreviations: IMV, invasive mechanical ventilation; N, sample size of group; n, number; NPPV, noninvasive positive pressure ventilation.

Other Outcomes

Conti et al (36) also measured a variety of additional outcomes during the 12 months of follow-up. Over the 12-month follow-up, there were no significant differences between the NPPV and IMV groups in terms of number of hospital readmissions (18 vs. 22; $P = 0.8$), ICU readmissions (3 vs. 2; *P* not reported), or patients with open tracheostomy (2 vs. 6; $P = 0.16$). In the NPPV group, however, significantly fewer patients required de novo permanent oxygen supplementation at home compared with the IMV group (0 vs. 5; $P = 0.01$). (36) In addition, patients in the IMV group had a significant increase in functional

[6] The published results by Jurjevic et al (7) only report the median duration of mechanical ventilation. The median duration of mechanical ventilation and range were converted into the mean and standard deviation using the methods outlined by Hozo et al. (35) Median duration of mechanical ventilation (range): NPPV, 3.92 days (2.91–8.79 days); invasive mechanical ventilation: 7.17 days (4.38–17.71 days). (7)

limitations due to COPD (visual analogue scale changed from 4.3 ± 1.4 to 5.3 ± 0.8, $P = 0.02$), but this change was not observed in the NPPV group. (36)

Quality of Evidence

The analysis was based on RCT evidence, but both had some serious methodological issues based on the information available in the published papers[7], including lack of allocation concealment, unclear methods used for randomization, lack of blinding without adequate objective outcome assessment, and inadequate sample sizes to eliminate type II error (based on post hoc sample size calculations when possible) (summarized in Table A17 in Appendix 4).

The GRADE system was used to evaluate the quality of the overall body of evidence on the use of NPPV compared with IMV for the treatment of ARF secondary to acute exacerbations of COPD after failing UMC. The GRADE level ranged from low to very low (Table A19 in Appendix 4). Due to the uncertainty associated with low and very low quality of evidence, further research is likely to have an impact on the confidence in the estimate of effect and is likely to change the estimate.

Summary of Findings

The 2 RCTs comparing NPPV and IMV for the treatment of ARF due to acute exacerbations of COPD in patients who have failed UMC alone were not pooled due to potential differences in the study populations. Due to the inconsistent and low quality of evidence, it is not possible to draw conclusions at this time.

NPPV for Weaning COPD Patients From IMV

This section of the evidence-based analysis addresses research question 2a: what is the effectiveness, cost-effectiveness, and safety of NPPV compared with IMV for weaning COPD patients from invasive mechanical ventilation?

Systematic Reviews

Five systematic reviews were identified that examined the published literature on the use of NPPV to wean people with COPD from IMV. (13;14;17;19;21)[8] Full details on the systematic reviews can be found in Appendix 2.

Randomized Controlled Trials

Two RCTs on the use of NPPV for weaning patients from IMV were identified. The trials by Nava et al (37) and Prasad et al (38) compared the use of NPPV and IMV for COPD patients being invasively ventilated who failed a T-piece weaning trial. The general study characteristics of these studies, including inclusion and exclusion criteria, length of follow-up, outcomes, and details about the NPPV and IMV protocols, as well as details on the patient populations included in each study are shown in Tables A14, A15, and A16 in Appendix 3.

A total of 80 participants were included in the 2 RCTs; the sample sizes of the studies were 30 and 50 patients, respectively. (37;38) The mean age of the participants ranged from 58 to 69 years of age. Based on either the Global Initiative for Chronic Obstructive Lung Disease (GOLD) COPD stage criteria or the mean percent predicted forced expiratory volume in 1 second (FEV_1), both studies included patients with very severe COPD. Both studies also included patients with very severe respiratory failure (mean pH of the study populations was less than 7.23). Chronic obstructive pulmonary disease patients receiving IMV

[7] It is possible that some of the methodological flaws which were identified in these studies were not actual flaws but the result of incomplete reporting in the published methods.

[8] Keenan et al (17), Caples et al 2005 (21), and Hess et al 2004 (19) are the same systematic reviews that were included in the systematic reviews on noninvasive ventilation for ARF section.

were enrolled in the study if they failed a T-piece weaning trial (spontaneous breathing test), so they could not be directly extubated from IMV. (37;38)

Both studies were conducted in the ICU. Patients in the NPPV group received weaning using either BiPAP or pressure support ventilation NPPV through a face mask, and patients in the IMV weaning group received pressure support ventilation. In both cases, weaning was achieved by tapering the ventilation level. (37;38)

Of note, the patient populations in the two studies had some significant differences. Independent 2 sample t-tests found that the FEV_1, mean age, and mean pH were significantly substantially different in the Nava et al (37) and Prasad et al (38) studies.

Mortality

Intensive care unit mortality and 30-day mortality rates were not significantly different between the NPPV and IMV groups in Prasad et al (38) (ICU mortality: 3 vs. 5 deaths; $P > 0.05$; 30-day mortality: 5 vs. 9 deaths; $P > 0.05$). In contrast, Nava et al (37) reported a significant reduction in mortality in the NPPV group compared with the IMV group at 60 days (2 vs. 7 deaths, $P = 0.009$). When the 30- and 60-day mortality results are pooled, a 53% reduction in the risk of death is observed in the NPPV group (RR, 0.47; 95% CI, 0.23–0.97; $P = 0.04$), which is statistically significant (Figure 8).

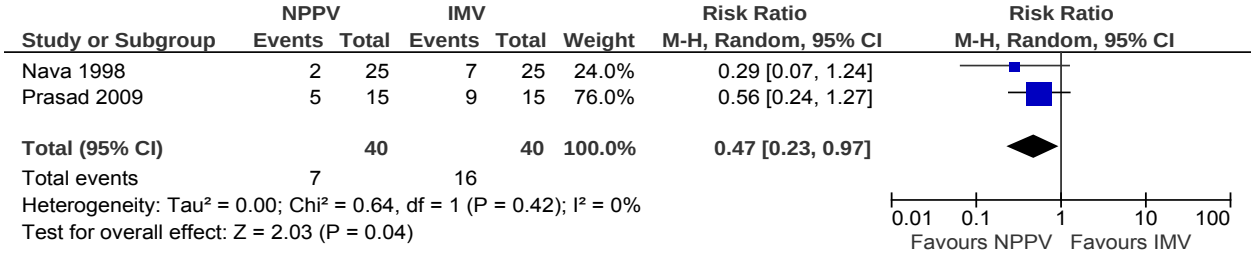

Figure 8: Pooled Mortality Results (NPPV Versus IMV for Weaning Comparison)*

*Abbreviations: CI, confidence interval; IMV, invasive mechanical ventilation; M–H, Mantel–Haenszel; NPPV, noninvasive positive pressure ventilation.

Intensive Care Unit (ICU) Length of Stay

Both Nava et al (37) and Prasad et al (38) reported a reduced ICU LOS in the NPPV group compared with the IMV group, but this reduction was only significant in the Nava et al (37) study. When the results are pooled, a nonsignificant reduction of 5.21 days (95% CI, −11.60 to 1.18; $P = 0.11$) in the ICU was found in the NPPV group compared with the IMV group (Figure 9).

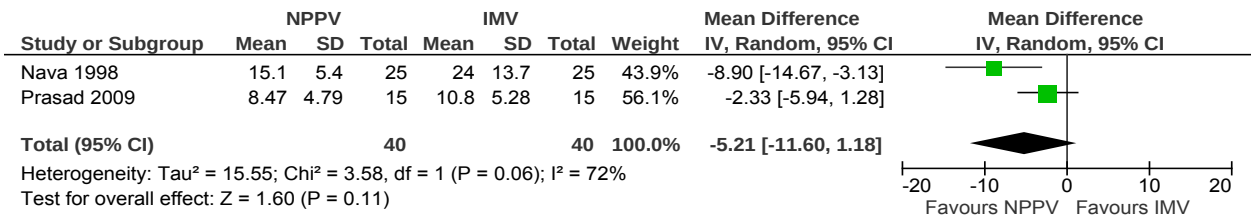

Figure 9: Pooled ICU Length of Stay Results (NPPV Versus IMV for Weaning Comparison)*

*Abbreviations: CI, confidence interval; ICU, intensive care unit; IMV, invasive mechanical ventilation; NPPV, noninvasive positive pressure ventilation; SD, standard deviation.

Duration of Mechanical Ventilation

Both studies showed a reduction in the duration of mechanical ventilation (including both invasive and noninvasive ventilation) in the NPPV group compared with the IMV group, but the difference was only significant in the Nava et al (37) study. (37;38) When the results are pooled, a nonsignificant reduction of 3.55 days (95% CI, −8.55 to 1.44 days; $P = 0.16$) of ventilation was found in the NPPV group compared with the IMV group (Figure 10).

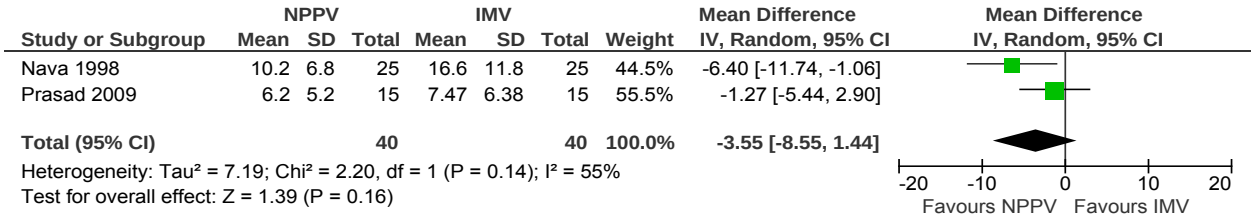

Figure 10: Pooled Duration of Mechanical Ventilation (NPPV Versus IMV for Weaning Comparison)*

*Abbreviations: CI, confidence interval; IMV, invasive mechanical ventilation; NPPV, noninvasive positive pressure ventilation; SD, standard deviation.

Complications

Both studies reported a lower incidence of nosocomial pneumonia in the NPPV group compared with the IMV group. When the results are pooled (Figure 11), an 84% reduction in the risk of nosocomial pneumonia was observed in the NPPV group (RR, 0.14; 95% CI, 0.03–0.71; $P = 0.02$). (37;38)

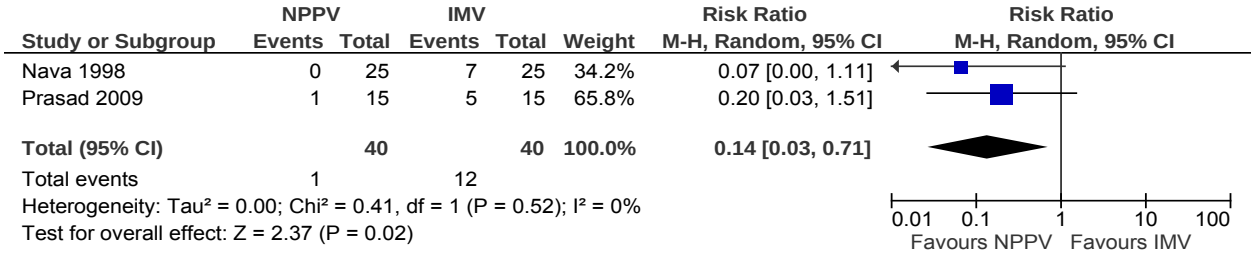

Figure 11: Pooled Incidence of Nosocomial Pneumonia (NPPV Versus IMV for Weaning Comparison)*

*Abbreviations: CI, confidence interval; IMV, invasive mechanical ventilation; M–H, Mantel–Haenszel; NPPV, noninvasive positive pressure ventilation.

Prasad et al (38) also reported the following complications related to NPPV: claustrophobia (n = 2), skin abrasions (n = 2), and gastric distension (n = 1). Similarly, Nava et al (37) reported cutaneous irritation of the nose (n = 20), nose abrasions (n = 14), and gastric distension (n = 2) in the NPPV group.

Other Outcomes

Weaning Failure

Nava et al (37) reported a significant reduction ($P = 0.02$) in the rate of weaning failure (defined as patients who could not be weaned because of death associated with mechanical ventilation, patients who were reintubated within 72 hours, and patients who could not be weaned within 60 days) in the NPPV group compared with the IMV group. The absolute rates of weaning failure were not reported in the published paper.

In the NPPV group, 1 patient could not be weaned after 60 days and was discharged with a prescription for nasal ventilation for 14 to 18 hours per day. In the IMV group, 2 patients could not be weaned after 60

days and were discharged with a prescription for at-home mechanical ventilation through a tracheostomy. (37)

Duration of Weaning
Prasad et al (38) observed a nonsignificant reduction in the duration of weaning in the NPPV group compared with the IMV group (35.17 ± 16.98 days vs. 47.05 ± 20.98 days; $P > 0.05$).

Health-Related Quality of Life
Nava et al (37) reported that most patients in the NPPV group experienced poor sleep quality, especially during the first few days of NPPV. No other measures of HRQOL were reported in either study.

Quality of Evidence
The quality of the overall body of evidence on the use of NPPV to wean COPD patients from IMV based on the GRADE criteria ranged from moderate to low (Table A20 in Appendix 4). The evidence was downgraded due to serious methodological limitations in the study design (Table A21 in Appendix 4.)

Summary of Findings
Moderate quality of evidence shows that weaning COPD patients who failed T-piece weaning trials using NPPV leads to significant reductions in mortality, nosocomial pneumonia, and weaning failure, compared with weaning patients using invasive pressure support ventilation.

NPPV After Extubation From IMV in COPD Patients

This section of the evidence-based review addresses the research questions 2b and 2c:

- What is the effectiveness, cost-effectiveness, and safety of NPPV for the prevention of ARF in COPD patients after extubation from IMV?
- What is the effectiveness, cost-effectiveness, and safety of NPPV for the treatment of ARF in COPD patients after extubation from IMV?

Systematic Reviews

Three systematic reviews were identified that examined the published literature on the use of NPPV after extubation from IMV to prevent or treat respiratory failure during the postextubation time period. (17;19;21)[9] The full details about the systematic reviews can be found in Appendix 2.

Early Application of NPPV to Prevent ARF After Extubation From IMV

Keenan et al (17) identified 4 studies which examined the use of NPPV after extubation to prevent deterioration and reintubation. Of those studies, 2 included patients with acute exacerbations of COPD. The results for the COPD patients are not presented separately in the review; the results for all patient groups combined showed statistically significantly reduced rates of reintubation (RR, 0.42; 95% CI, 0.25–0.70), ICU mortality (RR, 0.35, 95% CI, 0.16–0.78), and a nonsignificant reduction in the risk of hospital mortality (RR, 0.66; 95% CI, 0.42–1.04). (17)

The reviews by Caples et al (21) and Hess et al (19) did not address the use of NPPV for the prevention of ARF after extubation.

[9] Keenan et al 2011 (17), Hess et al 2004 (19), and Caples et al 2005 (21) are the same systematic reviews that were identified in the 2 previous sections.

Treatment of ARF After Extubation From IMV

The pooled analysis from Keenan et al (17) showed no significant difference between NPPV plus UMC versus UMC alone for the treatment of ARF after extubation from IMV (RR, 1.03; 95% CI, 0.84–1.25). The larger of the 2 trials showed a significant increase in the mortality rate in the NPPV group (28 of 114 patients vs. 15 of 107 patients, $P = 0.048$). Keenan et al (17) noted that both studies included very few COPD patients, so the overall conclusion was that "no recommendation (could be made) about the use of noninvasive positive pressure ventilation in patients who have COPD and postextubation failure, because of insufficient evidence."

Both Caples et al (21) and Hess et al (19) provided only a brief description of the included studies and did not conduct any pooled analyses. Caples et al (21) concluded that there is evidence from uncontrolled studies to support the use of NPPV after failed extubation from mechanical ventilation in patients with COPD. Furthermore, as the RCT evidence which showed no benefit from NPPV in this patient population included so few patients with COPD, it was not possible to generalize the higher quality evidence to the COPD patient population. (21) Hess et al (19) concluded that "the role of NPPV in the [periextubation] period remains to be determined."

Randomized Controlled Trials

Early Application of NPPV to Prevent ARF After Extubation From IMV

There were no RCTs identified that examined the early use of NPPV after patients have been extubated from IMV for the prevention of reintubation, which enrolled only COPD patients. Of the RCTs that were identified which enrolled mixed populations including some patients with COPD, the trials did not meet the inclusion criteria of this review because the results for the COPD patients were not presented separately. (39;40)

Treatment of ARF After Extubation From IMV

One RCT was identified that met the inclusion criteria of this analysis. Esteban et al (41) evaluated the use of NPPV plus UMC compared with UMC alone for the treatment of respiratory failure developed within 48 hours of extubation from IMV. Patients were enrolled in the study if they had received mechanical ventilation for at least 48 hours, were successfully extubated after a trial of spontaneous breathing, and then developed respiratory failure within 48 hours. Included patients had received mechanical ventilation for ARF due to pneumonia, postoperative respiratory failure, sepsis, trauma, cardiac failure, acute respiratory distress syndrome, and other causes, or acute-on-chronic respiratory failure due to COPD or asthma. (41)

Patients in the NPPV group received pressure support ventilation through a full facial mask continuously for 4-hour periods until the attending physician determined it was no longer necessary or the patient met the reintubation criteria. Patients in the UMC group received supplemental oxygen, respiratory physiotherapy, bronchodilators, and any other therapies that were needed. Patients were followed for the duration of their time in the ICU. (41)

Of the 221 patients included in the study, only 23 had COPD (14 in the NPPV group and 9 in the UMC group). The rate of reintubation was the only outcome that was reported for COPD patients separately. This post hoc analysis found a nonsignificant reduction in the rate of reintubation in the NPPV group compared with the UMC group (7 of 14 patients vs. 6 of 9 patients, $P = 0.67$). (41) The study was stopped early due a significant increase in mortality for the NPPV group compared with the UMC group (25% vs. 14%; RR, 1.78; 95% CI, 1.03–3.20; $P = 0.02$). It was noted that previous literature has shown NPPV to be more effective in the treatment of respiratory failure due to COPD compared to other etiologies, so there may also be a benefit in the postextubation period for COPD patients that could not be assessed in this study due to the small number of COPD patients enrolled. (41)

Quality of Evidence

While the Esteban et al (41) trial meets most of the methodological quality criteria (Table A22 in Appendix 4), the post hoc analysis with COPD patients is underpowered and the subgroup analysis breaks the study randomization. The overall quality of evidence evaluated using the GRADE criteria is low (Table A23 in Appendix 4).

Summary of Findings

At this time, there is inadequate evidence to reach conclusions on the comparative effectiveness of NPPV plus UMC and UMC alone for the prevention of recurrent respiratory failure in COPD patients after extubation from IMV or the treatment of recurrent respiratory failure in COPD patients following extubation from IMV.

Economic Analysis

The results of the economic analysis are summarized in issue 12 of the COPD series entitled *Cost-Effectiveness of Interventions for Chronic Obstructive Pulmonary Disease Using an Ontario Policy Model*. This report can be accessed at: www.hqontario.ca/en/mas/tech/pdfs/2012/rev_COPD_Economic_March.pdf.

Conclusions

The conclusions are summarized in Table 9.

Table 9: Summary of Findings by Research Question*

Intervention	Comparator	Study Population	No. Studies (N)	Summary of Findings	GRADE Quality of Evidence
Research Question 1: What is the effectiveness, cost-effectiveness, and safety of NPPV for the treatment of acute hypercapnic respiratory failure due to acute exacerbations of COPD compared with UMC or IMV?					
NPPV + UMC	UMC	COPD patients with ARF due to acute exacerbations of COPD	11 (1000)	NPPV significantly reduces the risk of endotracheal intubation and IMV, inhospital mortality, and mean length of hospital stay compared with UMC.	Moderate
				NPPV results in fewer complications compared with UMC.	Low
NPPV	IMV	COPD patients with ARF†	2 (205)	At this time, no conclusions can be drawn regarding the comparative effectiveness of NPPV and IMV for this patient population.	Low
Research Question 2a: What is the effectiveness, cost-effectiveness and safety of NPPV compared with IMV for weaning COPD patients from IMV?					
NPPV	Pressure support IMV	COPD patients being invasively ventilated who fail T-piece weaning trials	2 (80)	NPPV leads to significant reductions in mortality, nosocomial pneumonia, and weaning failure compared with pressure support IMV.	Moderate
Research Question 2b: What is the effectiveness, cost-effectiveness, and safety of NPPV compared with UMC for the prevention of ARF in COPD patients after they have been extubated from IMV?					
NPPV	UMC	COPD patients after they have been extubated from IMV	0 (0)	No evidence was identified to evaluate the use of NPPV after extubation of COPD patients from IMV.	n/a
Research Question 2c: What is the effectiveness, cost-effectiveness, and safety of NPPV compared with UMC for the treatment of ARF in COPD patients after they have been extubated from IMV?					
NPPV	UMC	COPD patients who develop respiratory failure within 48 hours of extubation from IMV	1 (23)	At this time, there is inadequate evidence to reach conclusions on the comparative effectiveness of NPPV and UMC for the treatment of COPD patients who have developed ARF following extubation from IMV.	n/a

*Abbreviations: ARF, acute respiratory failure; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IMV, invasive mechanical ventilation N, sample size; n/a, not applicable; No., number; NPPV, noninvasive positive pressure ventilation; UMC, usual medical care.

†The patient populations for these 2 studies are not clear: 1 study specifies that patients who were enrolled must have failed medical treatment, but 1 study does not specify this and may include patients who have not been treated first with UMC.

Glossary

6 Minute Walking Test (6MWT)	A measure of exercise capacity which measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes. A widely used outcome measure in respiratory rehabilitation of patients with COPD.
Acute exacerbations of chronic obstructive pulmonary disease (AECOPD)	A change in baseline symptoms that is beyond day-to-day variation, particularly increased breathlessness, cough, and/or sputum, which has an abrupt onset.
Admission avoidance hospital-at-home program	Treatment program for patients experiencing acute exacerbations of COPD which allows patients to receive treatment in their home and avoid admission to hospital. After patients are assessed in the emergency department for an acute exacerbation, they are prescribed the necessary medications and additional care needed (e.g., oxygen therapy) and then sent home where they receive regular visits from a medical professional until the exacerbation has resolved.
Ambulatory oxygen therapy	Provision of oxygen therapy during exercise and activities of daily living for individuals who demonstrate exertional desaturation.
Bilevel positive airway pressure (BiPAP)	A continuous positive airway pressure mode used during noninvasive positive pressure ventilation (see definition below) that delivers preset levels of inspiratory and expiratory positive airway pressure. The pressure is higher when inhaling and falls when exhaling, making it easier to breathe.
Cost-effectiveness acceptability curve (CEAC)	A method for summarizing uncertainty in estimates of cost-effectiveness.
Cor pulmonale	Right heart failure, as a result of the effects of respiratory failure on the heart.
Dyspnea	Difficulty breathing or breathlessness.
Early discharge hospital-at-home program	Treatment program for patients experiencing acute exacerbations of COPD which allows patients to receive treatment in their home and decrease their length of stay in hospital. After being assessed in the emergency department for acute exacerbations, patients are admitted to the hospital where they receive the initial phase of their treatment. These patients are discharged early into a hospital-at-home program where they receive regular visits from a medical professional until the exacerbation has resolved.
Forced expiratory volume in 1 second (FEV_1)	A measure of lung function used for COPD severity staging; the amount of air that can be forcibly exhaled from the lungs in the first second of a forced exhalation.
Forced vital capacity (FVC)	The amount of air that can be forcibly exhaled from the lungs after taking the deepest breath possible.

Fraction of inspired oxygen (FiO_2)	The percentage of oxygen participating in gas exchange.
Hypercapnia	Occurs when there is too much carbon dioxide in the blood (arterial blood carbon dioxide > 45 to 60 mm Hg).
Hypopnea	Slow or shallow breathing.
Hypoxemia	Low arterial blood oxygen levels while breathing air at rest. May be severe ($PaO_2 \leq 55$ mm Hg), moderate (56 mm Hg $\leq PaO_2 <$ 65 mm Hg), or mild-to-moderate (66 mm Hg $< PaO_2 \leq$ 74 mm Hg).[1]
Incremental cost-effectiveness ratio (ICER)	Ratio of the change in costs of a therapeutic intervention to the change in effects of the intervention compared to the alternative (often usual care).
Intention-to-treat analysis (ITT)	An analysis based on the initial treatment the participant was assigned to, not on the treatment eventually administered.
Invasive mechanical ventilation (IMV)	Mechanical ventilation via an artificial airway (endotracheal tube or tracheostomy tube).
Long-term oxygen therapy (LTOT)	Continuous oxygen use for about 15 hours per day. Use is typically restricted to patients fulfilling specific criteria.
Multidisciplinary care	Defined as care provided by a team (compared to a single provider). Typically involves professionals from a range of disciplines working together to deliver comprehensive care that addresses as many of the patient's health care and psychosocial needs as possible.
Nicotine replacement therapy (NRT)	The administration of nicotine to the body by means other than tobacco, usually as part of smoking cessation.
Noninvasive positive pressure ventilation (NPPV)	Noninvasive method of delivering ventilator support (without the use of an endotracheal tube) using positive pressure. Provides ventilatory support through a facial or nasal mask and reduces inspiratory work.
Partial pressure of carbon dioxide ($PaCO_2$)	The pressure of carbon dioxide dissolved in arterial blood. This measures how well carbon dioxide is able to move out of the body.
Partial pressure of oxygen (PaO_2)	The pressure of oxygen dissolved in arterial blood. This measures how well oxygen is able to move from the airspace of the lungs into the blood.
Palliative oxygen therapy	Use of oxygen for mildly hypoxemic or nonhypoxemic individuals to relieve symptoms of breathlessness. Used short term. This therapy is "palliative" in that treatment is not curative of the underlying disease.
Pulmonary rehabilitation	Multidisciplinary program of care for patients with chronic respiratory impairment that is individually tailored and designed to optimize physical and social performance and autonomy. Exercise training is the cornerstone of pulmonary rehabilitation programs.

[1] The mild-to-moderate classification was created for the purposes of the report.

Pulse oximetry	A noninvasive sensor, which is attached to the finger, toe, or ear to detect oxygen saturation of arterial blood.
Quality-adjusted life-years (QALYs)	A measure of disease burden that includes both the quantity and the quality of the life lived that is used to help assess the value for money of a medical intervention.
Respiratory failure	Respiratory failure occurs when the respiratory system cannot oxygenate the blood and/or remove carbon dioxide from the blood. It can be either acute (acute respiratory failure, ARF) or chronic, and is classified as either hypoxemic (type I) or hypercapnic (type II) respiratory failure. Acute hypercapnic respiratory failure frequently occurs in COPD patients experiencing acute exacerbations of COPD.
Short-burst oxygen therapy	Short-duration, intermittent, supplemental oxygen administered either before or after exercise to relieve breathlessness with exercise.
Sleep apnea	Interruption of breathing during sleep due to obstruction of the airway or alterations in the brain. Associated with excessive daytime sleepiness.
Smoking cessation	The process of discontinuing the practice of inhaling a smoked substance.
Spirometry	The gold standard test for diagnosing COPD. Patients breathe into a mouthpiece attached to a spirometer which measures airflow limitation.
SpO_2	Oxygen saturation of arterial blood as measured by a pulse oximeter.
Stable COPD	The profile of COPD patients which predominates when patients are not experiencing an acute exacerbation.
Supplemental oxygen therapy	Oxygen use during periods of exercise or exertion to relieve hypoxemia.
Telemedicine (or telehealth)	Refers to using advanced information and communication technologies and electronic medical devices to support the delivery of clinical care, professional education, and health-related administrative services.
Telemonitoring (or remote monitoring)	Refers to the use of medical devices to remotely collect a patient's vital signs and/or other biologic health data and the transmission of those data to a monitoring station for interpretation by a health care provider.
Telephone only support	Refers to disease/disorder management support provided by a health care provider to a patient who is at home via telephone or videoconferencing technology in the absence of transmission of patient biologic data.
Ventilator-associated pneumonia (VAP)	Pneumonia that occurs in patients undergoing mechanical ventilation while in a hospital.

Acknowledgements

Medical Information Officer

Kellee Kaulback

Editorial Staff

Jan Collins
Irina Alecu

COPD Expert Advisory Panel

The role of the expert panel was to provide direction on the scope of the project and the relevant outcomes measures of effectiveness, to review the evidence-based analyses and to identify any societal or systemic issues that are relevant to intervention effectiveness. However, the statements, conclusions and views expressed in this report do not necessarily represent the views of the expert panel members.

Jeremy Grimshaw, MD, MBChB, PhD (Chair)
Senior Scientist, Ottawa Hospital Research Institute
Professor, Department of Medicine, University of Ottawa

Dina Brooks, PhD
Professor, Department of Physical Therapy, University of Toronto

Debbie Coutts, RRT, CRE

Andrea Gershon, MD, MSc, FRCP(C)
Scientist, Institute for Clinical Evaluative Sciences
Respirologist, Sunnybrook Health Sciences Centre
Assistant Professor, Departments of Medicine and Health Policy, Management and Evaluation, University of Toronto

Mita Giacomini, BSc, MPH, MA, PhD
Professor, Department of Clinical Epidemiology & Biostatistics, McMaster University

Ron Goeree, BA, MA
Director, PATH Research Institute, St. Joseph's Hospital (Hamilton)
Associate Professor, Department of Clinical Epidemiology & Biostatistics, McMaster University

Roger Goldstein, MBCHB, FRCP(C), FRCP(UK)
NSA Chair in Respiratory Rehabilitation Research
Director, Respiratory Services, and Senior Scientist, West Park Healthcare Centre
Professor, Medicine and Physical Therapy, University of Toronto

Alan G Kaplan, MD, CCFP(EM), FCFP
Chairperson, Family Physician Airways Group of Canada
Chairperson, Special Interest Focused Care Group in Respiratory Medicine, College of Family Physicians of Canada
Clinical Lecturer, Department of Family and Community Medicine, University of Toronto

DE O'Donnell, MD, FRCP(C)
Director, COPD Centre, Kingston General Hospital
Professor, Department of Medicine, Queen's University

Asad Razzaque, MD
Family Physician

Holger Schünemann, MD, PhD, MSc, FRCP(C)
Michael Gent Chair in Healthcare Research
Chair, Department of Clinical Epidemiology & Biostatistics, McMaster University
Professor, Department of Clinical Epidemiology & Biostatistics and Medicine, McMaster University

Tasnim Sinuff, MD, PhD, FRCP(C)
Clinician Scientist, Sunnybrook Health Sciences Centre
Assistant Professor, Department of Medicine, University of Toronto

Laura Watling, RRT, BSc(HK)
Clinical Practice Leader/Clinical Coordinator, Respiratory Therapy, West Park Healthcare Centre

Appendices

Appendix 1: Literature Search Strategies

Search date: December 3, 2010
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, CINAHL, Centre for Reviews and Dissemination/International Agency for Health Technology Assessment

Database(s): Ovid MEDLINE(R) 1950 to November Week 3 2010

Search Strategy:

#	Searches	Results
1	exp Pulmonary Disease, Chronic Obstructive/	15011
2	(chronic obstructive adj2 (lung* or pulmonary or airway* or airflow or respiratory) adj (disease* or disorder*)).ti,ab.	21909
3	(copd or coad).ti,ab.	16795
4	chronic airflow obstruction.ti,ab.	493
5	exp Emphysema/	7051
6	((chronic adj2 bronchitis) or emphysema).ti,ab.	22960
7	or/1-6	54680
8	exp Respiration, Artificial/	51221
9	((artificial or non-invasive or noninvasive or invasive or nasal or mechanical or volume-controlled or pressure controlled or positive) adj2 (ventilat* or respiration)).ti,ab.	29829
10	(NIV or NPPV or NIPPV or NIAV or continous positive airway pressure or CPAP or bi-level positive pressure or ventilation support or BiPAP or endotracheal intubation or ventilat* failure).ti,ab.	10735
11	exp Ventilator Weaning/	2368
12	limit 11 to "all adult (19 plus years)"	1062
13	or/8-10	68682
14	7 and 13	3314
15	12 or 14	4228
16	limit 15 to (english language and humans and yr="2004 -Current")	1206

Database(s): EMBASE 1980 to 2010 Week 47
Search Strategy:

#	Searches	Results
1	exp chronic obstructive lung disease/	48840
2	(chronic obstructive adj2 (lung* or pulmonary or airway* or airflow or respiratory) adj (disease* or disorder*)).ti,ab.	26482
3	(copd or coad).ti,ab.	21755
4	chronic airflow obstruction.ti,ab.	551
5	exp emphysema/	25753
6	exp chronic bronchitis/	6600

7	((chronic adj2 bronchitis) or emphysema).ti,ab.	25596
8	or/1-7	89245
9	exp artificial ventilation/	86836
10	((artificial or non-invasive or noninvasive or invasive or nasal or mechanical or volume-controlled or pressure controlled or positive) adj2 (ventilat* or respiration)).ti,ab.	36697
11	(NIV or NPPV or NIPPV or NIAV or continous positive airway pressure or CPAP or bi-level positive pressure or ventilation support or BiPAP or endotracheal intubation or ventilat* failure).ti,ab.	13569
12	(ventilat* adj2 wean*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	971
13	limit 12 to (adult <18 to 64 years> or aged <65+ years>)	357
14	or/9-11	102073
15	8 and 14	6573
16	13 or 15	6871
17	limit 16 to (human and english language and yr="2004 -Current")	2094

CINAHL

#	Query	Results
S14	(S11 or S12) Limiters - Published Date from: 20040101-20101231; English Language	416
S13	(S11 or S12)	794
S12	s6 and s10	585
S11	(MH "Ventilator Weaning") Limiters - Age Groups: Aged: 65+ years	235
S10	S7 or S8 or S9	12790
S9	NIV or NPPV or NIPPV or NIAV or continous positive airway pressure or CPAP or bi-level positive pressure or ventilation support or BiPAP or endotracheal intubation or ventilat* failure	1689
S8	artificial N2 ventil* or non-invasive N2 ventil* or noninvasive N2 ventil* or invasive N2 ventil* or nasal N2 ventil* or mechanical N2 ventil* or volume-controlled N2 ventil*or pressure controlled N2 ventil*or positive N2 ventil* or artificial N2 respirat* or non-invasive N2 respirat* or noninvasive N2 respirat* or invasive N2 respirat* or nasal N2 respirat* or mechanical N2 respirat* or volume-controlled N2 respirat*or pressure controlled N2 respirat*or positive N2 respirat*	9597
S7	(MH "Respiration, Artificial+")	10081
S6	S1 or S2 or S3 or S4 or S5	7579
S5	chronic bronchitis or emphysema	1606
S4	(MH "Emphysema+")	982
S3	copd or coad	4153

S2	(chronic obstructive and (lung* or pulmonary or airway* or airflow or respiratory) and (disease* or disorder*))	5747
S1	(MH "Pulmonary Disease, Chronic Obstructive+")	4462

Appendix 2: Details About Included Systematic Reviews

NPPV for the Treatment of Acute Respiratory Failure due to Acute Exacerbations of COPD: Systematic Reviews

Although 12 systematic reviews were identified on this topic, only 8 of the reviews are summarized in the following tables. These 8 reviews were chosen because they are the 5 reviews that include statistical analyses and 3 of the less detailed reviews that provide a summary table of the included studies in addition to the narrative review.

Table A1: Comparison of Systematic Reviews Published Since 2000 and MAS Evidence-Based Reviews*

Component RCTs: Author, Year	Author, Year of Literature Search Inclusion for Identified Systematic Reviews								MAS Review	
	Keenan et al, 2009 (17)	Keenan et al, 2006† (2)	Quon et al, 2006 (18)	Caples et al, 2005 (21)	Hess et al, 2003 (19)	Keenan et al, 2002 (20)	Ram et al, 2003 (4)	Peter et al, 2000 (22)	Study Included	Reasons for Exclusion
Angus et al, 1996 (42)	‡	✓	✓		✓	✓		✓	X	NPPV versus Doxapram (drug not used in Ontario)
Avdeev et al, 1998 (43)	✓	✓			✓	✓	✓	✓	X	Not English
Barbe et al, 1996 (25)	✓	✓	✓		✓	✓	✓	✓	✓	
Bardi et al, 2000 (44)					✓			✓	X	Not randomized
Bott et al, 1993 (26)	†	✓	✓	✓	✓	✓	✓	✓	✓	
Brochard et al, 1995 (27)	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Carrera et al, 2009 (28)									✓	
Celikel et al, 1998 (45)	✓	✓	✓	✓	✓	✓	✓	✓	X	Mixed population§
Confalonieri et al, 1999 (46)		✓		✓		✓		✓	X	Patients with CAP and COPD‖
Conti et al, 2002 (36)	✓			✓			✓		✓	
Daskalopoulou et al, 1993 (47)			✓			✓		✓	X	Abstract

Component RCTs: Author, Year	Author, Year of Literature Search Inclusion for Identified Systematic Reviews								MAS Review	
	Keenan et al, 2009 (17)	Keenan et al, 2006† (2)	Quon et al, 2006 (18)	Caples et al, 2005 (21)	Hess et al, 2003 (19)	Keenan et al, 2002 (20)	Ram et al, 2003 (4)	Peter et al, 2000 (22)	Study Included	Reasons for Exclusion
Del Castillo et al, 2003 (48)	✓	✓					✓		X	Not English
Dhamija et al, 2005 (29)	✓	✓	✓						✓	
Dikensoy et al, 2002 (5)		✓	✓		✓	✓	✓		✓	
Honrubia et al, 2005 (49)	✓								X	Mixed population¶
Jurjevic et al, 2009 (7)									✓	
Keenan et al, 2005 (30)	✓	✓	✓						✓	
Khilnani et al, 2002 (50)						✓	✓		X	Abstract
Khilnani et al, 2010 (31)									✓	
Kramer et al, 1995 (9)	✓	✓	✓	✓		✓	✓	✓	✓	
Lapinsky et al, 1999 (51)								✓	X	Abstract
Liao et al, 2004 (52)	✓	✓							X	Not English
Martin et al, 2000 (53)			✓	✓		✓		✓	X	Mixed population#
Marvisi et al, 2004 (54)	✓								X	Outcomes
Matic et al, 2007 (55)	✓								X	Duplicate publication**
Matuska et al, 2006 (56)	✓	✓							X	Not English
Pastaka et al, 2007 (57)	✓								X	Patients have chronic respiratory failure
Plant et al, 2000 (32)	✓	✓	✓	✓	✓	✓	✓	✓	✓	

Component RCTs: Author, Year	Author, Year of Literature Search Inclusion for Identified Systematic Reviews								MAS Review	
	Keenan et al, 2009 (17)	Keenan et al, 2006† (2)	Quon et al, 2006 (18)	Caples et al, 2005 (21)	Hess et al, 2003 (19)	Keenan et al, 2002 (20)	Ram et al, 2003 (4)	Peter et al, 2000 (22)	Study Included	Reasons for Exclusion
Servillo et al, 1994 (58)			✓			✓	✓		X	Abstract
Thys et al, 2002 (59)							✓		X	Mixed population††
Wang et al, 2005 (33)	✓	✓	✓						✓	
Wood et al, 1998 (60)				✓				✓	X	Mixed population‡‡
Zhou et al, 2001 (61)	✓	✓					✓		X	Not English

*Abbreviations: ARF, acute respiratory failure; CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; MAS, Medical Advisory Secretariat; NPPV, noninvasive positive pressure ventilation; RCTs, randomized controlled trials.

† It is not clear from the methods section of the published paper, which years were included in the systematic search of the literature. The most recent included study was published in 2006, so that has been estimated as the year until which the literature was searched. (2)

‡The studies by Bott et al (26) and Angus et al (42) were identified by the reviews, but they were not included in the results because the patients who developed respiratory failure were not offered endotracheal intubation. (17)

§Celikel et al (45) enrolled COPD patients with respiratory failure caused by several etiologies including pneumonia, COPD exacerbations, and heart failure. Since the results for these groups were not presented separately, and the mechanism for ARF due to heart failure is different (Expert Opinion), this study is excluded from the MAS evidence-based review.

‖The primary diagnosis of patients in this study was respiratory failure due to community-acquired pneumonia rather than acute exacerbations of COPD. (46)

¶Includes patients with respiratory failure due to multiple etiologies, as well as both hypoxemic and hypercapnic respiratory failure. While some results are presented separately for the COPD group, the results are not stratified by hypoxemic and hypercapnic respiratory failure, so it was not possible to identify if the patients in the COPD group had hypercapnic and/or hypoxemic respiratory failure. (49)

#Martin et al (53) enrolled patients with ARF due to a variety of etiologies. Since the COPD patient group includes patients with both hypercapnic and hypoxemic respiratory failure and the results are not presented separately for the hypercapnic patients, this study has been excluded from the MAS evidence-based analysis.

**Matic et al (55) appears to be a duplicate publication that is updated in the Jurjevic et al (7) paper, so it was excluded. The authors of the paper have been contacted to confirm that the papers include some of the same patients, but no response has been received to date.

††Thys et al (59) enrolled patients with ARF due to a variety of etiologies. The results for the COPD patients are only presented separately for the arterial blood gas outcomes, outcomes which were out of scope of this analysis, so this study has been excluded from the MAS evidence-based analysis.

‡‡Wood et al (60) enrolled patients with ARF due to a variety of etiologies. The results for the COPD patients are not presented separately, so this study was excluded from the MAS evidence-based analysis.

Table A2: Summary of the Systematic Reviews' Methods*

Author, Year	Date Literature Current to	Databases Searched	Population Included	Included Study Designs	Total N (No. Studies)	Statistical Methods	Outcomes
Caples et al, 2005 (21)	2005†	MEDLINE, CINAHL, EMBASE, Web of Science	Use of NPPV in ICU settings for any etiology	RCTs, cohort, & observational studies‡	2068 (28)§	• Descriptive narrative of results	ETI or failure criteria, mortality, improvement in physiology, complications
Hess et al, 2004 (19)	2003†	PubMed	Adult patients with ARF Excluded: long-term NPPV for stable patients with pulmonary or neuromuscular disease	RCTs‡	NR (8)	• Relative risks were calculated • Pooled analyses were conducted using random effects models • Results for NPPV for COPD patients are based on results from other meta-analyses. The authors did not conduct their own analysis on this topic.	Not specified in methods. Outcomes included in the COPD section include treatment failure, mortality, intubation, and complications
Keenan et al, 2011 (17)	June 2009	MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effectiveness, Cochrane Database of Systematic Reviews, ACP Journal Club Database, MetaRegister of Controlled Trials, clinicaltrials.gov website, and Journals@OVID database	Hospitalized adult patients who had or who were at risk for ARF including both acute and acute-on-chronic respiratory failure. Included studies with predominately COPD patients. Excluded: studies of chronic respiratory failure in an outpatient setting	Parallel-design RCTs (abstracts excluded)	NR (16)‖	• Relative risks and weighted mean differences were calculated • Pooled analyses were conducted using random effects models • Subgroups included severe versus mild exacerbations and patients with acute exacerbations of COPD in the setting of severe CAP	Physiologic outcomes including arterial blood gases and vital signs; clinical outcomes including endotracheal intubation and hospital mortality In the section on NPPV vs. UMC, the following outcomes were reported: hospital mortality and ETI In the section on NPPV vs. conventional mechanical ventilation, the following outcomes were reported: hospital mortality, ICU mortality, and ETI avoidance
Keenan et al, 2009 (2)	2006†¶	PubMed, MEDLINE, EMBASE, Cochrane Database	Patients with ARF of any etiology Excluded: trials with mixed populations in which the data were not presented separately by etiology	RCTs (abstracts excluded)	1216 (17)	• Descriptive narrative of results • Results subgrouped by severity of COPD exacerbation	Failure rate, intubation rate, hospital mortality

Author, Year	Date Literature Current to	Databases Searched	Population Included	Included Study Designs	Total N (No. Studies)	Statistical Methods	Outcomes
Kennan et al, 2003 (20)	December 2002	MEDLINE, EMBASE, Cochrane Library (including Controlled Trial Registry), Database of Abstracts of Reviews of Effectiveness, Cochrane Database of Systematic Reviews, Methodology Database, abstracts of meetings from American Thoracic Society, American College of Chest Physicians, Society of Critical Care Medicine, European Society of Critical Care Medicine, European Respiratory Society, written request to authors for additional studies	Adults with an acute exacerbation of COPD who were hospitalized	RCTs (abstracts included)	628# (15)	• Summary risk differences and weighted mean differences were calculated • Pooled analyses were conducted using random effects models • Subgroup analyses included: severity of COPD exacerbation; full length published trials vs. abstracts; different NPPV failure definitions; different predefined intubation criteria	Endotracheal intubation, hospital LOS, inhospital mortality rate
Peter et al, 2002 (22)	2002†	MEDLINE, manual search of abstracts from American Journal of Respiratory and Critical Care Medicine, Chest, Critical Care Medicine, European Respiratory Journal, Intensive Care Medicine, Thorax, contacted industry for additional studies	Adult patients presenting with ARF Exclusions: studies on cardiogenic pulmonary edema, use of NIV in weaning and postintubation, postoperative NIV, studies comparing NIV with mechanical ventilation, and studies of NIV in specialized subgroups (e.g. cancer)	RCTs (abstracts included)	793 (15)	• Risk differences, weighted mean differences, and meta-analytic regression were calculated • Pooled analyses were conducted using fixed or random effects models depending on the amount of heterogeneity • Subgroups included: baseline risk, COPD vs. mixed patients, published vs. unpublished (abstracts)	Mortality, intubation, hospital LOS

Author, Year	Date Literature Current to	Databases Searched	Population Included	Included Study Designs	Total N (No. Studies)	Statistical Methods	Outcomes
Quon et al, 2008 (18)	November 2006	MEDLINE, EMBASE, Cochrane Database of Systematic Reviews	Adult patients experiencing an acute COPD exacerbation Excluded: patients with an alternative primary diagnosis	RCTs with Jadad score ≥ 2 (abstracts included)	979 (14)	• Relative risks and weighted mean differences were calculated • Pooled analyses were conducted using fixed effects or random effects models depending on amount of heterogeneity	Intubation, inhospital mortality, hospital LOS
Ram et al, 2004 (4)	September 2003	Cochrane Airways Group RCT register (includes MEDLINE, CINAHL, EMBASE, UK Research Register, abstracts from meetings of American Thoracic Society, British Thoracic Society, European Respiratory Society)	Adult patients with ARF and admitted to hospital due to an acute exacerbation of COPD with baseline admission $PaCO_2$ > 6 kPa Excluded: patients with primary diagnosis of pneumonia, weaning studies, patients with underlying pathologies, studies where CPAP or ETI preceded enrolment of patients into trial	RCTs (abstracts included)	758 (14)	• Relative risks and weighted mean differences or standardized mean differences were calculated • Pooled analyses were conducted using fixed effects or random effects models depending on amount of heterogeneity • Subgroups included: pH, location (ICU vs. ward), study quality, NPPV duration, type of mask, type of NPPV	Treatment failure (mortality, intubation, and intolerance to allocated treatment), inhospital mortality, ETI hospital LOS, ICU LOS, symptom scores (breathlessness scores), complications, arterial blood gas tensions 1-hour post intervention (pH, $PaCO_2$, PaO_2)

*Abbreviations: ARF, acute respiratory failure; CAP, community acquired pneumonia; CINAHL, the Cumulative Index to Nursing and Allied Health Literature; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; ETI, endotracheal intubation; ICU, intensive care unit; kPa, kilopascals; LOS, length of stay; N, sample size; NIV, noninvasive ventilation; no., number; NPPV, noninvasive positive pressure ventilation; NR, not reported; O_2, oxygen; $PaCO_2$, partial pressure of carbon dioxide in the arterial blood; PaO_2, partial pressure of oxygen in the arterial blood; RCTs, randomized controlled trials; UMC, usual medical care.

†Month was not specified in published results. (19;21;22)

‡Unclear from published methods whether abstracts were included.

§Includes studies with patients with respiratory failure due to any etiology, not just COPD patients.

‖16 RCTs that compared NPPV versus standard therapy and 2 RCTs that compared NPPV versus conventional mechanical ventilation were identified. The results from 2 of the trials on NPPV vs. standard medical therapy were excluded as they did not offer patients who developed respiratory failure endotracheal intubation and mechanical ventilation.

¶The systematic review was published in 2009. It is not clear from the methods which years were included in the systematic search of the literature. The most recent included study was published in 2006, so that has been estimated as the year until which the literature was searched.

#The sample size excludes non-COPD patients from those trials with mixed populations. (20)

Table A3: Summary of the Systematic Reviews' Results*

Author, Year	Findings
Caples et al, 2005 (21)	Pooled results were not reported.† Summary: "From these study results, treatment of hypercapnic patients with acute exacerbations of COPD can generally be expected to reduce intubation rates, mortality, and ICU or hospital LOS."
Hess et al, 2004 (19)	Pooled results were not reported. Summary: "Studies report benefit for (the COPD patient) population with the exception of patients suffering mild exacerbations. The use of NPPV for COPD-exacerbation patients is now considered a standard of care, the evidence for which is established in 2 meta-analyses".‡
Keenan et al, 2011 (17)	NPPV vs. standard medical therapy Intubation: RR, 0.39 (95% CI, 0.28–0.54)§ Hospital mortality: RR, 0.52 (95% CI, 0.36–0.76)‖ NPPV vs. conventional mechanical ventilation ICU mortality: RR, 1.24 (95% CI, 0.45–3.41) Recommendations: "We recommend the use of NPPV in addition to usual care in patients who have a severe exacerbation (pH < 7.35 and relative hypercarbia) of COPD (GRADE 1A). … We make no recommendation about the use of NPPV in patients who have a severe exacerbation of COPD that requires ventilatory support due to insufficient evidence."¶
Keenan et al, 2009 (2)	Pooled results were not reported. Summary: "9 of 16 studies found a lower failure rate with NIV than with standard therapy, and only 3 of the trials reported lower hospital mortality… NIV appears to offer the greatest absolute reduction in failure rate, intubation rate, and hospital mortality in patients with more severe COPD exacerbations. There is also benefit for patients with milder COPD exacerbations, although the evidence is not as strong and is of a lesser degree (lower absolute risk difference). … We recommend that NIV be considered first-line therapy for patients who present with respiratory distress and respiratory acidosis." #
Kennan et al, 2003 (20)	Mortality: risk reduction, 10% (95% CI, 5%–15%)** Intubation: risk reduction, 28% (95% CI, 15%–40%)**†† Hospital LOS: absolute reduction, 4.75 days (95% CI, 2.30–6.83 days)**††
Peter et al, 2002 (22)	Mortality (COPD subgroup): risk difference, −0.13 (95% CI, −0.21 to −0.06) Intubation (COPD subgroup): risk difference, −0.18 (95% CI, −0.33 to −0.03) Hospital LOS (COPD subgroup): −5.66 (95% CI, −10.10 to −1.23) Complications (all studies): risk difference, −15% (95% CI, −31.6% to1%), *P* = 0.07 Dropout due to mask intolerance: 14% (6 studies, all studies)
Quon et al, 2008 (18)	Intubation: RR, 0.35 (95% CI, 0.26–0.47)‡‡ Inhospital Mortality: RR, 0.45 (95% CI, 0.30–0.66) LOS: WMD, −1.94 (95% CI, −3.87 to −0.01)§§

Author, Year	Findings
Ram et al, 2004 (4)	Treatment failure: RR, 0.48 (95% CI, 0.37–0.63), $P < 0.001$‖‖ Mortality: RR, 0.52 (95% CI, 0.35–0.76), $P < 0.001$¶¶; NNT, 10 (95% CI: 7–20) Intubation: RR, 0.42 (95% CI, 0.33–0.53), $P < 0.001$; NNT, 4 (95% CI: 4–5) Hospital LOS: WMD, -3.24 (95% CI, −4.42 to −2.06), $P < 0.001$*** ICU LOS: −4.71 (95% CI, −9.59 to 0.16), $P = 0.06$*** *Symptom scores* Borg score: WMD, −0.31 (95% CI, −1.42 to 0.80), $P = 0.59$ Visual analogue scale: WMD, −2.11 (95% CI, −3.32 to −0.90), $P < 0.001$ Complications of treatment: RR, 0.38 (95% CI, 0.24–0.60), $P < 0.001$

*Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; LOS, length of stay; NNT, number needed to treat; NPPV, noninvasive positive pressure ventilation; NIV, noninvasive ventilation; RR, risk ratio; WMD, weighted mean difference.

†Caples et al (21) did not conduct a meta-analysis of the data, but instead presented a descriptive summary of the results of some key studies in the area. While studies on the topic were identified, results were only presented in terms of improved, declined, or stayed the same.

‡Hess et al (19) did not conduct a new meta-analysis of the data, but instead presented the pooled results for treatment failure, mortality, intubation, and complications from Lightowler et al (62) and provided a brief commentary on the overall evidence on this topic.

§For the subgroup of patients with milder exacerbations, the risk ratio was not significant (RR, 0.71; 95% CI, 0.16–3.08), but the reduction in endotracheal intubation in the subgroup of patients with community-acquired pneumonia was significant ($P = 0.005$). (17)

‖For the subgroup of patients with milder exacerbations, the risk ratio was not significant (RR, 1.05; 95% CI, 0.07–6.36) (17)

¶Very little data were provided in the published report, so the guideline recommendation has been summarized as well. (17)

#Only a descriptive narrative of the results were provided in the published report. (2)

**Greater reduction in subgroup of patients with severe COPD exacerbations (pH < 7.30 or hospital mortality rate > 10% in control group): inhospital mortality rate: risk reduction, 12% (95% CI, 6%–18%); rate of intubation: risk reduction, 34% (95% CI, 22%–46%); hospital LOS: absolute reduction, 5.59 days (95% CI, 3.66–7.52). Trials with mild COPD exacerbations did not find a benefit in hospital survival (risk reduction, 2%; 95% CI, −8% to 12%), intubation (risk reduction, 0%; 95% CI, −11% to 11%) or hospital LOS (absolute reduction, 0.82 days; 95% CI, −0.12 to 1.77). (20)

††Results were heterogeneous across studies ($P < 0.001$).

‡‡The benefits were modified by the average pH; the beneficial effects increased as the baseline pH decreased ($P = 0.047$). (18)

§§There was significant heterogeneity in these results. (18)

‖‖When the results are subgrouped by location, the benefit is larger for patients being treated in the ICU (RR, 0.29; 95% CI, 0.18–0.47) than patients being treated in wards (RR, 0.61; 0.44–0.86). (4)

¶¶When the results are subgrouped by location, the risk ratio is not significant (RR, 0.61; 95 %CI, 0.32–1.18) for patients being treated in the ICU but remains significant for patients being treated in wards (RR, 0.43; 95% CI, 0.26–0.71). (4)

##When the results are subgrouped by admission pH, the pooled risk ratio is not significant (RR, −0.89; 95% CI, −2.92 to 1.14) for the group with an admission pH between 7.35 and 7.30, but remains significant for the group with an admission pH below 7.30 (RR, −4.43; −5.88 to −2.98). (4)

***When the results are subgrouped by admission pH, the pooled risk ratio is not significant (WMD, −4.71; 95% CI, −9.59 to 0.16) for the group with an admission pH below 7.30. (4)

NPPV for Weaning COPD Patients From Invasive Mechanical Ventilation: Systematic Reviews

Although 5 systematic reviews were identified on this topic, only 4 of the reviews are summarized in the following tables. One systematic review is excluded from the tables because although its topic is NPPV for weaning, no results or conclusions on this topic were reported.

Table A4: Comparison of Systematic Reviews Published Since 2000 (NPPV for Weaning)*

Component RCTs: Author, Year	Author, Year of Literature Search Inclusion of Identified Systematic Reviews				MAS Review	
	Keenan et al, 2009 (17)	Burns et al, 2008 (14)	Hess et al, 2003 (19)	Burns et al, 2003 (13)	Study Included	Reasons for Exclusion
Chen et al, 2001 (63)	✓	✓		✓	X	Not English
Ferrer et al, 2003 (64)	✓	✓	✓	✓	X	Mixed population
Girault et al, 1999 (65)	✓	✓	✓	✓	X	Mixed population
Hill et al, 2000 (66)		✓		✓	X	Abstract
Nava et al, 1998 (37)	✓	✓	✓	✓	✓	
Prasad et al, 2008		✓			X	Unpublished thesis
Prasad et al, 2009 (38)					✓	
Rabie et al, 2004 (67)		✓			X	Abstract
Trevisan et al, 2008 (10)	✓	✓			X	Mixed population
Wang et al, 2004 (68)	✓	✓			X	Not English
Collaborating Research Group†, 2005 (6)	✓	✓			X	Not relevant to Ontario practice‡
Zheng et al, 2005 (69)	✓	✓			X	Not English
Zou et al, 2005 (70)	✓	✓			X	Not English

*Abbreviations: MAS, Medical Advisory Secretariat; NPPV, noninvasive positive pressure ventilation; RCTs, randomized controlled trials.

†Collaborating Research Group for Noninvasive Mechanical Ventilation of Chinese Respiratory Society

‡Expert opinion

Table A5: Summary of the Systematic Reviews' Methods (NPPV for Weaning)*

Author, Year	Date Literature Current to	Databases Searched	Population Included	Included Study Designs	Total N (No. Studies)	Statistical Methods	Outcomes
Burns et al, 2010 (14)	April 2008	Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, and conference proceedings from the American Journal of Respiratory and Critical Care Medicine, Intensive Care Medicine, Critical Care Medicine, and Chest	Ventilated adults with ARF of any etiology weaned using either a strategy of early extubation followed by immediate NPPV or continued IPPV weaning. Excluded: RCTs not weaning, immediate postoperative setting or following unplanned extubation, and the application of NPPV with supplemental O_2 compared with unassisted O_2 following elective or unplanned extubation	RCTs, quasi-randomized trials (abstracts included)	530 (12†)	• Relative risks and weighted mean differences were calculated • Pooled analyses were conducted using random effects models • Subgroup analyses compared results for COPD patients and mixed patient populations	All-cause mortality, weaning failure, VAP, ICU LOS, hospital LOS, total duration of MV, duration of mechanical support related to weaning, duration of ETMV, adverse events, QOL
Burns et al, 2006 (13)	July 2003	MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, abstracts published in conference proceedings of the American Journal of Respiratory and Critical Care Medicine, Intensive Care Medicine, Critical Care Medicine, and Chest	Adults invasively ventilated for at least 24 hr with ARF. Included study populations were predominately people with COPD. Excluded: NPPV and IPPV in immediate postoperative setting and application of NPPV and supplement O_2 to unassisted O_2 following elective or unplanned extubation	RCTs, quasi-randomized trials (abstracts included)	171 (5‡)	• Relative risks and weighted mean differences were calculated • Pooled analyses were conducted using random effects models • Subgroup analyses compared results for COPD patients and mixed patient populations	Mortality, incidence of VAP, weaning failure, ICU LOS, hospital LOS, total duration of MV, duration of MV related to weaning, duration of ETMV
Hess et al, 2004 (19)	2003‡	PubMed	Adult patients with ARF. Excluded: long-term NPPV for stable patients with pulmonary or neuromuscular disease	RCTs§	NR (2)	• Relative risks were calculated • Pooled analyses were conducted using random effects models • Results for NPPV for COPD patients are based on results from other meta-analyses. The authors did not conduct their own analysis on this topic.	Not specified in methods. Outcomes included in the COPD section on weaning success, duration of mechanical ventilation, survival, ICU LOS, hospital LOS

Author, Year	Date Literature Current to	Databases Searched	Population Included	Included Study Designs	Total N (No. Studies)	Statistical Methods	Outcomes
Keenan et al, 2011 (17)	June 2009	MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effectiveness, Cochrane Database of Systematic Reviews, ACP Journal Club Database, MetaRegister of Controlled Trials, clinicaltrials.gov website, and Journals@OVID database	Hospitalized adult patients who had or who were at risk for ARF including both acute and acute-on-chronic respiratory failure. Included studies with predominately COPD patients. Excluded: studies of chronic respiratory failure in an outpatient setting.	Parallel-design RCTs (abstracts excluded)	NR (9‖)	• Relative risks and weighted mean differences were calculated • Pooled analyses were conducted using random effects models	Physiologic outcomes including arterial blood gases and vital signs; clinical outcomes including endotracheal intubation and hospital mortality In the section on weaning, the following outcome was reported: hospital mortality

*Abbreviations: ARF, acute respiratory failure; COPD, chronic obstructive pulmonary disease; ETMV, endotracheal mechanical ventilation; Hr, hour; ICU, intensive care unit; IPPV, invasive positive pressure ventilation; LOS, length of stay; MV, mechanical ventilation; N, sample size; no. number; NPPV, noninvasive positive pressure ventilation; NR, not reported; O_2, oxygen; QOL, quality of life; RCTs, randomized controlled trials; VAP, ventilator-associated pneumonia.

†Includes 1 quasi-randomized trial (patients randomized based on order), 2 abstracts, and 1 unpublished doctoral dissertation

‡4 RCTs and 1 quasi-randomized trial

§Unclear from published results whether abstracts were included in the analysis.

‖Studies included in the section on weaning

Table A6: Summary of the Systematic Reviews' Results (NPPV for Weaning)*

Author, Year	Findings
Burns et al, 2010 (14)	Mortality: RR, 0.42 (95% CI, 0.25–0.69), *P* < 0.001† Weaning failure: RR, 0.50 (95% CI, 0.22–1.12), *P* = 0.09† Nosocomial pneumonia: RR, 0.29 (95% CI, 0.19–0.45), *P* < 0.001 ICU LOS: WMD, −6.27 (−8.77 to −3.78), *P* ≤ 0.001 Hospital LOS: WMD, −7.19 (95% CI, −10.80 to −3.58), *P* < 0.001 Average total duration of MV support: WMD, −5.64 (95% CI, −9.50 to −1.77), *P* = 0.004 Average duration of MV related to weaning: WMD, −0.94 (95% CI, −3.24 to 1.36), *P* = 0.42 Duration of ETMV: WMD, −7.81 (95% CI, −11.31 to −4.31), *P* < 0.001 <u>Adverse events</u> Reintubation: RR, 0.73 (95% CI, 0.40–1.34), *P* = 0.31 Tracheostomy: RR, 0.16 (95% CI, 0.04–0.75), *P* = 0.02 Arrhythmia: RR, 1.05 (95% CI, 0.17–6.67), *P* = 0.96
Burns et al, 2006 (13)	Mortality: RR, 0.25 (95% CI, 0.07–0.91), *P* = 0.04† Incidence of VAP: RR, 0.28 (95% CI, 0.09–0.85), *P* = 0.03 Weaning failure: RR, 0.38 (95% CI, 0.11–1.25), *P* = 0.11† ICU LOS: WMD, −6.88 (95% CI, −12.60 to −1.15), *P* = 0.02 Hospital LOS: WMD, −7.33 (95% CI, −14.05 to −0.61), *P* = 0.03 Total duration of MV: WMD, −7.33 (95% CI, −11.45 to −3.22), *P* < 0.001 Duration of MV related to weaning: WMD, −2.72 (95% CI, −15.58 to 10.14), *P* = 0.68 Duration of ETMV: WMD, −6.32 (−12.12 to −0.52), *P* = 0.03
Hess et al, 2004 (19)	Hess et al (19) did not report pooled analyses or a specific summary of the results of the 2 included trials on weaning.
Keenan et al, 2011 (17)	Recommendation: "We suggest that NPPV be used to facilitate early liberation from mechanical ventilation in patients who have COPD but only in centers that have expertise in NPPV (GRADE 2B)." (17)‡

*Abbreviations: CI, confidence intervals; COPD, chronic obstructive pulmonary disease; ETMV, endotracheal mechanical ventilation; ICU, intensive care unit; LOS, length of stay; MV, mechanical ventilation; N, sample size; no. number; NPPV, noninvasive positive pressure ventilation; RCT, randomized controlled trials; RR, relative risk; VAP, ventilator-associated pneumonia; WMD, weighted mean difference.

†Results are for the subgroup of patients with COPD only and exclude the results from the trials with mixed populations.

‡Only the results for the 3 trials including mixed population on hospital mortality were presented in the published report. Since inadequate data were presented, the guideline recommendation has been summarized instead.

NPPV for Acute Respiratory Failure After Extubation From Invasive Mechanical Ventilation: Systematic Reviews

Table A7: Comparison of Systematic Reviews Published Since 2000 (NPPV Postextubation from IMV)*

Component RCTs: Author, Year	Author, Year of Literature Search Inclusion of Identified Systematic Reviews			MAS Review	
	Keenan et al, 2009 (17)	Caples et al, 2006 (21)	Hess et al, 2003 (19)	Study Included	Reasons for Exclusion
Esteban et al, 2004 (41)†	✓	✓		✓‡	
Esteban et al, 2003 (71)†			✓	X	Abstract
Ferrer et al, 2006 (39)§	✓			X	Mixed population
Ferrer et al, 2009 (40)§‡	✓			X	Mixed population
Jiang et al, 1999 (11)§‡	✓	✓	✓	X	Mixed population
Keenan et al, 2002 (72)‡	✓	✓	✓	X	Mixed population
Luo et al, 2001 (73)§	✓			X	Not English
Nava et al, 2005 (74)§	✓			X	Mixed population

*Abbreviations: ARF, acute respiratory failure; IMV, invasive mechanical ventilation; MAS, Medical Advisory Secretariat; NPPV, noninvasive positive pressure ventilation; RCTs, randomized controlled trials.
†Studies examined the use of NPPV to treat respiratory failure that developed in patients after they were extubated from invasive mechanical ventilation.
‡One outcome (need for reintubation) was presented for the COPD group alone (post hoc analysis). (41)
§Studies examined the early application of NPPV after extubation to prevent the development of ARF after extubation from IMV.
Note: As these systematic reviews were also identified in other sections of this evidence-based analysis, for details on the methods of these reviews, refer to the tables above.

Appendix 3: Detailed Study Descriptions

NPPV for the Treatment of ARF due to Acute Exacerbations of COPD: NPPV Plus UMC Versus UMC Alone

Table A8: General Study Characteristics (NPPV Plus UMC Versus UMC Alone)*

Author, Year	Country, Number of Sites	Sample Size	Location†	Inclusion Criteria	Exclusion Criteria	Length of Follow-Up	Outcomes
NPPV + UMC vs. UMC Alone							
Barbe et al, 1996 (25)	Spain, 1	24‡	Respiratory ward	Patients with ARF with severe COPD	NR	Duration of hospital stay	Pulmonary function, breathlessness, hospital mortality, intubation, NPPV tolerance, hospital LOS, respiratory muscle function, arterial blood gases
Bott et al, 1993 (26)	England, 3	60	Ward	Patients admitted for an acute exacerbation of chronic obstructive airway disease, aged ≤ 80 years, arterial PaO_2 < 7.5 kPa, arterial $PaCO_2$ > 6 kPa	Severe disease not attributable to COPD, severe psychiatric disease, used NPPV at home	At least 30 days	Hospital LOS, arterial blood gases, breathlessness, quality of sleep, general well-being, nursing care, survival
Brochard et al, 1995 (27)	France, Italy, Spain, 5	85	ICU	Adult patients hospitalized for acute exacerbations of COPD with known disease or a high probability of disease (based on clinical history, physical exam, and chest film) with respiratory acidosis and an elevated bicarbonate level. Patients must have an exacerbation of dyspnea lasting less than 2 weeks and at least 2 of the following: respiratory rate > 30 breaths/minute, a PaO_2 < 45 mm Hg, and an arterial pH below 7.35 after patient had been breathing room air for at least 10 minutes.	Respiratory rate < 12 breaths/ minute, need for immediate intubation, a tracheotomy or endotracheal intubation performed before admission, administration of sedative drugs within previous 12 hours, CNS disorder related to hypercapnic encephalopathy or hypoxemia, cardiac arrest (within previous 5 days), cardiogenic pulmonary edema, kyphoscoliosis, upper airway obstruction or asthma, clear cause of decompensation requiring specific treatment, facial deformity, or enrolment in other investigative protocols, patients refusing intubation	Until discharge from hospital, 3 months for some outcomes	Need for endotracheal intubation, hospital LOS, complications, duration of ventilatory assistance, hospital mortality rate, pulmonary function, arterial blood gases, respiratory rate, encephalopathy score

Author, Year	Country, Number of Sites	Sample Size	Location†	Inclusion Criteria	Exclusion Criteria	Length of Follow-Up	Outcomes
Dhamija et al, 2005 (29)	Turkey, 1	29	Respiratory ward	Patients with COPD exacerbation complicated by mild to moderate respiratory failure (acute or chronic) not requiring invasive mechanical ventilatory support and stable enough to be admitted to the general respiratory ward. Patients with pulmonary function tests suggesting COPD, chest radiograph showing no evidence of acute infection or any other pulmonary disease, and presence of any of the following: pH more than 7.25, arterial $PaCO_2$ > 45 mmHg on room air	Respiratory rate > 35 breaths/minute, pH < 7.25, $PaCO_2$ > 70 mmHg, need for urgent intubation, medically unstable, unable to protect airways, excessive secretions, pulmonary tuberculosis (past or present), history of recent MI or abdominal surgery, any other respiratory disorder	Duration of hospital stay	Arterial blood gases, need for intubation, heart rate, breathlessness, hospital LOS, respiratory rate
Dikensoy et al, 2002 (5)	Turkey, 1	34‡	General ward	Patients with an acute exacerbation of COPD, arterial pH < 7.35, and arterial $PaCO_2$ > 45 mmHg	Urgent need for intubation, haemodynamic instability (systolic blood pressure < 90 mmHg, heart rate > 140 beats/minute), excessive secretions, lack of patient compliance with the study protocol or refusal to participate in the study	Duration of hospital stay	Respiratory rate, arterial blood gases, heart rate, blood pressure, need for intubation due to treatment failure, mortality, hospital LOS, compliance, complications
Keenan et al, 2005 (30)	Canada, 1	52	Respiratory ward	Patients with COPD (documented in prior admission to hospital or received diagnosis from GP and being treated with medication), presented with recent onset of shortness of breath, pH > 7.30	Respiratory arrest, decreased level of consciousness, hemodynamic instability, excess secretions, inability to communicate with patient, use of CPAP at home, associated pneumonia demonstrated on chest radiograph, patient judged to be in respiratory extremis by the admitting physician	Duration of hospital stay	Breathlessness, need for intubation, duration of further mechanical ventilation (if necessary), inhospital LOS, ICU LOS, hospital mortality, pulmonary function, arterial blood gases

Author, Year	Country, Number of Sites	Sample Size	Location†	Inclusion Criteria	Exclusion Criteria	Length of Follow-Up	Outcomes
Khilnani et al, 2010 (31)	India, 1	40	ICU	Patients with an acute exacerbation of COPD (diagnosis based on findings from history and clinical examination with typical radiograph abnormalities) leading to hypoxemia and respiratory acidosis with pH < 7.35 and $PaCO_2$ > 45 mmHg admitted to the ICU	Respiratory arrest, hemodynamic instability, altered sensorium, copious secretions, uncooperative patients	Duration of hospital stay	Need for intubation (primary outcome), hospital mortality, hospital LOS, clinical and blood gas parameters, complications
Kramer et al, 1995 (9)	United States, 2	23§	ICU or step down unit	Patients with ARF upon admission or during hospitalization who are otherwise stable. Selection criteria: respiratory distress evidenced by moderate to severe dyspnea, accessory muscle use, or abdominal paradox and ARF as evidenced by pH < 7.35, $PaCO_2$ > 45 mmHg, and respiratory rate > 24 breaths/minute	Respiratory arrest or need for immediate intubation, hypotension (systolic BP < 90 mmHg), uncontrolled arrhythmias, upper airway obstruction or facial trauma, inability to clear secretions, inability to cooperate or fit mask	Duration of hospital stay	Need for intubation (primary outcome), arterial blood gases, heart and respiratory rate, breathlessness, pulmonary function, nursing and respiratory therapy time, difficulty of caring for patients, hospital LOS, morality, charges for total hospital stay and respiratory services, and complications
Plant et al, 2000/2001 (32;34)‖	United Kingdom, 14¶	236	General medical and respiratory wards	Adult patients admitted with an acute exacerbation of COPD (on basis of clinical history, physical examination and chest radiograph), who were tachypnoeic with a respiratory rate > 23 breaths/minute and pH 7.25 – 7.35 and $PaCO_2$ > 6 kPa on arrival to general respiratory ward (after initial treatment in ED and within a maximum of 12 hours of admission)	Glasgow coma score < 8, pneumothorax, active treatment deemed inappropriate	Until hospital discharge and long-term survival (up to 26 months maximum)	Need for intubation (primary outcome), respiratory rate, arterial blood gases, mobility, nutritional status, mask comfort and tolerance, breathlessness, nursing workload In a second publication (34), long-term survival and factors associated with failure of treatment were reported
Wang et al, 2005 (33)	China, 19	342	General ward	Patients with definite or probable COPD (based on clinical history, examination, chest radiography, spirometry, and arterial blood gas findings), acute exacerbation of COPD (characterized by an exacerbation of dyspnea, cough	Refused to receive NPPV, pH < 7.25, Glasgow Coma Score < 8, airway or facial deformity, pneumothorax or pneumomediastinum, unable to spontaneously clear secretions from their airway, systolic BP < 80 mmHg, uncontrolled cardiac	Duration of hospital stay	Need for intubation (primary outcome), hospital mortality, hospital LOS, respiratory rate, heart rate, blood pressure, arterial blood gases, breathlessness, accessory muscle use, adverse effects of NPPV

Author, Year	Country, Number of Sites	Sample Size	Location†	Inclusion Criteria	Exclusion Criteria	Length of Follow-Up	Outcomes
				and increase of sputum production and changes in chest radiograph), age < 85 years, pH > 7.25, $PaCO_2$ > 45 mmHg on arrival to the general ward	arrhythmias, unable to cooperate with the application of NPPV, severe organ dysfunction, severe abdominal distension, or NPPV duration < 3 days		
NPPV + UMC vs. Sham + UMC							
Carrera et al, 2009 (28)	Spain, 7	75‡	Respiratory ward	Patients with an acute exacerbation of COPD (increase in dyspnea, cough and/or sputum production of recent onset – last 2 weeks – in absence of another diagnosis) requiring hospitalization, arterial pH between 7.25 and 7.35, $PaCO_2$ > 50 mmHg 30–60 minutes after intensive medical management had been started in the ED, recruitment into study within 24 hours of admission	Respiratory rate < 12 breaths/minute or need for immediate intubation for resuscitation, Glasgow coma score < 8, administration of sedatives within previous 12 hours, neuromuscular disorders, thoracoplasty, kyphoscoliosis, known cause of decompensation requiring specific treatment, history of sleep apnea, asthma, or severe systemic disease, BMI > 40 kg/m^2, facial deformities, history of acute episodes requiring NPPV in the past or chronic NPPV treatment, history of alcohol or drug abuse, and/or refusal to participate	Until discharge from hospital	Need for intubation (primary outcome), arterial blood gases, hospital LOS

*Abbreviations: ARF, acute respiratory failure; BMI, body mass index; BP, blood pressure; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; ED, emergency department; GP, general practitioner; ICU, intensive care unit; kg/m^2, kilogram per square meter; kPa, kilopascals; LOS, length of stay; MI, myocardial infarction; mmHg, millimeters of mercury; NPPV, noninvasive positive pressure ventilation; NR, not reported; $PaCO_2$, partial pressure of carbon dioxide in the arterial blood; PaO_2, partial pressure of oxygen in the arterial blood; UMC, usual medical care.

†ICU, general or respiratory hospital ward, or emergency department

†Consecutive patients

§31 patients were enrolled in the study, but only 23 patients had respiratory failure due to acute exacerbations of COPD. Since this is the patient population of interest in this analysis, only the results for this patient population are presented when possible. (31)

‖Two papers by Plant et al (32;34) were identified. Both report on the same study and patient population; however, the second publication provides results on some additional outcomes not reported in the first paper.

¶14 hospitals participated from which 22 wards were used as sites for NPPV. (32)

Table A9: General Study Characteristics – Intervention and Control Group Details (NPPV Plus UMC Versus UMC Alone)*

Author, Year	Ventilation Mode	Interface	Pressures	Ventilator Schedule	Usual Medical Care	A Priori Intubation Criteria	Severity of Respiratory Failure Categorization†
NPPV + UMC vs. UMC Alone							
Barbe et al, 1996 (25)	BiPAP	Nasal mask	*Expiratory pressure:* set at 5 cm H_2O *Inspiratory pressure:* set to maximum tolerated value in each patient (mean ± SEM, 14.8 ± 0.5 cm H_2O) Ventilatory regimen was not modified during the 3 days of support.	6 hours per day (3 hours in the morning, 3 in the afternoon) during first 3 days in hospital	Aerosolized salbutamol, intravenous prednisolone, and controlled oxygen therapy	No	Moderate
Bott et al, 1993 (26)	Volume cycled	Nasal mask	NR	Encouraged to use NPPV for up to 16 hours per day including all night, with ventilation discontinued for eating, drinking, and moving around. As patients improved, NPPV duration was reduced first during the day and then at night.	Oxygen, inhaled bronchodilators, and all or a combination of antibiotics, diuretics, respiratory stimulants, intravenous or oral corticosteroids, and bronchodilators. Patients who required it were treated by a physiotherapist.	No	Moderate
Brochard et al, 1995 (27)	Pressure support ventilation	Face mask	*Expiratory pressure:* atmospheric *Inspiratory pressure:* 20 cm H_2O and lower levels used in the case of leaks	Ventilation for at least 6 hours each day; time could be lengthened based on clinical tolerance. Overall duration determined on basis of clinical criteria and arterial blood gas levels. 2 hours each day, patients allowed to breathe spontaneously with oxygen but without assistance	Oxygen, subcutaneous heparin, antibiotic agents, bronchodilators (subcutaneous terbutaline, aerosolized and intravenous albuterol, corticosteroids or intravenous aminophylline or both) with correction of electrolyte abnormalities	Yes	Severe
Dhamija et al, 2005 (29)	BiPaP	Face or nasal mask	NR	6 hours per day in 2 sittings of 3 hours each for 3 days (patients were admitted for a minimum of 3 days)	Controlled oxygen, nebulised salbutamol, nebulised ipratropium bromide, oral prednisolone, antibiotics, aminophylline, and diuretics	Yes	Mild

Author, Year	Ventilation Mode	Interface	Pressures	Ventilator Schedule	Usual Medical Care	A Priori Intubation Criteria	Severity of Respiratory Failure Categorization†
Dikensoy et al, 2002 (5)	BiPAP	Full face mask	*Inspiratory pressure:* 9 cm H_2O increasing to highest tolerable level by 1 cm H_2O increments (mean, 15.3 ± 4.3 cm H_2O) *Expiratory pressure:* 3 cm H_2O	Continued until respiratory rate < 25 breaths/minute, pH > 7.35, and sPO_2 > 88% (during oxygen inhalation)	Oxygen therapy, salbutamol, nebulised ipratropium bromide, prednisolone, aminophylline infusion, enoxaparin sodium, and antibiotics	No	Severe
Keenan et al, 2005 (30)	BiPAP	Full face mask or nasal mask‡	*Expiratory pressure:* 4 cm H_2O (mean, 4.7 ± 0.6 cm H_2O) *Inspiratory pressure:* 9 cm H_2O (mean, 9.8 ± 0.6 cm H_2O) Spontaneous mode was used and pressures were titrated as necessary for patient comfort	Initiated within 24 hours of arrival at ED; 8 hours on first day, 6 hours on second day, and 4 hours on third day and then stopped	Supplemental oxygen, pharmacotherapy with inhaled beta-agonists and inhaled ipratropium bromide as clinically indicated, systemic steroids, and antibiotics for infectious exacerbations not due to pneumonia	Yes	Mild
Khilnani et al, 2010 (31)	BiPAP	Nasal mask	*Expiratory pressure:* 4 cm H_2O *Inspiratory pressure:* 8 cm H_2O Adjustments were made according to need of patient and results of blood gas analysis (each inspiration triggered by patient's spontaneous breath)	Encouraged to use NPPV up to 16 hours per day including day and night, discontinued for eating and drinking	Oxygen, bronchodilators, (inhaled salbutamol, ipratropium bromide, subcutaneous terbutaline, and steroids [IV hydrocortisone]), intravenous antibiotics	Yes	Very severe
Kramer et al, 1995 (9)	BiPAP	Nasal mask or oronasal face mask§	*Expiratory pressure:* lowest possible setting (about 2 cm H_2O) *Inspiratory pressure:* 8 cm H_2O increased by 1 cm H_2O every 15 to 30 minutes or as tolerated during initial trial	Encouraged to use NPPV for as long as tolerated aiming for at least 8 hours per day. Mask could be removed for meals, conversation, comfort, and respiratory treatments as needed	Supplemental oxygen, corticosteroids, frequent respiratory treatments, antibiotics	Yes	Severe

Author, Year	Ventilation Mode	Interface	Pressures	Ventilator Schedule	Usual Medical Care	A Priori Intubation Criteria	Severity of Respiratory Failure Categorization†
Plant et al, 2000/2001 (32;34)	BiPAP	Face or nasal mask	*Expiratory pressure :* 4 cm H_2O *Inspiratory pressure :* initially set at 10 cm H_2O and increased in increments of 5 cm H_2O to 20 cm H_2O, or the maximum tolerated over 1 hour	Encouraged to use NPPV as much as possible on day 1, 16 hours on day 2, 12 hours on day 3. NPPV was routinely discontinued on day 4 but was continued if clinically indicated.	Oxygen, nebulised salbutamol or terbutaline, nebulised ipratropium bromide, corticosteroids (prednisolone), and an antibiotic. Aminophylline and doxapram could also be used.	Yes	Moderate
Wang et al, 2005 (33)	BiPAP	Oronasal mask	*Expiratory pressure:* 2–4 cm H_2O and increased to 4–6 cm H_2O gradually (mean, 4.3 ± 1.2 cm H_2O) *Inspiratory pressure:* 6–8 cm H_2O which was adjusted in increments of 2 cm H_2O to obtain satisfactory spontaneous breathing pattern in every 5 to 6 minutes or to the maximum tolerated value (mean, 12.9 ± 3.7 cm H_2O)	At least 12 hours for the first 3 days, and 8 hours for days 4 and 5. At least 5 days of continuous ventilatory support should be given for all patients and 7 to 10 days was recommended	Oxygen, steroids, beta-agonists, theophylline, mucolytics, respiratory stimulants, and antibiotics	Yes	Mild
NPPV + UMC vs. Sham + UMC							
Carrera et al, 2009 (28)	BiPAP	Facial masks	*Expiratory pressure:* set at 4 cm H_2O *Inspiratory pressure:* adjusted individually to maximum tolerated in assisted/controlled mode	During the first 3 days of hospitalization for as much time as possible between 3:00 pm and 8:00 am (started in respiratory ward). Routinely discounted on 4th day of hospitalization	Supplementary oxygen, bronchodilators, steroids, and antibiotics when indicated	Yes	Severe

*Abbreviations: BiPAP, bilevel positive airway pressure; cm, centimeters; COPD, chronic obstructive pulmonary disease; ED, emergency department; H_2O, water; NPPV, noninvasive positive pressure ventilation; NR, not reported; SEM, standard error of the mean; sPO_2, saturation of peripheral oxygen, UMC, usual medical care.

†As outlined in the methods section, severity of respiratory failure was defined based on the mean pH of the study population into the following categories: mild (pH ≥ 7.35), moderate (7.30 ≤ pH < 7.35), severe (7.25 ≤ pH < 7.30), and very severe (pH < 7.25) respiratory failure.

‡Patients who could not tolerate the full face mask could be switched to the nasal mask. (30)

§Patients who could not tolerate the nasal mask or there was excessive air leakage through the mouth were switched to oronasal face masks. (9)

Table A10: Characteristics of the Patients in the Included Studies (NPPV Plus UMC Versus UMC Alone)*

Author, Year	N		FEV_1 % Predicted		Age, Mean (SD), (Years)		Percent Male		pH, Mean (SD)		$PaCO_2$, Mean (SD), mmHg		PaO_2, Mean (SD), mmHg	
	NPPV	UMC	NPPV	UMC	NPPV	UMC	NPPV	UMC	NPPV	UMC	NPPV	UMC	NPPV	UMC
NPPV + UMC vs. UMC Alone														
Barbe et al, 1996 (25)	14†	10	36 (4)	30 (3)	70 (2)	65 (3)	100	100	7.33 (0.01)		7.9 (0.3)‡		6.0 (0.2)‡	
Bott et al, 1993 (26)	30	30	NR	NR	NR	NR	NR	NR	7.34 (0.07)‡	7.33 (0.07)‡	8.6 (1.4)‡§	8.6 (1.67)‡§	5.28 (1.0)‡§	5.2 (1.07)‡§
Brochard et al, 1995 (27)	43	42	NR	NR	71 (9)	69 (10)	NR	NR	7.27 (0.10)	7.28 (0.11)	70 (12)	67 (16)	41 (10)	39 (12)
Dhamija et al, 2005 (29)	14	15	NR	NR	NR	NR	NR	NR	7.37 (0.06)	7.38 (0.06)	62.6 (5.2)	58.2 (5.6)	43.3 (6.4)	50.6 (9.8)
Dikensoy et al, 2002 (5)	17	17	37.9 (14.3)	42.2 (11.7)	65 (6)	64 (8)	47	71	7.28 (0.8)‖	7.29 (0.5)‖	78.4 (9.7)	64.3 (8.4)	56 (13)	50.7 (14)
Keenan et al, 2005 (30)	25	27	36 (12)	31 (15)	69 (9)	71 (8)	40	52	7.40 (0.04)	7.40 (0.05)	50 (15)	51 (17)	NR	NR
Khilnani et al, 2010 (31)	20	20	NR	NR	55 (10)	60 (11)	75	80	7.23 (0.07)	7.23 (0.07)	85.4 (14.9)	81.1 (11.7)	61.2 (14.7)	61.5 (15.1)
Kramer et al, 1995 (9) §	11	12	NR	NR	67 (2)¶	70 (2)¶	56	60	7.27 (0.02)¶#	7.29 (0.02)¶#	80.9 (5.9)¶#	80.6 (9.3)¶#	61.0 (4.4)¶#	56.8 (5.6)¶#
Plant et al, 2000 (32)	118	118	NR	NR	69 (7)	69 (8)	46	53	7.32 (range, 7.25–7.35)**	7.31 (range, 7.26–7.35)**	8.820 (1.15)‡	8.65 (1.70)‡	6.88 (range, 4.50–13.8)‡**	7.00 (range, 4.71–12.31)‡**
Wang et al, 2005 (33)	171	171	FEV_1: 0.6 (0.5) L	FEV_1: 0.6 (0.4) L	69 (10)	70 (8)	66	58	7.34 (0.06)	7.35 (0.06)	66 (13)	65 (12)	PaO_2/FiO_2: 254 (68)	PaO_2/FiO_2: 255 (75)

Author, Year	N		FEV_1 % Predicted		Age, Mean (SD), (Years)		Percent Male		pH, Mean (SD)		$PaCO_2$, Mean (SD), mmHg		PaO_2, Mean (SD), mmHg	
	NPPV	UMC	NPPV	UMC	NPPV	UMC	NPPV	UMC	NPPV	UMC	NPPV	UMC	NPPV	UMC
NPPV + UMC vs. Sham NPPV + UMC														
Carrera et al, 2009 (28)	37	38	39 (11)††	37 (11)††	72 (10)	69 (7)	NR	NR	7.31 (0.02)	7.31 (0.05)	69 (14)	69 (13)	43 (9)‡‡	48 (9)‡‡

*Abbreviations: ARF, acute respiratory failure; FEV_1, forced expiratory volume in 1 second; FiO_2, fraction of inspired oxygen; mmHg, millimeters of mercury; N, sample size; NPPV, noninvasive positive pressure ventilation; NR, not reported; $PaCO_2$, partial pressure of carbon dioxide in the arterial blood; PaO_2,partial pressure of oxygen in the arterial blood; SD, standard deviation; UMC, usual medical care.

†The published results state that half of the patients were randomized to NPPV, which would be 12 patients; however, the abstract and discussion both state that 14 patients were randomized to NPPV. (25)

‡kPa

§Data were obtained from the Ram et al (4) systematic review as the results by NPPV versus UMC were presented stratified by centre in the published results; however, Ram et al (4) obtained data from the authors.

‖ $P < 0.05$ (5)

¶Mean ± standard error

#Patients with ARF due to various etiologies were enrolled in the study. Patient population characteristics are listed for only the COPD patient group where possible and are indicated by this symbol. (9)

**Ranges in parentheses are median data with 5th and 95th percentiles.

††FEV_1 at discharge

‡‡$P = 0.05$

NPPV for the Treatment of Acute Respiratory Failure due to Acute Exacerbations of COPD: NPPV Versus IMV

Table A11: General Study Characteristics (NPPV Versus IMV)*

Author, Year	Country, Number of Sites	Sample Size	Location	Inclusion Criteria	Exclusion Criteria	Length of Follow-Up	Outcomes
Conti et al, 2002 (36)	Italy, 1	49	ICU	Patients with ARF due to COPD who failed a course of medical treatment. Patients with ARF defined as respiratory acidosis with pH lower than 7.32, bicarbonate levels higher than 30 mEq/l, hypoxemia with PaO_2 < 45 mmHg while breathing room air, respiratory rate > 30 breaths/minute, history of worsening dyspnea < 2 weeks duration. Of these patients, those who required ventilatory support in ICU deteriorated despite medical treatment and met at least 1 of the following criteria: pH less than 7.20, arterial oxygen saturation > 90% with a fraction of inspired oxygen of 0.35 or higher, respiratory rate < 35 breaths/minute, or severe deterioration in mental status with Kelly score ≥ 4 were included	Presence of tracheostomy or endotracheal intubation performed before ICU admission, facial deformities, upper airway obstruction, recent surgery, trauma, CNS alterations unrelated to hypercapnic encephalopathy, presence of cardiogenic pulmonary edema, pneumothorax, pulmonary thromboembolism, hemoptysis, neoplasms, septic shock, need for urgent intubation	12 months	ICU LOS, arterial blood gases, duration on mechanical ventilation, complications, ICU mortality, inhospital mortality, 1-year survival, need for intubation, hospital readmissions, requirement for de novo oxygen supplementation
Jurjevic et al, 2009 (7)	Croatia, 1	156	ICU	Patients with COPD	Expected mechanical ventilation duration < 24 hours, use of mechanical ventilation on admission to ICU, patients in coma, patients in shock, patients who had cardio-respiratory arrest within 5 days, patients scheduled for organ donation, patients admitted to ICU because of ARF due to COPD within 3 months	Duration of ICU stay	Total duration ventilation, ICU LOS, success of mechanical ventilation, need for tracheotomy, incidence of VAP, ICU mortality, need for intubation in NPPV group

*Abbreviations: ARF, acute respiratory failure; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IMV, invasive mechanical ventilation; LOS, length of stay; mEq/l, milliequivalents per litre; mmHg, millimeters of mercury; NPPV, noninvasive positive pressure ventilation; VAP, ventilator-associated pneumonia.

Table A12: General Study Characteristics – Intervention and Control Group Details (NPPV Versus IMV)*

	Noninvasive Positive Pressure Ventilation				Invasive Mechanical Ventilation
Author, Year	**Ventilation Mode**	**Interface**	**Pressures**	**Ventilator Schedule**	**Pressure Settings and Weaning**
Conti et al, 2002 (36)	BiPAP	Full face mask	Initial level of pressure support (16 ± 2 cm H_2O) adjusted to obtain tidal volume 8–10 ml/kg and respiratory rate of 25 breaths/minute. CPAP pressure of 5 cm H_2O. Settings were adjusted on the basis of continuous oximetry and measurements of arterial blood gases. Weaning Pressure support was decreased progressively with degree of clinical improvement by 3 cm H_2O steps (twice a day) and discontinued when patient maintained respiratory rate < 30 breaths/minute with pH higher than 7.35 and SaO_2 higher than 90% with a FiO_2 of 0.28 in presence of normal mental and hemodynamic status.	During first 12 hours, NPPV was administered continuously and then interrupted for short periods of oxygen supplementation alone (FiO_2 28%) to allow drinking and expectorating.	Initial ventilator setting was assist-control with a delivered tidal volume of 8–10 ml/kg and a respiratory rate of 10–14 breaths/minute and FiO_2 of 0.35. PEEP was set at 5 cm H_2O and trigger at −1 cm H_2O. IV propofol at 2 mg/kg was given for sedation at time of intubation. When spontaneous breathing reappeared, ventilator settings were changed to pressure support ventilation (14–20 cm H_2O) titrated to achieve a spontaneous tidal volume of 8–10 ml/kg, respiratory rate < 25 breaths/minute, and disappearance of accessory muscle activity. After 24 hours, pressure support ventilation was progressively reduced by 3 cm H_2O steps (twice daily). Weaning Patients who tolerated a pressure support level of 8 cm H_2O underwent a 2-hour T-piece trial at FiO_2 0.28. If patients maintained a respiratory rate < 30 breaths/minute, SaO_2 > 90%, pH higher than 7.35, and normal mental and hemodynamic status, then they were extubated. If after 12 days, patients were still intubated, and receiving mechanical ventilation, a tracheostomy was performed. If patients were still ventilator-dependant after 60 days, physicians had the option of discharging patients on home-care ventilation.
Jurjevic et al, 2009 (7)	BiPAP	Nasal or face mask	Ventilator parameters were set to: CPAP to 0 cm H_2O, PSV 10 cm H_2O, and FiO_2 adjusted to reach $SatO_2$ > 90%. Then, set to CPAP 3-5 cm H_2O, PSV 10-25 cm H_2O to reach tidal volume > 5 ml/kg and respiratory rate < 30 breaths/minute. According to patient's development, ventilatory support level was reduced until ventilation could be discontinued.	NR	Patients received the lowest respiratory support level that secured SaO_2 > 90% with FiO_2 ≤ 0.6, $PaCO_2$ ≤ 45 mmHg, and stable hemodynamic patient condition. Weaning Weaning process was conducted using pressure support ventilation. Initial pressure support was 18 cm H_2O which was then reduced by 2–4 cm H_2O depending on clinical status, pulmonary mechanics, biochemistry, and circulation. Patients were extubated at pressure support of 5 cm H_2O.

*Abbreviations: BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; FiO_2,fraction of inspired oxygen; H_2O, water; IV, intravenous; kg, kilograms; ml, milliliters; mmHg, millimeters of mercury; NPPV, noninvasive positive pressure ventilation; NR, not reported; $PaCO_2$, partial pressure of carbon dioxide in the arterial blood; PEEP, positive end-expiratory pressure; PSV, pressure support ventilation; SaO_2,oxygen saturation of arterial blood

Table A13: Characteristics of the Patients in the Included Studies (NPPV Versus IMV)*

Author, Year	Sample Size		FEV_1 % Predicted		Age, Mean (SD), Years		Percent Male		pH, Mean (SD)		$PaCO_2$, Mean (SD), mmHg		PaO_2, Mean (SD), mmHg	
	NPPV	IMV	NPPV	IMV	NPPV	IMV	NPPV	IMV	NPPV	IMV	NPPV	IMV	NPPV	IMV
Conti et al, 2002 (36)	23	26	28 (5)	33 (10)	73 (8)	71 (8)	NR	NR	7.2 (0.05)	7.2 (0.05)	85 (16)	87 (14)	PaO_2:FiO_2 ratio: 168 (38)	PaO_2:FiO_2 ratio: 171 (38)
Jurjevic et al, 2009 (7)	78	78	NR	NR	Median, 58 (range, 35–82)	Median, 54 (range, 38–78)	68	64	7.21 (0.09)	7.22 (0.07)	84 (18)	83 (16)	66 (15)	66 (12)

*Abbreviations: FEV_1, forced expiratory volume in 1 second; FiO_2, fraction of inspired oxygen in a gas mixture; IMV, invasive mechanical ventilation; mmHg, millimeters of mercury; NPPV, noninvasive positive pressure ventilation; NR, not reported; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen; SD, standard deviation.

NPPV for Weaning COPD Patients from Invasive Mechanical Ventilation

Table A14: General Study Characteristics (NPPV Versus IMV for Weaning)*

Author, Year	Country, Number of Sites	Sample Size	Patient Population	Inclusion Criteria	Exclusion Criteria	Length of Follow-Up	Outcomes
Nava et al, 1998 (37)	Italy, 3	50	Patients with acute exacerbations of COPD who required IMV and failed a T-piece weaning test	Patients with known COPD admitted for an acute relapse defined as respiratory acidosis (pH ≤ 7.33 while breathing room air), elevated bicarbonate levels, hypoxemia ($PaCO_2$ ≤ 45 mmHg while breathing room air), and severe dyspnea in the absence of an objectively documented cause such as pneumonia, who needed intubation, were eligible for the study. Those patients who had satisfactory neurologic status, body temperature of 37°C or less, were hemodynamically stable, and had SaO_2 ≥ 88% for an FiO_2 of 40% during a brief discontinuation of mechanical ventilation were given a T-piece trial. Those patients who failed the T-piece trial (had any of the following: respiratory rate > 35 breaths/minute, PaO_2 < 50 mmHg for an FiO_2 of 40%, heart rate more than 145 beats/minute or sustained increase or decrease in heart rate of more than 20%, severe arrhythmia, systolic BP > 180 mmHg or < 70 mmHg, agitation, anxiety, or diaphoresis) were eligible for inclusion in the trial.	Concomitant severe diseases, cardiac arrest, cardiogenic pulmonary edema, cardiogenic shock, aortic aneurysm, acute MI, gastrointestinal perforation, obstruction or bleeding, sepsis, trauma, metabolic coma, diabetic ketoacidosis, drug overdose, coagulopathy, other hematologic diseases, postoperative patients, and patients who have a successful T-piece trial	ICU stay (up to 60 days)	Arterial blood gases, pulmonary function, complications, duration of mechanical ventilation, ICU LOS, % patients who could not be weaned (due to death, reintubation within 72 hours, and failure to be weaned at 60 days), mortality
Prasad et al, 2009 (38)	India, 1	30	Patients admitted to ICU with acute exacerbation of COPD and needing IMV	Patients with acute hypercapnic respiratory failure in COPD defined as severe dyspnea in the absence of objectively documented causes such as pneumonia and with the following arterial blood gases: pH < 7.33	Patients who died immediately during intubation, patients with successful T-piece trials, patients with concomitant neurological disease (other than hypercapnic encephalopathy), cardiac arrest, cardiogenic pulmonary edema,	ICU stay (up to 30 days)	Duration of mechanical ventilation, duration of ICU stay, duration of weaning, nosocomial pneumonia, mortality at discharge from ICU and 30-day discharge

Author, Year	Country, Number of Sites	Sample Size	Patient Population	Inclusion Criteria	Exclusion Criteria	Length of Follow-Up	Outcomes
			who failed a T-piece weaning test	(breathing at room air), PaO_2 < 50 mmHg, $PaCO_2$ > 50 mmHg who were intubated. T-piece weaning trial was given to the patients when they were judged to have reached satisfactory neurological status, clinical and biochemical parameters with an SaO_2 of ≥ 88% for a FiO_2 of 40% after a minimum of 24 hours of ventilation. T-piece weaning failure was characterized by any of the following: PaO_2 < 50 mm for a FiO_2 of 40%, pH < 7.35, respiratory rate > 35 breathes/minute, heart rate > 145 beats/minute, systolic BP > 180 mmHg or < 70 mmHg, significant arrhythmia, or agitation, anxiety or diaphoresis. Those patients that failed the T-piece trial were enrolled in the study.	cardiogenic shock, acute MI, gastrointestinal perforation/obstruction, metabolic coma, coagulopathy, postoperative respiratory failure		

*Abbreviations: BP, blood pressure; COPD, chronic obstructive pulmonary disease; FiO_2, fraction of inspired oxygen; ICU, intensive care unit; IMV, invasive mechanical ventilation; LOS, length of stay; MI, myocardial infarction; mmHg, millimeters of mercury; NPPV, noninvasive positive pressure ventilation; PaO_2, partial pressure of oxygen in the arterial blood; $PaCO_2$, partial pressure of carbon dioxide in the arterial blood; SaO_2, saturation of oxygen of arterial blood.

Table A15: General Study Characteristics – Intervention and Control Group Details (NPPV Versus IMV for Weaning)*

Author, Year	Initial IMV Settings and Protocol	NPPV Weaning Protocol				IMV Weaning Protocol
		Ventilation Mode	Interface	Pressures	Ventilator Schedule	Pressure Settings and Protocol
Nava et al, 1998 (37)	Patients ventilated in controlled mode during the first 12 hours (sedated and curarized and airway secretions suctioned frequently during first 6–8 hours) with the following settings: tidal volume: 8–10 mL/kg, respiratory rate: 12–16 breaths/minute, FiO_2 as required to obtain SaO_2 of 95%. Then, patients were given pressure support ventilation (21 ± 2 cm H_2O) for an additional 24–36 hours. Extrinsic positive end-expiratory pressure was added when intrinsic positive end-expiratory pressure was clinically suspected. Then, a T-piece weaning trial was given to those patients who were judged to have satisfactory neurological status, body temperature of 37°C or less, hemodynamically stable, SaO_2 of 88% or more for an FiO_2 of 40% during a brief discontinuation of mechanical ventilation. After failure of T-piece weaning trial, patients were reconnected to the ventilator in pressure support ventilation mode until the previous $PaCO_2$ and pH values were reached (30–60 minutes) and the respiratory rate under ventilation was ≤ 30 breaths/minute.	Pressure support ventilation	Face mask	Patients received ventilation with level of pressure support (19 ± 2 cm H_2O) that was adjusted to achieve satisfactory blood gases and respiratory rate < 25 breaths/minute.	During the first 48 hours, NPPV was delivered until it was well tolerated (20–22 hours/day) spaced by periods of spontaneous inhalation of oxygen during meals and to expectorate. The level of pressure support was decreased by 2 or 4 cm H_2O per day in patients with good tolerance and patients were allowed to breathe spontaneously. At least 2 trials of spontaneous breathing of gradually increased duration were attempted each day.	The pressure was titrated to achieve a breathing frequency of ≤ 25 breaths/minute. Pressure support ventilation was initially set at 17.6 ± 2.1 cm H_2O and then the level was gradually decreased and intermittent trials of spontaneous breathing were performed 2 times/day by using a T-tube circuit or a continuous-flow circuit with a continuous positive airway pressure < 5 cm H_2O.
Prasad et al, 2009 (38)	Patients were ventilated with control/assist mode in a step-wise manner (considering their level of consciousness, sedation, and improvement in arterial blood gases). Muscle relaxants and sedation were used as required. The following ventilator settings were	BiPAP	Full face mask	Level of IPAP and EPAP support was used to achieve satisfactory blood gases and a respiratory rate < 25 breaths/minute. Once that was	Patients received NPPV continuously except for meals and expectoration.	Patients received pressure support ventilation with a particular level of pressure support that achieved satisfactory blood gases and a respiratory rate < 25 breaths/minute. Once that was achieved, pressure support was decreased by 2 cm H_2O every 4 hours with a good tolerance. As soon as the pressure support and PEEP reached 10 and 5 cm H_2O, respectively, with a pH ≥ 7.35, SaO_2 ≥ 90%, FiO_2 ≤ 40%, and respiratory rate <

Author, Year	Initial IMV Settings and Protocol	NPPV Weaning Protocol				IMV Weaning Protocol
		Ventilation Mode	Interface	Pressures	Ventilator Schedule	Pressure Settings and Protocol
	used: respiratory rate of 12 breaths/minute, tidal volume 8–10 mL/kg, FiO_2 to obtain SaO_2 of 90% with PEEP of 5 cm H_2O and an I:E ratio of 1:2.5–3.0. T-piece weaning trials were given to patients that were judged to have satisfactory neurological status, clinical and biochemical parameters with an $SaO_2 \geq 88\%$ for a FiO_2 of 40% after a minimum of 24 hours of ventilation. After failure of T-piece weaning trial, patients were put back on control/assist ventilation mode until previous $PaCo_2$ and pH values were reached with a respiratory rate ≤ 30 breaths/minute.			achieved, pressure support was decreased by 2 cm H_2O every 4 hours with a good tolerance. As soon as the IPAP and EPAP levels were reduced to 8 and 4 cm H_2O, respectively, with a satisfactory pH ≥ 7.35, $SaO_2 \geq 90\%$, $FiO_2 \leq 40\%$, and respiratory rate < 30 breaths/minute, patients were allowed to breathe spontaneously.		30 breaths/minute, patients were extubated and allowed to breathe spontaneously.

*Abbreviations: BiPAP, bilevel positive airway pressure; cm H_2O, centimeters of water; E, expiratory; EPAP, expiratory positive airway pressure; FiO_2, fraction of inspired oxygen; I, inspiratory; IMV, invasive mechanical ventilation; IPAP, inspiratory positive airway pressure; NPPV, noninvasive positive pressure ventilation; NR, not reported; $PaCO_2$, partial pressure of carbon dioxide in the arterial blood; PEEP, positive end-expiratory pressure; SaO_2, oxygen saturation of arterial blood; SIMV, synchronous intermittent mechanical ventilation.

Table A16: Characteristics of the Patients in the Included Studies (NPPV Versus IMV for Weaning)*

Author, Year	Sample Size		FEV_1 % Predicted		Age, Mean (SD), Years		Percent Male		pH, Mean (SD)		$PaC0_2$, Mean (SD), mmHg		PaO_2, Mean (SD), mmHg	
	NPPV	IMV	NPPV	IMV	NPPV	IMV	NPPV	IMV	NPPV	IMV	NPPV	IMV	NPPV	IMV
Nava et al, 1998 (37)	25	25	16.9 (10)	17.4 (9)	68.7 (8.5)	67.0 (9.2)	NR	NR	7.22 (0.07)	7.22 (0.08)	96.3 (19.6)	91.9 (13.8)	PaO_2: FiO_2 ratio: 1.48 (0.3)	PaO_2:FiO_2 ratio: 1.42 (0.4)
Prasad et al, 2009 (38)	15	15	29.77 (6.98)	29.33 (5.61)	57.7 (11.2)	61.1 (8.1)	80	60	7.13 (0.06)	7.13 (0.07)	95.98 (21.28)	102.54 (28.36)	NR	NR

*Abbreviations: FEV_1, forced expiratory volume in 1 second; FiO_2, fraction of inspired oxygen; IMV, invasive mechanical ventilation; mmHg, millimeters of mercury; NPPV, noninvasive positive pressure ventilation; NR, not reported; $PaCO_2$, partial pressure of carbon dioxide in the arterial blood; PaO_2, partial pressure of oxygen in the arterial blood; SD, standard deviation.

Appendix 4: Summary Tables of Study Methodological Quality and GRADE Quality of Evidence

NPPV for the Treatment of ARF due to Acute Exacerbations of COPD: NPPV for ARF

Table A17: Summary of Study Methodological Characteristics That Impact Study Quality (NPPV Plus UMC Versus UMC Alone or IMV)*

Author, Year	Sample Size	Adequate Randomization Methods	Adequate Allocation Concealment	Blinding	Power	Loss to Follow-Up	Intention-to-Treat
NPPV + UMC vs. UMC Alone							
Barbe et al, 1996 (25)	24	Unclear†	Unclear	X‡	X§	NR	X‖
Bott et al, 1993 (26)	60	Unclear†	Unclear	X‡	X§	NR	Some outcomes¶
Brochard et al, 1995 (27)	85	Unclear†	Unclear	n/a#	✓**	NR	✓
Carrera et al, 2009 (28)	75	✓	✓	✓††	X§	0%	✓
Dhamija et al, 2005 (29)	29	✓	Unclear	n/a#	X§	NR	X‡‡
Dikensoy et al, 2002 (5)	34	X§§	Unclear	X‡	Some outcomes‖ ‖	NR	X¶¶
Keenan et al, 2005 (30)	52	✓	✓	X‡	X##	NR	✓
Khilnani et al, 2010 (31)	40	✓	Unclear	X‡	Some outcomes***	NR	✓
Kramer et al, 1995 (9)	23	Unclear†	Unclear	n/a#	X †††	NR	✓
Plant et al, 2000 (32)	236	✓	✓	n/a#	Some outcomes‡‡‡	0%	✓
Wang et al, 2005 (33)	342	Unclear§§§	Unclear	n/a#	Some outcomes‖ ‖ ‖	NR	✓
NPPV vs. IMV							
Conti et al, 2002 (36)	156	Unclear¶¶¶	Unclear¶¶¶	n/a#	X§	0%	✓
Jurjevic et al, 2009 (7)	49	Unclear###	✓	n/a#	Some outcomes****	NR	✓

*Abbreviations: BiPAP, bilevel positive airway pressure; IMV, invasive mechanical ventilation; n/a, not applicable; LOS, length of stay; NPPV, noninvasive positive pressure ventilation; NR, not reported; UMC, usual medical care.

†The study is identified as randomized, but the methods of randomization are not reported.

‡The study was not blinded. Some of the outcomes could have been influenced by lack of blinding (e.g., if there were no a priori intubation criteria, if patients were discharged by a physician who was not blinded, and/or if the study used subjective outcome measurements).

§The study did not report an a priori sample size calculation, and post hoc power calculations show that the study was underpowered.

‖The 4 patients who could not tolerate NPPV were excluded from the published analysis. (25)

¶The survival analysis is performed using intention-to-treat; however, the symptom assessments were not, as patients with missing data were excluded. (26)

#While the study was not blinded, most outcomes were objective and so the impact of the lack of blinding was minimized.

**The study did not report an a priori sample size calculation. Post hoc power calculations show that the study was adequately powered for some outcomes (complication rate and intubation rate). While the post hoc power calculations show the other outcomes were underpowered, the results were statistically significant, so type II error is unlikely. (27)

††Sham BiPAP machine was used and those physicians making treatment decisions were blinded to treatment group. (28)

‡‡One patient who could not tolerate the mask in the NPPV group was excluded from the analysis.

§§The randomization method is reported as direct enumeration which does not provide adequate information to assess the method of randomization. Patients who did not comply with the study treatment were excluded from the study and then randomization continued with the next patient. (5)

‖‖While the study did not report an a priori sample size calculation, and post hoc power calculations showed that it was underpowered for most outcomes, the study was adequately powered for hospital LOS. In addition, the results for the need for intubation were statistically significant, which suggests type II error is not an issue for this outcome.

¶¶The 2 patients who were not compliant to NPPV were excluded from the analysis.

##While an a priori sample size calculation is provided, due to changes in funding at the hospital in which the study was conducted, the study did not enrol adequate patients to reach their sample size target to achieve 80% power. (30)

***While the study did not report an a priori sample size calculation and post hoc power calculations showed that some outcomes were underpowered, some outcomes were adequately powered.

†††While the study did not report an a priori sample size calculation and post hoc power calculations showed that the outcomes were underpowered, one outcome did show a significant result which suggests type II error is not an issue for this outcome.

‡‡‡A priori sample size calculation was reported for the primary outcome (need for intubation); however, post hoc power calculations show that the study was underpowered to assess mortality.

§§§A centralized, interactive voice system was used to randomize patients. Inadequate information on this method of randomization was provided to determine if this is an appropriate and adequate method of randomization.

‖‖‖While no a priori sample size calculation was reported, post hoc power calculations show that the study was adequately powered to assess the primary outcome (need for intubation), but not mortality or hospital LOS.

¶¶¶Random assignment was made with sealed envelopes, however, this is not enough information to determine if the methods of randomization are adequate, and since the envelopes were not specified as opaque, it was not possible to assess adequacy of allocation concealment either. (36)

###Patients were randomized using closed, non-transparent envelopes; however, this is not enough information to determine if the methods of randomization are adequate. (7)

****The study reported an a priori sample size calculation, but the paper did not report what outcome this sample size calculation referred to. Post hoc power calculations show that some outcomes are underpowered (mortality and success of treatment) while others (incidence of ventilator-associated pneumonia and tracheotomy) are adequately powered.

Table A18: GRADE Quality of Evidence (NPPV Plus UMC Versus UMC Alone)*

Number of Studies	Design	Study Quality	Consistency	Directness	Imprecision	Other Modifying Factors	Overall Quality of Evidence
Outcome: need for endotracheal intubation							
11	RCT	Serious limitations†	No serious limitations	No serious limitations	No serious limitations	n/a	Moderate
Outcome: inhospital mortality							
9	RCT	Serious limitations†	No serious limitations	No serious limitations	No serious limitations	n/a	Moderate
Outcome: 30-day mortality							
1	RCT	Serious limitations†	n/a	No serious limitations	No serious limitations	n/a	Low
Outcome: long-term survival							
1	RCT	Serious limitations†	n/a	No serious limitations	No serious limitations	n/a	Moderate
Outcome: hospital length of stay							
11	RCT	Serious limitations†	No serious limitations	No serious limitations	No serious limitations	n/a	Moderate
Outcome: dyspnea							
8	RCT	Serious limitations†	Serious limitations‡	No serious limitations	No serious limitations	n/a	Low
Outcome: complications							
5	RCT	Serious limitations†	Serious limitations§	No serious limitations	No serious limitations	n/a	Low

*Abbreviations: n/a, not applicable; NPPV, noninvasive positive pressure ventilation; RCT, randomized controlled trial; UMC, usual medical care.

†Study quality was downgraded due to the serious limitations shown in Table A17 above.

‡Downgraded due to lack of consistency in the results, with some studies showing significantly faster improvements in dyspnea in the NPPV plus UMC group compared with the UMC group, and other studies showing no significant difference between the 2 groups.

§Brochard et al (27) reported 232 complications in the UMC group, whereas the other studies which reported complications in the UMC group reported 10 or fewer complications.

Table A19: GRADE Quality of Evidence (NPPV Versus IMV)*

No. of Studies	Design	Study Quality	Consistency	Directness	Imprecision	Other Modifying Factors	Overall Quality of Evidence
Outcome: ICU mortality							
2	RCT	Serious limitations†	Serious limitations‡	Serious limitations§	Serious limitations	n/a	Very low
Outcome: inhospital mortality							
1	RCT	Serious limitations†	n/a	No serious limitations	Serious limitations‖	n/a	Low
Outcome: 1-year mortality							
1	RCT	Serious limitations†	n/a	No serious limitations	Serious limitations‖	n/a	Low
Outcome: successful treatment							
1	RCT	Serious limitations†	n/a	No serious limitations	Serious limitations‖	n/a	Low
Outcome: ICU length of stay							
2	RCT	Serious limitations†	Serious limitations‡	Serious limitations§	Serious limitations	n/a	Very low
Outcome: duration of mechanical ventilation							
2	RCT	Serious limitations†	Serious limitations‡	Serious limitations§	No serious limitations	n/a	Very low
Outcome: ventilator-associated pneumonia							
2	RCT	Serious limitations†	Serious limitations‡	Serious limitations§	No serious limitations	n/a	Very low
Outcome: tracheotomy							
2	RCT	Serious limitations†	No serious limitations‡	Serious limitations§	No serious limitations	n/a	Very low

*Abbreviations: ICU, intensive care unit; IMV, invasive mechanical ventilation; n/a, not applicable; No., number; NPPV, noninvasive positive pressure ventilation; RCT, randomized controlled trial.

†Downgraded due to serious limitations in individual study quality which are outlined in Table A17.

‡Downgraded due to inconsistency between the results of the 2 studies. One study showed significant benefits in the NPPV group and the other showed no significant differences between the 2 groups.

§Downgraded because the generalizability of the Jurjevic et al (7) is unknown due to the lack of clear inclusion criteria in the study.

‖Downgraded due to imprecision.

NPPV for Weaning COPD Patients from IMV: NPPV Versus IMV

Table A20: GRADE Quality of Evidence (NPPV Versus IMV for Weaning)*

Number of Studies	Design	Study Quality	Consistency	Directness	Imprecision	Other Modifying Factors	Overall Quality of Evidence
Outcome: mortality							
2	RCT	Serious limitations†	No serious limitations	No serious limitations	No serious limitations	n/a	Moderate
Outcome: ICU length of stay							
2	RCT	Serious limitations†	No serious limitations	No serious limitations	Serious limitations‡	n/a	Low
Outcome: duration of mechanical ventilation							
2	RCT	Serious limitations†	No serious limitations	No serious limitations	Serious limitations‡	n/a	Low
Outcome: nosocomial pneumonia							
2	RCT	Serious limitations†	No serious limitations	No serious limitations	No serious limitations	n/a	Moderate
Outcome: other complications							
2	RCT	Serious limitations†	Serious limitations§	No serious limitations	No serious limitations	n/a	Low
Outcome: weaning failure							
1	RCT	Serious limitations†	n/a	No serious limitations	No serious limitations	n/a	Moderate

*Abbreviations: ICU, intensive care unit; IMV, invasive mechanical ventilation; NPPV, noninvasive positive pressure ventilation; n/a, not applicable; RCT, randomized controlled trial.

†Individual study quality was downgraded due to serious limitations in study methodology shown in Table A21.

‡Downgraded due to imprecision in the pooled summary estimates.

§Downgraded due to inconsistency in the number of complications, with one study having a much higher incidence of complications than the other.

Table A21: Summary of Study Methodological Characteristics That Impact Study Quality (NPPV Versus IMV for Weaning)*

Author, Year	Sample Size	Adequate Randomization Methods	Adequate Allocation Concealment	Blinding	Power	Loss to FUP	ITT	Weaning Criteria (refer to methods section for more details on these criteria)					
								Daily Screening	Criteria to Identify Weaning Candidates	Weaning Protocols / Guidelines	Criteria for Failed SBT	Criteria for Discontinued MV	Criteria for Reintubation
NPPV vs. IMV to wean patients from IMV													
Nava et al, 1998 (37)	50	Unclear†	✓	Some outcomes‡	Some outcomes§	NR	✓	X	✓	✓	✓	✓‖	✓
Prasad et al, 2009 (38)	30	✓	Unclear	Some outcomes‡	X¶	NR	✓	X	✓	✓	✓	✓	✓

*Abbreviations: FUP, follow-up; IMV, invasive mechanical ventilation; ICU, intensive care unit; ITT, intention-to-treat; MV, mechanical ventilation; NPPV, noninvasive positive pressure ventilation; NR, not reported; SBT, spontaneous breathing trial.

†Methods of randomization are not provided in the published report.

‡The study was not blinded; however, some of the outcomes are objective and should be less impacted by lack of blinding. Some outcomes such as length of stay may be more likely to be affected.

§No a priori sample size is reported. Based on post hoc power calculations, the study is adequately powered to assess ICU length of stay. The study was underpowered for mortality and duration of mechanical ventilation, these outcomes were significant, and so type II error is unlikely. Finally, the study was underpowered to assess ventilator-associated pneumonia based on post hoc power calculations.

‖MV was discontinued after a successful spontaneous breathing test of at least 3 hours. (37)

¶No a priori sample size calculation is reported, and based on post hoc power calculations, the study was underpowered.

NPPV for ARF After Extubation From IMV: NPPV Plus UMC Versus UMC Alone

Table A22: Summary of Study Methodological Characteristics That Impact Study Quality (NPPV Versus UMC After Extubation)*

Author, Year	Sample Size	Adequate Randomization Methods	Adequate Allocation Concealment	Blinding	Power	Loss to Follow-Up	Intention-to-Treat
Esteban et al, 2004 (41)	23	✓	✓	✓†	X‡	NR	✓

*Abbreviations: COPD, chronic obstructive pulmonary disease; NPPV, noninvasive positive pressure ventilation; UMC, usual medical care.

†While the study was not blinded, need for reintubation was based on a priori criteria which were based primarily on objective measurements.

‡While the study reported an a priori sample size calculation for the COPD patients separately, the study was underpowered based on a post hoc power analysis.

Table A23: GRADE Quality of Evidence (NPPV Versus UMC After Extubation)*

Number of Studies	Design	Study Quality	Consistency	Directness	Imprecision	Other Modifying Factors	Overall Quality of Evidence
Outcome: reintubation							
1	RCT	Serious limitations†	n/a	No serious limitations	Serious limitations‡	n/a	Low

*Abbreviations: n/a, not applicable; NPPV, noninvasive positive pressure ventilation; RCT, randomized controlled trial; UMC, usual medical care.

†Post hoc analysis from an RCT, which breaks the study randomization

‡One study with a very small sample size (n = 23)

Appendix 5: Subgroup Analyses

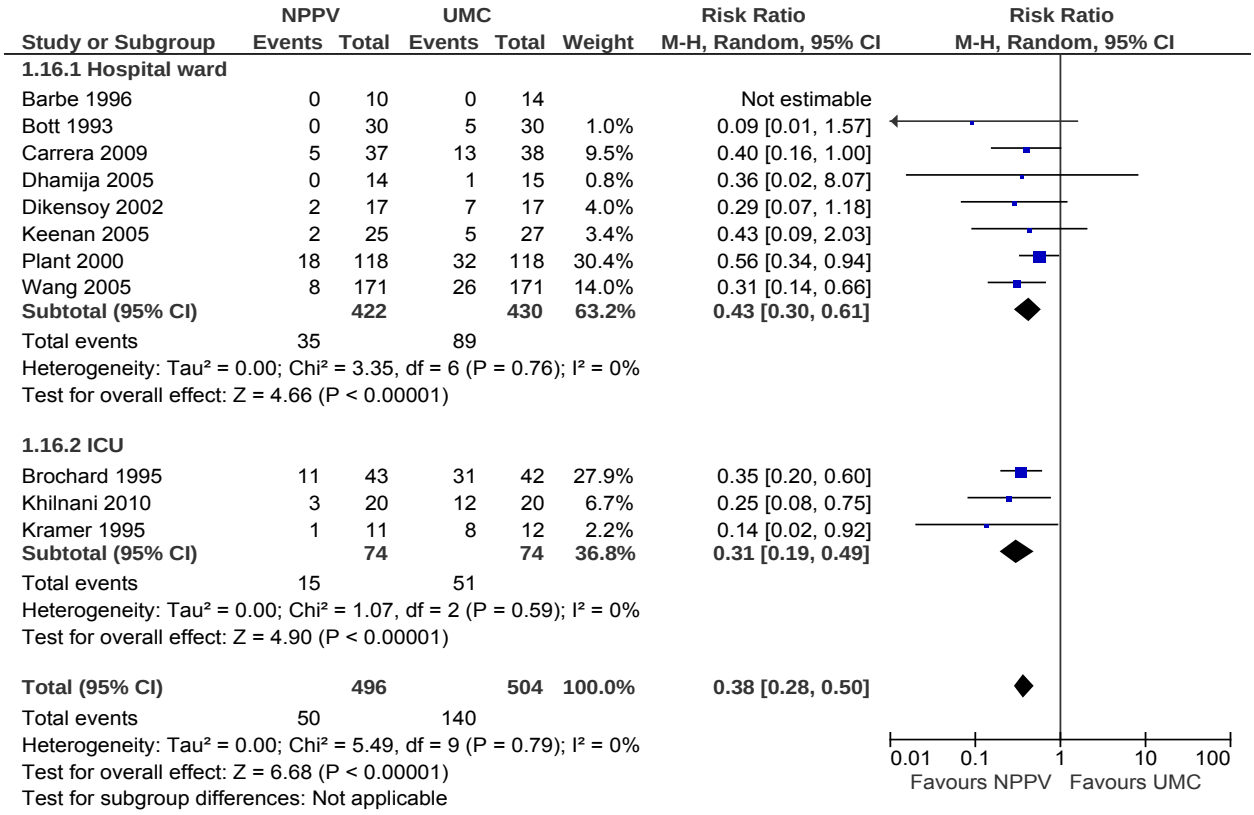

Figure A1: Pooled Results for the Need for Endotracheal Intubation by Hospital Ward or ICU (NPPV Plus UMC Versus UMC Alone)*

*Abbreviations: CI, confidence interval; ICU, intensive care unit; M–H, Mantel–Haenszel; NPPV, noninvasive positive pressure ventilation; UMC, usual medical care.

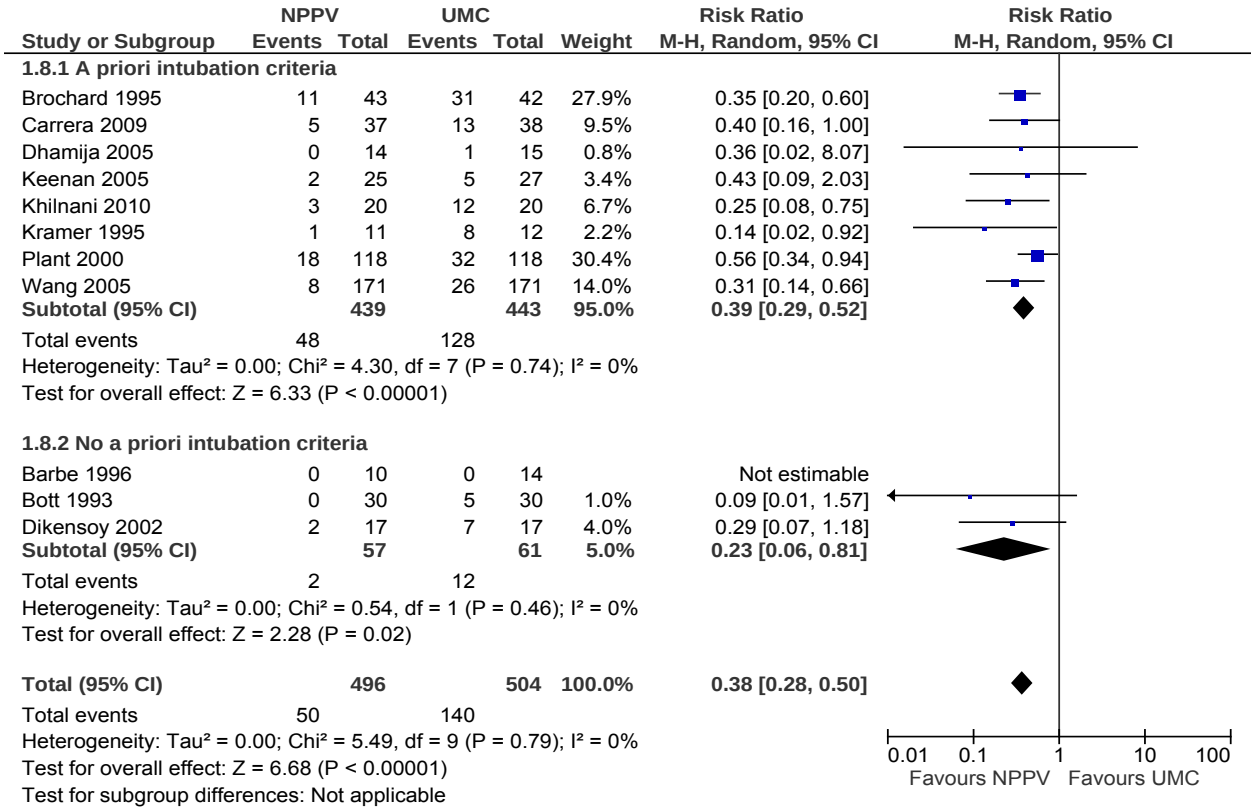

Figure A2: Pooled Results for the Need for Endotracheal Intubation by Presence of A Priori Intubation Criteria (NPPV Plus UMC Versus UMC Alone)*

*Abbreviations: CI, confidence interval; M–H, Mantel–Haenszel; NPPV, noninvasive positive pressure ventilation; UMC, usual medical care.

References

(1) Kaynar AM, Sharma S. Respiratory Failure [Internet]. [updated 2010 Sep 28; cited 2011 May 6]. Available from: http://emedicine.medscape.com/article/167981-overview

(2) Keenan SP, Mehta S. Noninvasive ventilation for patients presenting with acute respiratory failure: the randomized controlled trials. Respir Care. 2009;54(1):116-26.

(3) Ward NS, Dushay KM. Clinical concise review: Mechanical ventilation of patients with chronic obstructive pulmonary disease. Crit Care Med. 2008 May;36(5):1614-9.

(4) Ram FSF, Picot J, Lightowler J, Wedzicha JA. Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease. Cochrane Database Sys Rev. 2004, Issue 3. Art. No.:D004104.DOI: 10.1002/14651858.CD004104.pub3.

(5) Dikensoy O, Ikidag B, Filiz A, Bayram N. Comparison of non-invasive ventilation and standard medical therapy in acute hypercapnic respiratory failure: a randomised controlled study at a tertiary health centre in SE Turkey. Int J Clin Pract. 2002 Mar;56(2):85-8.

(6) Collaborating Research Group for Noninvasive Mechanical Ventilation of Chinese Respiratory Society. Pulmonary infection control window in treatment of severe respiratory failure of chronic obstructive pulmonary diseases: a prospective, randomized controlled, multi-centred study. Chin Med J (Engl). 2005 Oct 5;118(19):1589-94.

(7) Jurjevic M, Matic I, Sakic-Zdravcevic K, Sakic S, Danic D, Bukovic D. Mechanical ventilation in chronic obstructive pulmonary disease patients, noninvasive vs. invasive method (randomized prospective study). Coll Antropol. 2009 Sep;33(3):791-7.

(8) Bolton R, Bleetman A. Non-invasive ventilation and continuous positive pressure ventilation in emergency departments: Where are we now? Emerg Med J. 2008;25(4):190-4.

(9) Kramer N, Meyer TJ, Meharg J, Cece RD, Hill NS. Randomized, prospective trial of noninvasive positive pressure ventilation in acute respiratory failure. Am J Respir Crit Care Med. 1995 Jun;151(6):1799-806.

(10) Trevisan CE, Vieira SR, Research Group. Noninvasive mechanical ventilation may be useful in treating patients who fail weaning from invasive mechanical ventilation: a randomized clinical trial. Crit Care. 2008;12(2):R51.

(11) Jiang JS, Kao SJ, Wang SN. Effect of early application of biphasic positive airway pressure on the outcome of extubation in ventilator weaning. Respirology. 1999 Jun;4(2):161-5.

(12) Review Manager (RevMan) [Computer program]. Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011.

(13) Burns KE, Adhikari NK, Meade MO. A meta-analysis of noninvasive weaning to facilitate liberation from mechanical ventilation. Can J Anaesth. 2006 Mar;53(3):305-15.

(14) Burns KEA, Adhikari NKJ, Keenan SP, Meade MO. Noninvasive positive pressure ventilation as a weaning strategy for intubated adults with respiratory failure. Cochrane Database Syst Rev. 2010, Issue 8. Art. No.:CD004127.DOI:10.1002/14651858.CD004127.pub2.

(15) Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. BMJ. 2004 Jun 19;328(7454):1490.

(16) Goodman, C. Literature searching and evidence interpretation for assessing health care practices. Stockholm, Sweden: Swedish Council on Technology Assessment in Health Care; 1996 81 p. SBU Report No. 119E.

(17) Keenan SP, Sinuff T, Burns KE, Muscedere J, Kutsogiannis J, Mehta S, et al. Clinical practice guidelines for the use of noninvasive positive-pressure ventilation and noninvasive continuous positive airway pressure in the acute care setting. CMAJ. 2011 Feb 14;183(3):E195-E214.

(18) Quon BS, Gan WQ, Sin DD. Contemporary management of acute exacerbations of COPD: a systematic review and metaanalysis. Chest. 2008 Mar;133(3):756-66.

(19) Hess DR. The evidence for noninvasive positive-pressure ventilation in the care of patients in acute respiratory failure: a systematic review of the literature. Respir Care. 2004 Jul;49(7):810-29.

(20) Keenan SP, Sinuff T, Cook DJ, Hill NS. Which patients with acute exacerbation of chronic obstructive pulmonary disease benefit from noninvasive positive-pressure ventilation? A systematic review of the literature. Ann Intern Med. 2003 Jun 3;138(11):861-70.

(21) Caples SM, Gay PC. Noninvasive positive pressure ventilation in the intensive care unit: a concise review. Crit Care Med. 2005 Nov;33(11):2651-8.

(22) Peter JV, Moran JL, Phillips-Hughes J, Warn D. Noninvasive ventilation in acute respiratory failure--a meta-analysis update. Crit Care Med. 2002 Mar;30(3):555-62.

(23) Jarvis H. Exploring the evidence base of the use of non-invasive ventilation. Br J Nurs. 2006 Jul 27;15(14):756-9.

(24) Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2007 Sep 15;176(6):532-55.

(25) Barbe F, Togores B, Rubi M, Pons S, Maimo A, Agusti AG. Noninvasive ventilatory support does not facilitate recovery from acute respiratory failure in chronic obstructive pulmonary disease. Eur Respir J. 1996 Jun;9(6):1240-5.

(26) Bott J, Carroll MP, Conway JH, Keilty SE, Ward EM, Brown AM, et al. Randomised controlled trial of nasal ventilation in acute ventilatory failure due to chronic obstructive airways disease. Lancet. 1993 Jun 19;341(8860):1555-7.

(27) Brochard L, Mancebo J, Wysocki M, Lofaso F, Conti G, Rauss A, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. N Engl J Med. 1995 Sep 28;333(13):817-22.

(28) Carrera M, Martin J, Anton A, Chiner E, Alonso ML, Masa JF, et al. A controlled trial of noninvasive ventilation for chronic obstructive pulmonary disease exacerbations. J Crit Care. 2009 Sep;24(3):473.e7-14.

(29) Dhamija A, Tyagi P, Caroli R, Ur RM, Vijayan VK. Noninvasive ventilation in mild to moderate cases of respiratory failure due to acute exacerbation of chronic obstructive pulmonary disease. Saudi Med J. 2005 May;26(5):887-90.

(30) Keenan SP, Powers CE, McCormack DG. Noninvasive positive-pressure ventilation in patients with milder chronic obstructive pulmonary disease exacerbations: a randomized controlled trial. Respir Care. 2005 May;50(5):610-6.

(31) Khilnani GC, Saikia N, Banga A, Sharma SK. Non-invasive ventilation for acute exacerbation of COPD with very high PaCO(2): A randomized controlled trial. Lung India. 2010 Jul;27(3):125-30.

(32) Plant PK, Owen JL, Elliott MW. Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial. Lancet. 2000 Jun 3;355(9219):1931-5.

(33) Wang C. Early use of non-invasive positive pressure ventilation for acute exacerbations of chronic obstructive pulmonary disease: A multicentre randomized controlled trial. Chin Med J (Engl). 2005;118(24):2034-40.

(34) Plant PK, Owen JL, Elliott MW. Non-invasive ventilation in acute exacerbations of chronic obstructive pulmonary disease: long term survival and predictors of in-hospital outcome. Thorax. 2001 Sep;56(9):708-12.

(35) Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005;5(13):[10 p.].

(36) Conti G, Antonelli M, Navalesi P, Rocco M, Bufi M, Spadetta G, et al. Noninvasive vs. conventional mechanical ventilation in patients with chronic obstructive pulmonary disease after failure of medical treatment in the ward: a randomized trial. Intensive Care Med. 2002 Dec;28(12):1701-7.

(37) Nava S, Ambrosino N, Clini E, Prato M, Orlando G, Vitacca M, et al. Noninvasive mechanical ventilation in the weaning of patients with respiratory failure due to chronic obstructive pulmonary disease. A randomized, controlled trial. Ann Intern Med. 1998 May 1;128(9):721-8.

(38) Prasad SBN, Chaudhry D, Khanna R. Role of noninvasive ventilation in weaning from mechanical ventilation in patients of chronic obstructive pulmonary disease: An Indian experience. Indian J Crit Care Med. 2009;13(4):207-12.

(39) Ferrer M, Valencia M, Nicolas JM, Bernadich O, Badia JR, Torres A. Early noninvasive ventilation averts extubation failure in patients at risk: a randomized trial. Am J Respir Crit Care Med. 2006 Jan 15;173(2):164-70.

(40) Ferrer M, Sellares J, Valencia M, Carrillo A, Gonzalez G, Badia JR, et al. Non-invasive ventilation after extubation in hypercapnic patients with chronic respiratory disorders: randomised controlled trial. Lancet. 2009 Sep 26;374(9695):1082-8.

(41) Esteban A, Frutos-Vivar F, Ferguson ND, Arabi Y, Apeztequia C, Lez M, et al. Noninvasive positive-pressure ventilation for respiratory failure after extubation. N Engl J Med. 2004 Jun 10;350(24):2452-60.

(42) Angus RM, Ahmed AA, Fenwick LJ, Peacock AJ. Comparison of the acute effects on gas exchange of nasal ventilation and doxapram in exacerbations of chronic obstructive pulmonary disease. Thorax. 1996 Oct;51(10):1048-50.

(43) Avdeev SN, Tret'iakov AV, Grigor'iants RA, Kutsenko MA, Chuchalin AG. [Study of the use of noninvasive ventilation of the lungs in acute respiratory insufficiency due exacerbation of chronic obstructive pulmonary disease]. Anesteziol Reanimatol. 1998 May;(3):45-51.

(44) Bardi G, Pierotello R, Desideri M, Valdisserri L, Bottai M, Palla A. Nasal ventilation in COPD exacerbations: early and late results of a prospective, controlled study. Eur Respir J. 2000 Jan;15(1):98-104.

(45) Celikel T, Sungur M, Ceyhan B, Karakurt S. Comparison of noninvasive positive pressure ventilation with standard medical therapy in hypercapnic acute respiratory failure. Chest. 1998 Dec;114(6):1636-42.

(46) Confalonieri M, Potena A, Carbone G, Porta RD, Tolley EA, Umberto MG. Acute respiratory failure in patients with severe community-acquired pneumonia. A prospective randomized evaluation of noninvasive ventilation. Am J Respir Crit Care Med. 1999 Nov;160(5 Pt 1):1585-91.

(47) Daskalopoulou E, Teara V, Fekete K, et al. Treatment of acute respiratory failure in COPD patients with positive airway pressure via nasal mask. Chest. 1993;103:271S.

(48) del Castillo D, Barrot E, Laserna E, Otero R, Cayuela A, Castillo GJ. [Noninvasive positive pressure ventilation for acute respiratory failure in chronic obstructive pulmonary disease in a general respiratory ward]. Med Clin (Barc). 2003 May 10;120(17):647-51.

(49) Honrubia T, Garcia Lopez FJ, Franco N, Mas M, Guevara M, Daguerre M, et al. Noninvasive vs conventional mechanical ventilation in acute respiratory failure: a multicenter, randomized controlled trial. Chest. 2005 Dec;128(6):3916-24.

(50) Khilnani GC, Saikia N, Sharma S. Efficacy of non-invasive positive pressure ventilation (NPPV) for management of COPD with acute or acute on chronic respiratory failure: A randomized controlled trial [abstract]. Am J Respir Crit Care Med. 2002;165(8).

(51) Lapinsky SE, Aubin M. Randomized trial of noninvasive ventilation in acute respiratory failure - factors affecting mortality. Am J Respir Crit Care Med. 1999;160:1585-91.

(52) Liao X, Li Q, Lin K, Zhang Q, Wang C, Qian G. Non-invasive positive pressure ventilation for early treatment of respiratory failure due to exacerbation of chronic obstructive pulmonary disease: a random controlled trial. Di 3 Jun Yi Da Xue Xue Bao. 2004;26:739-41.

(53) Martin TJ, Hovis JD, Costantino JP, Bierman MI, Donahoe MP, Rogers RM, et al. A randomized, prospective evaluation of noninvasive ventilation for acute respiratory failure. Am J Respir Crit Care Med. 2000 Mar;161(3 Pt 1):807-13.

(54) Marvisi M, Brianti M, Marani G, Turrini G, Zambrelli P, Ajolfi C, et al. Acute antiarrhythmic effects of bi-level positive airway pressure ventilation in patients with acute respiratory failure

caused by chronic obstructive pulmonary disease: a randomized clinical trial. Respiration. 2004 Mar;71(2):152-8.

(55) Matic I, Sakic-Zdravcevic K, Jurjevic M. Comparison of invasive and noninvasive mechanical ventilation for patients with chronic obstructive pulmonary disease: Randomized prospective study. Period Biol. 2007;109(2):137-45.

(56) Matuska P, Pilarova O, Merta Z, Skrickova J. [Non-invasive ventilation support in patients with acute exacerbation of chronic obstructive pulmonary disease (COPD)]. Vnitr Lek. 2006 Mar;52(3):241-8.

(57) Pastaka C, Kostikas K, Karetsi E, Tsolaki V, Antoniadou I, Gourgoulianis KI. Non-invasive ventilation in chronic hypercapnic COPD patients with exacerbation and a pH of 7.35 or higher. Eur J Intern Med. 2007;18(7):524-30.

(58) Servillo G, Ughi L, Rossano F, Leone D. Non invasive mask pressure support ventilation in COPD patients. Intensive Care Med. 1994;40(S54).

(59) Thys F, Roeseler J, Reynaert M, Liistro G, Rodenstein DO. Noninvasive ventilation for acute respiratory failure: a prospective randomised placebo-controlled trial. Eur Respir J. 2002 Sep;20(3):545-55.

(60) Wood KA, Lewis L, Von HB, Kollef MH. The use of noninvasive positive pressure ventilation in the emergency department: results of a randomized clinical trial. Chest. 1998 May;113(5):1339-46.

(61) Zhou R, Chen P, Luo H, Xiang XD. [Effects of noninvasive positive pressure ventilation on gas exchange and patients' transformation in chronic obstructive pulmonary disease and respiratory failure]. Hunan Yi Ke Da Xue Xue Bao. 2001 Jun 28;26(3):261-2.

(62) Lightowler JV, Wedzicha JA, Elliott MW, Ram FS. Non-invasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of chronic obstructive pulmonary disease: Cochrane systematic review and meta-analysis. BMJ. 2003 Jan 25;326(7382):185.

(63) Chen J, Qiu D, Tao D. Time for extubation and sequential noninvasive mechanical ventilation in COPD patients with acute exacerbated respiratory failure who received invasive ventilation. Zhonghua Jie He He Hu Xi Za Ahi. 2001;1(24):99-100.

(64) Ferrer M, Esquinas A, Arancibia F, Bauer TT, Gonzalez G, Carrillo A, et al. Noninvasive ventilation during persistent weaning failure: a randomized controlled trial. Am J Respir Crit Care Med. 2003 Jul 1;168(1):70-6.

(65) Girault C, Daudenthun I, Chevron V, Tamion F, Leroy J, Bonmarchand G. Noninvasive ventilation as a systematic extubation and weaning technique in acute-on-chronic respiratory failure: a prospective, randomized controlled study. Am J Respir Crit Care Med. 1999 Jul;160(1):86-92.

(66) Hill NS, Lin D, Levy M, O'Brien A. Noninvasive positive pressure ventilation (NPPV) to facilitate extubation after acute respiratory failure: a feasibility study. Am J Respir Crit Care Med. 2000;161:B18.

(67) Rabie GM, Mohamed AZ, Mohamed R. Noninvasive ventilation in the weaning of patients with acute-on-chronic respiratory failure due to COPD. Chest. 2004;126:755S.

(68) Wang X, Due X, Zhang W. Observation of the effect and the time for extubation and sequential noninvasive mechanical ventilation in COPD patients with exacerbated respiratory failure who received invasive ventilation. Shandong Medical Journal. 2004;44(7):4-6.

(69) Zheng R, Liu L, Yang Yi, et al. Prospective randomized controlled clinical study of sequential non-invasive following invasive mechanical ventilation in patients with acute respiratory failure induced by COPD. Chinese J Emerg Med. 2005;14(1):21-5.

(70) Zou SH, Zhou R, Chen P, Luo H, Xiang XD, Lu YD, et al. [Application of sequential noninvasive following invasive mechanical ventilation in COPD patients with severe respiratory failure by investigating the appearance of pulmonary-infection-control-window]. Zhong Nan Da Xue Xue Bao Yi Xue Ban. 2006 Feb;31(1):120-4.

(71) Esteban A, Ferguson ND, Frutos-Vivar F, et al. Non-invasive positive pressure ventilation does not prevent reintubation and may be harmful in patients with post-extubation respiratory distress: results of a randomized controlled trial. Am J Respir Crit Care Med. 2003;167(7 Suppl):A301.

(72) Keenan SP, Powers C, McCormack DG, Block G. Noninvasive positive-pressure ventilation for postextubation respiratory distress: a randomized controlled trial. JAMA. 2002 Jun 26;287(24):3238-44.

(73) Luo H, Cheng P, Zhou R. [Sequential BiPAP following invasive mechanical ventilation in COPD patients with hypercapnic respiratory failure]. Hunan Yi Ke Da Xue Xue Bao. 2001 Dec 28;26(6):563-5.

(74) Nava S, Gregoretti C, Fanfulla F, Squadrone E, Grassi M, Carlucci A, et al. Noninvasive ventilation to prevent respiratory failure after extubation in high-risk patients. Crit Care Med. 2005 Nov;33(11):2465-70.

Health Quality Ontario
130 Bloor Street West, 10th Floor
Toronto, Ontario
M5S 1N5
Tel: 416-323-6868
Toll Free: 1-866-623-6868
Fax: 416-323-9261
Email: MASinfo@hqontario.ca
www.hqontario.ca

ISSN 1915-7398 (online)
ISBN 978-1-4435-7014-5 (PDF)