



Early View

Task Force Report

European Respiratory Society Guideline on Long-term Home Non-Invasive Ventilation for Management of Chronic Obstructive Pulmonary Disease

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European Respiratory Society Guideline on Long-term Home Non-Invasive Ventilation for Management of Chronic Obstructive Pulmonary Disease

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Take home message

Managing hypercapnia may be an important intervention for improving the outcome

of COPD patients with chronic respiratory failure. This ERS Task Force suggests the application of long-term home non-invasive ventilation to improve health outcomes by targeting a reduction in carbon dioxide in COPD patients with persistent hypercapnic respiratory failure.

Abstract

Background

While the role of acute non-invasive ventilation (NIV) has been shown to improve outcome in acute life-threatening hypercapnic respiratory failure in chronic obstructive pulmonary disease (COPD), the evidence of clinical efficacy of long-term home NIV (LTH-NIV) for management of COPD is less. This document provides evidence-based recommendations for the clinical application of LTH-NIV in chronic hypercapnic COPD patients.

Materials and methods

The European Respiratory Society Task Force (TF) committee was composed of clinicians, methodologists and experts in the field of LTH-NIV. The committee developed recommendations based on the GRADE (Grading, Recommendation, Assessment, Development and Evaluation) methodology. The GRADE Evidence to Decision framework was used to formulate recommendations. A number of topics were addressed under a narrative format which provides a useful context for clinicians and patients.

Results

The TF committee delivered conditional recommendations for four actionable PICO (target population-intervention-comparator-outcome) questions, (1) suggesting for

the use of LTH-NIV in stable hypercapnic COPD; (2) suggesting for the use of LTH-NIV in COPD patients following a COPD exacerbation requiring acute NIV (3) suggesting for the use of NIV settings targeting a reduction in carbon dioxide and (4) suggesting for using fixed pressure support as first choice ventilator mode.

Conclusions

Managing hypercapnia may be an important intervention for improving the health outcome of COPD patients with chronic respiratory failure. The TF conditionally supports the application of LTH-NIV to improve health outcome by targeting a reduction in carbon dioxide in COPD patients with persistent hypercapnic respiratory failure. These recommendations should be applied in clinical practice by practitioners that routinely care for chronic hypercapnic COPD patients.

Introduction

Scope and purpose

Non-invasive ventilation (NIV) is increasingly being used as a long-term treatment in patients with hypercapnic chronic respiratory failure (CRF) due to various conditions [1,2]. While the role of acute NIV has been shown to improve outcome in acute life-threatening hypercapnic respiratory failure due to chronic obstructive pulmonary disease (COPD) exacerbations, the evidence of clinical efficacy of long-term home NIV (LTH-NIV) for management of COPD with hypercapnic CRF

is less [3]. Thus, there is an ongoing discussion on whether LTH-NIV should be used in COPD patients or not [4]. For this reason, the European Respiratory Society (ERS) created a Task Force (TF) to develop guidelines aimed at providing evidence-based recommendations on the application of LTH-NIV in CRF for patients with hypercapnic COPD.

Materials and methods

TF panel composition

The TF panel consisted of 15 clinical experts in the field of NIV and one clinical practice physiotherapist from ERS Assembly 2 Respiratory Intensive Care, one clinician representing ERS Assembly 4 Sleep and Breathing Disorders; and Clinical Physiology, one ERS methodologist (TT) and two clinician-methodologists (BR, SO) with experience in evidence synthesis and guideline development using GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) methodology. During evidence to decision process, a representative (JB) from European Lung Foundation (ELF) provided COPD patient's perspective from the findings of their home mechanical ventilation survey [5].

Conflict of Interest Policy

The TF panel members signed a confidentiality agreement and disclosed all potential

financial conflicts of interest in accordance with ERS policy.

Question Generation

An initial list of PICO (target population-intervention-comparator-outcome) questions was developed by the TF chairs (RS, WW), which was discussed and prioritized in detail by TF members considering the clinical importance, availability of evidence, and patient perspectives. PICOs were then finalized at the September 2017 TF meeting at the ERS conference in Milan. The TF selected six questions for the guideline to address, four PICO questions (Table 1), and two descriptive questions to be addressed in a narrative format, which the TF believed would provide useful contextual for clinicians and patients.

Evidence summary and generation of clinical recommendations for PICO questions

Following the GRADE procedure, the TF rated each outcome for its perceived importance for clinical decision-making (from a patient perspective) on a scale of 1-9, with mean scores of 7-9 indicating a 'critical' outcome, 4-6 indicating 'important but not critical' and 1-3 indicating 'not important' [6]. The panel identified five 'critical' outcomes, which would take priority in guideline decision-making for all PICO questions: mortality (short-term and long-term), hospitalization, COPD exacerbation, dyspnea, and health-related quality of life (HRQL). Data on non-critical outcomes (gas exchange, lung function, exercise tolerance, sleep quality) were also

collected and considered, however not prioritized in recommendation generation.

For the four PICO questions, the two methodologists (SO, BR) conducted searches of the medical literature with the assistance of a medical librarian, drawing upon and updating literature searches for each PICO question from existing systematic reviews on the topic of LTH-NIV in COPD [7-9]. Medline, Embase, Cochrane CENTRAL, CINAHL, and Web of Science were searched from January 2014 to January 2018 for English-language randomized controlled trials (RCTs) addressing the PICO questions. The search was updated in January 2019. The two methodologists screened the retrieved references for inclusion in the evidence summaries (Supplementary figure 1).

Data from retrieved studies was entered into Revman v.5.3 software. For each PICO, the methodologists, with input from the TF chairs, developed an evidence profile. Following GRADE principles, the TF rated the certainty of evidence for each outcome as 'high,' 'moderate,' 'low,' or 'very low.' The TF initially categorized the certainty of evidence for each outcome as high if it originated from RCTs and low if it originated from observational data. The quality of the evidence was subsequently downgraded by one or two levels if results from individual studies were at serious or very serious risk of bias [10], there were serious inconsistencies in the results across studies [11], the evidence was indirect [12], the data were imprecise [13], or publication bias was thought to be likely.

The TF developed recommendations for each PICO question by working

through the GRADE Evidence to Decision Framework (EtD), which considers the quality of evidence, balance of desirable and undesirable effects, patient values and preferences, resource use, health equity, acceptability of an intervention, and feasibility of implementation [14,15]. Each recommendation was designated as "strong" or "conditional," using the phrasing "we recommend" for strong recommendations and "we suggest" for conditional recommendations [16]. Direction and strength of recommendations was decided by consensus at an in-person meeting September 17, 2018 at the ERS International Congress in Paris.

Manuscript preparation

Following the generation of recommendations, the TF divided up into working groups, which for each PICO question summarized the recommendation, provided a narrative summary of the evidence (highlighting the largest and most relevant clinical trials for each PICO question), issues raised in the EtD framework, and a justification for the final recommendation considering the above, along with implementation considerations and future research directions. Editing and feedback on the manuscript was conducted electronically, and coordinated by the TF chairs. The final wording of all recommendations and justifications was agreed upon the entire TF, and the final manuscript was submitted to the ERS for review and approval.

How to use these guidelines

Due to limitations in the certainty of the available evidence, all four PICO recommendations are weak/conditional, and therefore require consideration of individual preferences, resource considerations, technical expertise, and clinical circumstances prior to implementation in clinical practice. While we have tried to consider a wide spectrum of such factors when making recommendations, we cannot account for all conditions. For each recommendation, we discuss evidence limitations, issues when moving from evidence to recommendations, and implementation concerns. By reading these guidelines, and considering their applicability to their current situation, we hope these ERS guidelines will help patients, clinicians, policy makers, and other health-care stakeholders to make rational, evidence-based, decisions with regard to the use of LTH-NIV in COPD, across a variety of settings. In table 2, we provide a high-level summary of how these guidelines can be applied [17,18].

Results

Evidence summaries (including forest plots from meta-analyses) and EtD tables for each PICO can be found in Supplementary Material 1.

PICO Question 1: Should LTH-NIV be used in stable patients with COPD as compared to not using NIV?

Recommendation: The ERS TF suggests LTH-NIV be used for patients with chronic stable hypercapnic COPD (conditional recommendation, low certainty evidence).

Background: COPD can cause both hypoxemic and hypercapnic CRF resulting in a high impact on mortality and economic burden of disease [19,20]. So far, long-term oxygen therapy (LTOT), which has been shown to improve survival, is the standard of care in COPD patients with hypoxemic CRF. COPD patients with chronic hypercapnia are more likely to be admitted to hospital, and once admitted experience a more rapid clinical deterioration [21,22]. The presence of hypercapnia has been shown to be a determinant of mortality [23-25].

Correcting hypercapnia may be an important intervention aiming at improving the prognosis of these patients. NIV in this setting is increasingly being used [26,27]. The favorable impact of the reduced lung hyperinflation on respiratory muscles workload and the increased ventilatory chemo-sensitivity to carbon dioxide have been demonstrated as the main mechanisms that may explain the effectiveness of NIV in stable hypercapnic COPD patients [28-30].

Many patients with advanced COPD have severe comorbidities (most importantly cardiovascular diseases), which independently impact their

prognosis. Therefore, improving survival in hypercapnic COPD patients is challenging. The inconsistent results evident between early studies [26] are likely due to a number of factors, including heterogeneous patient populations (including different degrees of hypercapnia), different NIV ventilators, varied ventilator settings and interfaces, wide range of NIV application time and patient's compliance.

In 2009, McEvoy et al. randomized 144 severe hypercapnic COPD patients either to NIV+LTOT or LTOT alone and demonstrated a slight survival benefit with NIV (median 28 months vs 20.5 months), but decreased HRQL [31]. The mean inspiratory positive airway pressure (IPAP) was 13 cmH₂O and the mean expiratory positive airway pressure (EPAP) was 5 cmH₂O, which corresponded to an inspiratory pressure support (PS, difference between inspiratory and expiratory pressures) of 8 cmH₂O. There was no decrease in partial pressure of carbon dioxide in arterial blood (PaCO₂) level during follow-up. Subsequent clinical observation studies and randomized cross-over clinical trials reported that targeting maximal reduction of carbon dioxide by high inspiratory pressures and high back-up rates, or so called high-intensity NIV, improved gas exchange, lung function and respiratory muscle function [32-35]. A multicentre RCT included 195 patients with stable chronic hypercapnia (mean PaCO₂ 59mmHg in the NIV group and 58mmHg in the control group) and randomized patients to either LTOT alone or LTH-NIV in addition to LTOT ventilation targeting carbon dioxide reduction (mean IPAP of 22cmH₂O with a mean EPAP of 5 cmH₂O employed to decrease PaCO₂ by at least 20% from baseline

or to achieve $\text{PaCO}_2 < 48\text{mmHg}$). Results showed a 1-year survival benefit in patients randomized to LTH-NIV with an increase in HRQL [36].

Long-term prognosis following hospitalization in COPD is poor, with 5-year mortality rates of around 50% [37]. Therefore, one of the overall goals in the management of COPD is to minimize the number of disease-related hospitalizations, especially in those patients at high risk of developing hypercapnic acute respiratory failure (ARF). LTH-NIV, initiated when the patient is in stable condition, may reduce the number of future hospitalizations in these patients. Clini et al. reported that overall hospital admissions were lower in patients randomized to NIV and LTOT as compared with LTOT alone (-45% vs + 27%) [38]. In the study by Köhnlein et al., a decrease in emergency hospital admissions was observed in the NIV group when compared to the control group (2.2 and 3.1 exacerbation/patient/year, respectively) [36].

Evidence Summary: Overall 13 RCTs (Comparators to NIV are shown in the appendix) evaluated the effect of LTH-NIV on survival in stable hypercapnic patients with COPD; pooled analysis showed that NIV may have little effect on mortality (relative risk [RR] 0.86, 95% confidence interval [CI] 0.58-1.27, low certainty) [31,36,38-48] or hospitalizations (mean difference [MD] 1.26 fewer hospitalizations, 95% CI 0.08-2.59, low certainty) [36,38,49].

Although the presence of hypercapnia is one of the primary indicators to

prescribe LTH-NIV in COPD, data suggest only a limited effect of NIV on this outcome. The pooled data over 12 RCTs showed that PaCO₂ decreased by 3.37mmHg (95% CI 0.99 lower to 5.75 lower, moderate certainty) and partial pressure of oxygen in arterial blood (PaO₂) increased by 3.09mmHg (95% CI 1.45 higher to 4.74 higher, moderate certainty) following NIV therapy [31,36,39,41,43-50]. This minimal effect may be due to the fact that ventilator settings were not titrated to target normal PaCO₂ levels. In a subgroup analysis of 5 RCTs in which NIV was used to target normal PaCO₂ levels, the PaCO₂ decrease was larger (4.92mmHg reduction, 95% CI 2.90 lower to 6.94 lower) [36,39,46-48]. There was no effect of NIV upon lung function as assessed by forced expiratory volume in one second (FEV₁) (standardized mean difference [SMD] 0.07 higher, 95% CI 0.14 lower to 0.27 higher, low certainty) or forced vital capacity (FVC) (SMD 0.10 higher, 95% CI 0.06 lower to 0.26 higher, low certainty) [31,36,38,39,41,44,46-48,50].

Dyspnea, exercise capacity, and HRQL are recognized as the most important patient-centered outcomes in COPD population. Pooled analysis of 5 RCTs shows that NIV may decrease dyspnea scores (SMD 0.51 lower, 95% CI 0.06 lower to 0.95 lower, moderate certainty) [39,43,46,47,50]. NIV may improve exercise capacity and outcomes of pulmonary rehabilitation by resting chronically fatigued respiratory muscles, ameliorating lung mechanics, and daytime gas exchange [39]. Pooled analysis demonstrated an improvement in 6-minute walk distance (6MWD) (MD 32.03 meters, 95% CI 10.79 to 53.26 meters, moderate certainty), which was higher

than minimal important difference (26 meters) for severe COPD, in those using NIV [36,38,39,41,45-47,49-52].

Seven RCTs evaluated HRQL with a follow-up period ranging between 3 to 12 months; the pooled analysis demonstrated that HRQL was higher with NIV (SMD 0.49 higher, 95%CI 0.01 lower to 0.98 higher, very low certainty) [31,36,39,43,46,47,50]. Included studies had to use one of the multiple validated scales/questionnaires in this population to assess HRQL. Whether NIV using high inspiratory pressure support values might be associated with higher HRQL remains unclear. In the multicenter study of Köhnlein et al, Severe Respiratory Insufficiency (SRI) Questionnaire summary scale score, general health perception subscale of Short Form 36 (SF-36) and St. George Respiratory Questionnaire (SGRQ) summary score improved more with NIV than with LTOT alone [36].

The effect of LTH-NIV on sleep quality has been studied to a lesser extent and only based on subjective assessments. Pooled analysis suggested sleep efficiency was slightly lower in those randomized to NIV (SMD 0.55 lower, 95% CI 1.13 lower to 0.03 higher, low certainty), but the clinical relevance of this is unclear due to heterogeneous measurements of sleep [38,41,46]. Minor adverse events such as discomfort, skin damage, or rash were more common with NIV therapy (RR 10.35 95% CI 2.45-43.71, low certainty) when compared to LTOT alone. However, most of these effects are interface-related and may be straightforward to manage [53,54].

Justification: The guideline panel decided on a conditional recommendation for NIV in the setting of stable chronic hypercapnic COPD patient. This recommendation was based on the evidence suggesting improvements in HRQL, dyspnea, and exercise tolerance. Even though the certainty in evidence for these outcomes was low to moderate, all were felt to be very important to patients. The evidence also suggested the possibility of small reductions in mortality and hospitalizations, with LTH-NIV, though there was significant imprecision in the pooled effects. Overall, the benefits were felt to outweigh the potential harms including minor adverse events.

In terms of costs, frequent exacerbations and hospital readmissions account for the greatest part of economic burden in COPD patients, and economic data from the included trials suggest that NIV is cost-effective, especially in patients with frequent exacerbations and hospital admissions. Historically, LTH-NIV has been shown to reduce disease-related cost by decreasing the rate of outpatient visits, the hospital admissions, and the length of stay in the hospital [55]. The overall cost-effectiveness of NIV therapy depends on further variables such as strategy for initiating NIV and close monitoring and follow-up including home care. LTH-NIV has evolved over the last 20 years and today's technology gives us the opportunity to monitor, even remotely, many physiological parameters by built-in software systems of NIV devices [56]. While in higher developing countries there has been a widespread use of LTH-NIV, in the countries with lower income economies, financial constraints may be a major limiting factor for patients who may benefit of LTH-NIV,

including those with stable COPD [57].

PICO Question 2: Should LTH-NIV be used after an episode of acute hypercapnic respiratory failure in patients with COPD as compared to not using NIV?

Recommendation: The ERS TF suggests LTH-NIV be used in patients with COPD following a life-threatening episode of acute hypercapnic respiratory failure requiring acute NIV, if hypercapnia persists following the episode (conditional recommendation, low certainty evidence).

Background:

Severe COPD patients with chronic hypercapnia are most likely to experience re-hospitalization after a life-threatening episode of acute on chronic respiratory failure. These so-called "revolving doors" patients, are often discharged with a PaCO₂ above 55 mmHg after a decompensated or compensated episode of respiratory acidosis due to COPD exacerbation on the background of at least two hospital admission episodes in the previous year [55,58].

Four RCTs have evaluated the use of LTH-NIV after acute hypercapnic respiratory failure (AHRF) [59-62]. The first clinical trial randomized 40 patients with severe stable COPD (PaCO₂ ≥55 mm Hg) after hospital discharge from AHRF to NIV or standard treatment for 2 years. The use of NIV was not associated with a

reduction in mortality but improved several physiological (e.g. arterial PaCO₂ and PaO₂, 6MWD, mean pulmonary artery pressure), patient-centered (e.g. anxiety, depression, dyspnea) and healthcare centered (e.g. hospitalization rates) outcomes [59]. The second trial was a pilot RCT designed to compare continuation of NIV from hospital to home, with sham continuous positive airway pressure (CPAP) used as control, in severe COPD patients who had survived an acute episode treated with NIV and showed persistent hypercapnia at discharge (mean PaCO₂ ~50 mmHg). A total of 47 patients were randomized and the proportion of patients developing an acute exacerbation during the time course of the study was statistically higher in the CPAP group. Of note, 8/23 (35%) of the LTH-NIV patients were withdrawn from the study before completion [60].

Two larger RCTs investigated the clinical efficacy of NIV as a bridging treatment from hospital to the home following a life-threatening exacerbation of COPD requiring acute NIV. In the RESCUE trial, 201 COPD patients admitted to hospital with a life-threatening episode of AHRF and prolonged hypercapnia (mean PaCO₂ ~48 mmHg) greater than 48 hours after termination of ventilatory support were randomized to NIV in addition to LTOT or LTOT alone. After one year, there was no difference between the two groups in the primary outcome of time to readmission or death. Although NIV was effective in reducing daytime and nighttime PaCO₂, a similar reducing in PaCO₂ was observed in the control group [61].

The HOT-HMV trial studied 116 COPD patients with persistent hypercapnia ($\text{PaCO}_2 > 53 \text{ mmHg}$) at 2 to 4 weeks after a life-threatening episode of acute on chronic respiratory failure treated with acute NIV, were randomized to receive LTH-NIV, in addition LTOT, or LTOT alone. The NIV+LTOT group, compared to the LTOT group, resulted in an increased time to readmission or death within 12 months (4.3 months vs. 1.4 months) [62].

It is difficult to translate the results from the earlier studies into advice for the practicing clinician due to the small sample sizes, lack of standard definition of acute COPD exacerbation, and lower pressure support levels compared to the later studies. However, major clinical interest was raised by the latter trials, which despite similar trial design and primary outcome measure had differing results in terms of admission-free survival. It is likely that the higher level of PaCO_2 at enrolment (mean 48 mmHg vs. 53 mmHg), the higher exacerbations rate prior to enrolment and the timing selection of patients with persistent hypercapnia at 2-4 weeks following a life-threatening exacerbation were major determinants of the enhanced outcome in the HOT-HMV trial. Conversely, the early within-hospital assessment of hypercapnia in the RESCUE trial may have led to the inclusion of a subset of patients with spontaneously reversible hypercapnia who do not take benefits from LTH-NIV treatment and consequently a better prognosis. The trajectory of recovery of hypercapnia is likely to have an influence on the outcome and the timing of this recovery needs clarification [24].

Another RCT evaluated the effects of stopping NIV after 6 months post-hospitalization, finding that patients who remained hypercapnic after 6 months of therapy had clinical worsening and reduced 6MWD after stopping NIV, compared to those who continued, indicating the importance of careful selection of patients who will continue to benefit from LTH-NIV [63].

Evidence summary

Use of LTH-NIV after ARF was not associated with a reduction in mortality (RR 0.92, 95% CI 0.67 to 1.25, low certainty), but may reduce exacerbations (SMD 0.19 SD, 95% CI -0.40 to 0.01 SD, low certainty) and hospitalizations (RR 0.61, 95% CI 0.30 to 1.24, very low certainty) though the study by Cheung *et al*, at high risk of bias, and with unclear definition of acute exacerbation, makes interpretation of these outcomes difficult. Reassuringly, sensitivity analysis excluding Cheung *et al*. does not significantly affect the conclusions made for these outcomes. Similarly, NIV may be associated with improvements in dyspnea scores measured using Medical Research Council Dyspnea score (MD 0.8 points lower, 95% CI 2.17 lower to 0.58 higher, low certainty) and HRQL measured using SRI (MD 2.89 higher, 95% CI 1.03 lower to 6.8 higher) but these results are limited by imprecision and are of low certainty. NIV likely reduces PaCO₂ (MD -3.41 mmHg, 95% CI -4.09 to -2.73, moderate certainty).

Justification of recommendation

The recommendation was primarily based upon the desirable effects of LTH-

NIV after a life-threatening episode of acute on chronic respiratory failure, which suggest a small potential reduction in exacerbations and hospitalizations, though the overall certainty of evidence is low, primarily due to imprecision as well as reservations about the risk of bias. The TF considered indirect evidence from PICO Q1 with regard to minor adverse effects and resources required to help to inform the recommendations here, and noted that reassuringly similar desirable effects of NIV were seen in the COPD population both in stable (PICO 1) and in post-ARF phase (PICO 2), with few undesirable effects seen. Other outcome data from PICO Q1 was used for Q2 analysis or recommendation generation. Similarly the TF considered that the potential significant variability in values and trade-offs between mortality and HRQL with the use of NIV may play a role in shared decision-making about its use in this population, and ultimately the acceptability of NIV as an intervention. The TF considered the resources used similar to that in PICO Q1, though the feasibility of initiating NIV post-exacerbation may be higher, as in some centers clinical pathways exist post discharge to facilitate initiation of LTH-NIV. Considering all of the above in light of the limitations of the evidence, the TF panel chose to make only a conditional recommendation for the use of LTH-NIV after ARF. Lastly, there was discussion that patients may continue to improve for several weeks post-exacerbation; for this reason, reassessment of hypercapnia 2-4 weeks after the initial episode, as was done in the HOT-HMV trial, could be considered to identify those patients who are most likely to benefit from LTH-NIV.

PICO Question 3: When using LTH-NIV in COPD patients, should NIV settings be titrated to normalize or at least cause a significant reduction in PaCO₂ as compared to titrating not according to PaCO₂ levels?

Recommendation: The ERS TF suggests titrating LTH-NIV to normalize or reduce PaCO₂ levels in patients with COPD (conditional recommendation, very low certainty evidence).

Background: In the last two decades, a number of published RCTs aimed at exploring the role of LTH-NIV in those with hypercapnic COPD, however most did not specifically target normalization or significant reduction in PaCO₂ or directly address nocturnal alveolar hypoventilation. High-intensity NIV, a form of pressure-limited controlled ventilation, that combined stepwise titration of IPAP up to 30 cmH₂O with an high back up rate just below the patient's spontaneous breathing frequency, was introduced as a novel therapeutic option in an attempt to maximally decrease elevated PaCO₂ to normal levels and, at the same time, to achieve the total control of the patient's spontaneous respiratory activity aiming for substantial rest of the diaphragm [35,64,65]. Given to the greater capability of correcting nocturnal alveolar hypoventilation, high-intensity NIV has been reported to be more efficient in terms of clinical and physiological benefits (reduction of nocturnal and diurnal

PaCO₂ levels; improvement in FEV₁, patient-reported exercise-related dyspnea score, 6MWD and HRQL) than conventional "low-intensity" NIV. Paradoxically, delivery of higher levels of pressure support was associated with better compliance to the treatment, probably as consequence of a greater subjective benefits perceived by chronically symptomatic patients [64-67].

A strategy based on the combination of high pressure support levels and low backup rate –termed "high-pressure" NIV- has been shown to provide the same physiological and clinical improvement in stable hypercapnic COPD compared with "high-intensity" NIV, suggesting that the use of a high backup rate is not necessary to achieve these benefits in such patients [67]. However, the number of patients in this study was considerably small requiring further investigations.

In consideration of the greater hemodynamic impact of "high-intensity" NIV as compared to "low intensity" NIV - positive intrathoracic swing pressures-induced decrease in right heart preload and elevated lung volume-induced increase in pulmonary vascular resistance, detrimental cardiovascular effects (i.e. reduced cardiac output) could develop under very high IPAP levels in very selected phenotypes of COPD patients especially if pre-existing severe cardiovascular diseases coexist [64,65]. However, the clinical significance of these effects needs further evaluation. Although it appears that high inspiratory pressure NIV leads to a reduction in hypercapnia, the impact on some patient important outcomes, such as sleep quality, is less certain [66,67].

Finally, it should be considered that the definition of hypercapnia used amongst the studies targeting NIV to PaCO₂ normalization in stable hypercapnic COPD patients was quite different, sometimes with very low mean baseline PaCO₂ levels [61]. Independently from the baseline degree of hypercapnia, a normalization of elevated PaCO₂ levels is unlikely to be achieved in all COPD patients even under high IPAP levels.

Evidence Summary: Even if one short-term trial reported physiologic benefits of NIV targeted to reduce chronic hypercapnia, we did not find any long-term RCTs directly comparing LTH-NIV strategies targeting PaCO₂ reduction in those with chronic COPD versus those that did not. For this reason, to address this question, we considered subgroup analysis from PICO 1 comparing studies that targeted normalization of PaCO₂ as compared to studies that did not target normalization.

Pooled analysis of five RCTs demonstrated that while “high-intensity” NIV decreases PaCO₂ levels at 6 weeks (MD -4.93 mmHg, 95% CI -7.43 to -2.42, low certainty) as compared to “low-intensity” NIV, there was no effect on HRQL as assessed by the SRI (MD 0.95 points higher, 95% CI 8.33 lower to 6.42 higher, low certainty) in the “high intensity” subgroup [34,64-66]. There was no effect demonstrated with “high-intensity” NIV on FEV₁ (MD 0.04 L higher, 95% CI 0.34 lower to 0.42 higher, low certainty), 6MWD (MD 14 meters higher, 95% CI 70.42 lower to 98.42 higher, low certainty), sleep comfort measured by VAS scale (MD 1cm

higher, 95% CI 28.42 lower to 30.42 higher; very low certainty) or PaO₂ levels at 6 weeks (MD 3.4 mmHg higher, 95% CI 2.39 lower to 9.19 higher, low certainty).

Justification: The TF panel decided on a conditional recommendation for targeted reduction of PaCO₂ in COPD patients with persistent hypercapnic respiratory failure. Although the benefit was uncertain, this recommendation was driven by the minimal potential harms of targeted PaCO₂ reduction [64,65] though it is recognized that this is unlikely to be achieved in all patients. While there is low certainty of evidence of benefit, the anticipated harms have not been clearly demonstrated, and as such the panel felt the overall balance favored the intervention. Setting NIV to target a reduction in PaCO₂ may require more time spent in hospital [34], and therefore possibly increase costs and decrease feasibility of NIV, however, adherence was significantly better using this strategy.

PICO Question 4: When using LTH-NIV in COPD patients, should we use fixed pressure modes as compared to adaptive or auto-titrating pressure modes?

Recommendation: The ERS TF suggests using fixed pressure support mode as first-choice ventilator mode in patients with COPD using LTH-NIV (conditional recommendation, very low certainty evidence).

Background:

In general, classical modes of LTH-NIV comprise both pressure-targeted and volume-targeted NIV. During pressure-targeted NIV the inspiratory pressure is set, while the delivered inspiratory volumes vary according to the impedance of the respiratory system and the patient's respiratory efforts. In contrast, during volume-targeted NIV, a predetermined inspiratory volume is set, while inspiratory pressures are variable. Accordingly, the physiological advantage of volume-targeted NIV is the stability of tidal volume, while pressure-targeted NIV is advantageous regarding leak compensation when the inspiratory flow is increased in case of leak-related dropping pressure. Even though, physiological and short-term clinical studies indicate that pressure-targeted NIV is better tolerated due to less varying peak inspiratory pressures, both modes are reported to be comparably effective in providing non-invasive ventilation, though the majority of studies have investigated heterogeneous patient cohorts and not exclusively patients with COPD [68-75]. Long-term studies comparing currently available ventilator modes do not exist, limiting the potential for strong conclusions. However, nearly all studies providing evidence for the use of LTH-NIV in COPD in PICO Q1 and PICO Q2 used pressure-targeted modes rather than volume-targeting modes of NIV, making pressure volume modes the *de facto* standard in LTH-NIV for COPD.

Recent developments seek to combine the advantages of volume- and pressure-targeted NIV, while avoiding their disadvantages [76]. In addition, there is a

physiological rationale supporting the interest in continuously adapting ventilator parameters to fluctuating patient needs during the night and also over the long term. In addition, upper airway patency may vary with body position and sleep stage, especially during rapid eye movement (REM) sleep. Respiratory mechanics may also change as an individual's disease worsens over time. Ideally, LTH-NIV aims to deliver the adequate inspiratory pressure support to achieve targeted minute ventilation and sufficient expiratory pressure for complete stabilization of the upper airway.

The so called adaptive or auto-titrating modes have been designed to achieve these objectives even if applied with different software. There was also the hope that automatically identifying adequate settings for a given patient would allow implementation of NIV in non-specialized centers, thus favoring the widespread application of the technique. Conversely, there are certain complications and pitfalls related to these hybrid modes as depicted in detail elsewhere [76].

Evidence summary:

Six RCTs compared adaptive or auto-titrating pressure modes (eg. iVAPS™, Resmed, Australia; AVAPS™, Philips, US) to classical pressure support modes [77-82]. These studies were generally not blinded, and of short duration, prohibiting assessment of long-term outcomes such as mortality or hospitalizations. Six studies demonstrated that use adaptive or auto-titrating modes may result a small reduction

in PaCO₂ (MD 1.95 mmHg lower, 95% CI 4.29 mmHg lower to 0.40 mmHg higher, low certainty) and little to no difference in oxygenation (SMD -0.04, 95% CI -0.33 to 0.26, low certainty) compared to conventional NIV. Adaptive or auto-titrating modes did not significantly improve HRQL using the SGRQ or the SRI (SMD 0.28, 95% CI -0.66 to 0.10 SD, low certainty evidence), sleep quality measured using a variety of validated instruments (SMD -0.14, 95% CI -0.53 to 0.26 SD, very low certainty), or exercise tolerance (SMD -0.1, 95% CI -0.51 to 0.30, low certainty compared to conventional fixed modes of NIV).

Adherence to NIV was equivalent when comparing adaptive or auto-titrating modes to conventional assist modes in five studies [77-81]. Regarding patient-centered outcomes, no improvement in self-reported tolerance [78,80] or self-reported comfort [77,78] was achieved with the newer modes. One study used a specific questionnaire to assess acceptability, but again no difference was demonstrated [82].

Justification

While the pooled analyses suggests a small potential benefit to adaptive or auto-titrating modes in PaCO₂ reduction, and acceptable adherence, our recommendation is conditional for fixed modes owing to substantial uncertainty of the effects of adaptive or auto-titrating modes, and the heterogeneity across studies for algorithms, brands of devices and lack of detailed information regarding the way

adaptive modes function. Moreover, there is uncertain risk of harm with adaptive/auto-titrating modes when there is severe air leak, a common clinical scenario, as adaptive modes require the ventilator to accurately measure/estimate tidal volumes [76]. This raises safety concerns, as inappropriate low volumes could be delivered in this situation, resulting in hypoventilation. The short follow-up of the available trials means there is little data on this potentially serious risk. Furthermore, there may be substantial additional cost to patients to upgrade to a machine equipped with these newer ventilatory modes if a patient is already using an older ventilator; however for patients starting with new devices the costs may be similar.

Narrative Questions

1. Do other factors impact the effectiveness of LTH-NIV in COPD?

i. Patient related factors

Age and comorbidities

The impact of age of a patient on outcome of LTH-NIV has not been evaluated. Previous RCTs excluded patients above 75 or 80 years old [31,38,44], more recently studies have not made age exclusion criteria, however, the elderly consisted of a very small proportion of the eligible subjects and the average age was mid-sixties [36,61,62]. Köhnlein et al. excluded patients with “impaired general condition that could preclude regular follow-up visits” when evaluating survival benefit in stable COPD patients [36]. Borel et al., [83] in multivariate analysis of

prospective, observational, survey (213 subjects, oldest age patient 76 years old) showed that older age is independently associated with poorer prognosis. Age itself cannot be considered an exclusion criterion. However, associated mental and/or physical disability and a lack of sufficient help of care-givers may significantly impair the efficacy of LTH-NIV. This issue should be addressed by the providers.

All but one RCT [61] excluded subjects with comorbidities such as: malignancy, severe heart failure, obstructive sleep apnea syndrome (OSAS), obesity, unstable angina [31,36,38,44, 48, 60, 62, 63]. As a result, the studied population was very homogenous, pure COPD, so called "respiratory COPD" [84]. It is, therefore, difficult to answer whether the coexistence of the main COPD comorbidities has any impact on efficacy of LTH-NIV. However, the pathophysiological effect of airway positive pressure can provide additional positive outcomes in COPD patients with comorbidities, specifically, patients with pulmonary congestion or central apnea due to heart failure, hypoventilation in obese patients and OSAS. Borel et al. demonstrated better prognosis in obese subjects versus non-obese, moreover, the effect was independent on coexisting OSAS [83]. There was no benefit of the use of LTH-NIV in COPD patients with heart failure, however, it is worthy noticing that in the cohort of Borel et al. the proportion of subjects with heart failure; and hypertension was higher in the obese group with better prognosis than in the non-obese group with worse outcomes [83].

Cachexia is a frequent comorbidity in COPD and is associated with respiratory muscle atrophy-induced dysfunction [84]. Borel et al. found that lower body mass index (BMI) is independently associated with poorer prognosis [83]. The majority of RCTs average BMI was about 25 kg/m² and subjects with BMI <19 kg/m² practically were not enrolled. However, two RCTs on LTH-NIV after acute exacerbation, which enrolled subject with relatively low BMI 19 kg/m² [60] and 21 kg/m² [62], demonstrated significant prolongation of the time to readmission due to acute exacerbation. Finally, a previous study has demonstrated weight gain following NIV commencement, and this was particularly true for cachectic patients [85]. This suggests that cachectic COPD patients who usually suffer from severe dyspnea and weakness of the respiratory muscles may benefit from LTH-NIV .

In summary, comorbidities are not contraindications to LTH-NIV. Obese patients and patients with overlap syndrome (COPD+OSAS) make up the subgroup, which may benefit the most from LTH-NIV V. The initiation of LTH-NIV in patients with advanced COPD requires a high amount of motivation and cooperation and it is necessary to allow the patient sufficient time to adapt to NIV, especially when high inspiratory pressures are used [2].

Adherence

Adherence to therapy has a key role in the efficacy of LTH-NIV. However, there is no clear picture of the relationship between the number of hours per night

use and the outcomes [38]. Mean compliance in RCTs which showed survival benefits of LTH-NIV were 4.5 [31] and about 6h/d [36], respectively. However, McEvoy et al. found the survival advantage was found to be better in the per-protocol analysis (subjects with compliance > 4h/d, 60% of all) than in intention to treat analysis [31]. Conversely, Struik et al., found no correlation between number of hours of NIV per night and decrease in PaCO₂ [61]. One uncontrolled trial demonstrated that adherence higher than 5 h/d improves survival in obese, but not non-obese COPD patients [83]. Interestingly, authors found high adherence over 9 h/d was a marker of worse prognosis. One explanation is increased dependence on NIV is due to the worsening of the patient status. A minimum use of 5 hours per night was found to be needed to reach significant change in PaCO₂ after three months of treatment in the meta-analysis using individual patient's data of all studies on LTH-NIV [7]. In conclusion, 5 hours of NIV per day would be a reasonable target however if patients do not achieve this, they may still receive clinical benefit.

ii. Equipment related factors

Many technical details with home ventilators, masks, tubes and humidification can decrease tolerance, efficacy and produce secondary effects, affecting adherence to the treatment [1,86]. NIV can be delivered at home for COPD patients through nasal, oronasal, or full face mask. Although nasal masks offer greater patient comfort, they often have the problem of oral leaks especially during sleep, which in

turn influence alveolar ventilation and sleep quality [1]. Currently, prescribers in Europe reported using oronasal masks more often as alveolar ventilation is much better with these than nasal masks, especially when high IPAP levels are used [27,87,88]. Full-face masks can serve as a supplement or an alternative to existing ventilation masks in the event of problems with pressure ulcers. Patients with frequent cough or abundant secretions either chronically or during an exacerbation usually do not tolerate oronasal masks and may use a nasal mask temporarily. There is no evidence that a particular interface guarantees greater benefit from LTH-NIV, so the choice should be carefully tailored to the patient choice.

Home ventilators can be used with a single circuit ventilation system with vented masks. The advantage of single circuits is their lower weight compared to double circuit systems and simpler handling, which is particularly important at home.

Circuits with expiratory valves can be also used. The expiration valve is located within the tubing circuit or in the ventilator. In an experimental study, the use of active valve circuits was associated with more efficient PaCO₂ reduction when compared to leak port circuits [90], but it remains unclear how this is translated in clinical long-term application.

Ventilators without battery will be used when NIV is used for less time per 24 hours. If the patient uses it for a longer duration (approximately 12h / day depending on individual circumstances) a ventilator with internal battery should be considered.

However, upgrading to a device with an internal battery does incur a significantly greater cost and this added burden may not be feasible across a range of health systems with lower income economies. As a matter of fact, the ventilator-dependence threshold for transitioning to a device with an internal battery may be variable among the different countries [57].

Active humidification is sometimes suggested for NIV [91] as it may improve adherence and comfort, but there is not clear consensus on whether or not additional heat and humidity are always necessary when the upper airway is not bypassed, such as in NIV. Thus, it could be added if mucosal dryness becomes an issue. Two systems, active humidification through a heated humidifier (HH) and passive humidification through a heat and moisture exchanger (HME), are available for warming and humidifying gases. Use of an HME is not beneficial in patients on NIV with intentional leaks, as the patient does not exhale enough tidal volume to replenish heat and moisture to adequately condition the inspired gas. HME may add additional work of breathing and use of an HME increases dead space and PaCO₂ and may increase ventilatory requirements [92]. With HH and intentional leaks, aerosolize contaminated condensate may increase the risk for infection.

iii. Additional therapies

Supplemental oxygenation (LTOT+NIV)

Usually CRF in the course of COPD starts with hypoxemia and the first modality of treatment is LTOT, which improves survival [93]. The aim of oxygen therapy when added to LTH-NIV is to maintain the adequate oxygenation if this is not achieved by the correction of hypoventilation. The clinician needs to be aware that dose of oxygen which maintains oxygen saturation when awake can be insufficient during sleep with NIV.

Pulmonary rehabilitation

Pulmonary rehabilitation (PR) is a cost-effective treatment for patients with COPD with the associated benefits of improved HRQL and increased exercise capacity [94-96]. Studies showed an increase in exercise tolerance with the addition of NIV whilst exercising [97-101]. Unfortunately, according to recent systematic reviews and British Thoracic Society (BTS) guidelines the benefits from using NIV during exercise training as add-on treatment to PR in patients with COPD were unclear, probably because of insufficient pressures applied [102-105].

Conversely, the addition of nocturnal LTH-NIV to daytime PR in COPD stable patients is likely to give more benefits. Garrod and co-workers [43] performed the first study evaluating nocturnal NIV+PR to PR alone non hypercapnic or hypoxic patients. They showed arterial blood gas (ABG) values improved in the NIV+PR

group they also had a greater improvement in exercise tolerance and HRQL than PR alone. Duiverman et al. [106] compared PR to PR+NIV over 2 years in hypercapnic severe COPD in a RCT. PR+NIV improved HRQL, mood, dyspnea, ABG's, exercise tolerance and prevented as rapid decline of lung function. However, exacerbation frequency and mortality were not significantly different between groups. Coquart et al. [107] found home based PR in patients with NIV is feasible. They compared PR in patients on nocturnal CPAP, nocturnal NIV, LTOT or no additional equipment. They showed that the NIV group significantly increased walking distance when compared to the other conditions. Marquez-Martin and co-workers [50] performed a RCT over 12 weeks comparing groups allocated to either PR, NIV and PR+NIV. Patients reportedly received 6-8 hours per night of NIV. There were improvements in exercise capacity for the PR and PR+NIV groups but not the NIV group alone. There were improvements in ABG's for the NIV and NIV+PR groups and the improvement were greater in the NIV+PR group.

There is a lack of data on enhancing of LTH-NIV by PR; however, the addition of PR to nocturnal NIV in COPD may have potential benefits of increasing exercise capacity and HRQL.

Strategies to manage bronchopulmonary secretions

Consideration may be given to the use of airway clearance techniques for patients with COPD in both acute and stable disease, however current studies

suggest that the benefits achieved may be small [108]. Airway clearance techniques in COPD patients may decrease hospitalizations [109]. It is logical that being free of secretions would help with adherence to NIV as there would be less coughing which can be a barrier to the use of ventilatory support. Moreover, being secretion free reduces the resistance of airways, and consequently improves ventilation, which may also contribute to improvements in ABG's. Mechanical insufflation-exsufflation devices are used in patients with NIV. There is no evidence that these devices increase cough effectiveness in patients with COPD [110], unless they have respiratory muscle weakness. However, no studies have compared LTH-NIV versus LTH-NIV and airway clearance techniques in patients with COPD.

Mucolytics are potentially useful for the management of COPD in patients that have tenacious secretions. A Cochrane review [111] and meta-analysis [112] found that mucolytic therapy led to an increase possibility of being exacerbation free compared to placebo. However, due to much heterogeneity between the studies, these data should be interpreted with caution. More recently, a European Respiratory Society/American Thoracic Society guideline [113] recommends an oral mucolytic in patients with moderate to severe airflow obstruction and exacerbations despite optimal inhaled therapy. No studies have compared LTH-NIV versus LTH-NIV and mucolytics in patients with COPD. However, it would seem reasonable to treat patients who complain of secretion retention to prevent secretions being a barrier to LTH-NIV in COPD.

2. How can clinicians monitor and follow-up patients during LTH-NIV?

The recommendation of using high inspiratory pressure levels in COPD receiving LTH-NIV is to achieve a substantial decrease in PaCO₂. The key thing is to document a reduction in PaCO₂ during NIV. More sophisticated monitoring should be reserved for cases when expected results with NIV are not achieved. In a recent preliminary study, pressure titration with simplified methods in a cohort of COPD-OSAS overlap patients achieved similar clinical effectiveness in terms of change in 3-month daytime PaCO₂, HRQL and sleep quality compared to polysomnography-based pressure titration [114].

The American Sleep Association recommends for the follow-up the assessment of clinical symptoms and an analysis of oxygenation and PaCO₂ values during wakefulness and quiet breathing [115]. The outpatient control, with associated cost savings is possible following a strict protocol based on symptoms, ABG assessment, and simple monitoring tools [116]. Clinical evaluation should be focused on symptoms of nocturnal hypoventilation and discomfort with the device [1].

Nocturnal gas exchange monitoring (continuous oxygen saturation and transcutaneous PCO₂ (PtcCO₂) measure) is common in clinical practice [1,61,62, 117,118]. Since home-ventilated COPD patients often receive oxygen therapy with NIV negating the usefulness of oxygen saturation with pulse oximetry (SpO₂)

monitoring for detecting nocturnal hypoventilation. On the other hand, isolated values of daytime PaCO₂ cannot rule out nocturnal hypoventilation, particularly in neuromuscular patients [119]. Nocturnal monitoring with PtcCO₂ allows detecting nocturnal hypoventilation as there is minimal drift with modern devices [120]. In the recent HOT-HMV trial, there was a statistically significant reduction in nocturnal PtcCO₂ levels on the night after initiation of noninvasive ventilation, which reportedly persisted to 12 months [62]. Finally, uncontrolled nocturnal hypoventilation seems to be related to increased risk of exacerbations and pulmonary hypertension [121]. End tidal carbon dioxide monitoring should never be used to approximate PaCO₂ in patients with COPD during spontaneous breathing or NIV and is even less reliable in patients with invasive ventilation [122,123]

In recent years, improvements introduced by manufacturers in their models have led these devices to act both as ventilators and monitors. Data stored in the internal memory of such devices provide information about compliance, pattern of usage, respiratory rate, percentage of patient triggered breaths, leakage, and in some models, "breath to breath" display of pressure and flow time waveforms. Changes in some of the recorded parameters (eg. respiratory rate and patient triggered breaths) in the preceding days have been able to predict exacerbations in COPD patients receiving LTH-NIV [124]. In addition, some manufacturers have developed algorithms for automatic estimation of leaks and residual upper airway obstructions (UAO). Residual UAO is common in patients undergoing nocturnal NIV

[125] and their lack of correction has been associated with increased mortality in amyotrophic lateral sclerosis patients [126]. UAO estimation by algorithms showed reasonable accuracy compared with PSG and manual scoring [127]. For the near future, technical advances in this field would allow to integrate them in telemedicine programs, although specific studies in COPD home ventilated patients are lacking. Interestingly, telemonitoring added to standard care did not alter time to next acute hospital admission, increase hospital admissions and home visits overall, and did not improve HRQL in a cohort of patients with CRF in a randomized crossover trial [128].

Finally, patient-ventilator asynchrony (PVA) may occur during the night. Theoretically, these events can compromise the effectiveness of the ventilation, but their importance remains unknown, mainly for two reasons: the absence of validated guidelines containing the classification of PVA and the scoring procedure in home mechanically ventilated patients, and the limited number of studies addressing this issue, with conflicting results. In a small cohort of COPD patients receiving NIV at home, the adjustments directed towards the decrease in PVA improved morning breathlessness [129]. However, in another study PVA has been demonstrated to have no impact on overnight gas exchange during set-up of LTH-NIV [130].

In summary, monitoring of COPD patients on LTH-NIV is focused on the control of nocturnal hypoventilation with overnight CO₂ monitoring. Further research on patient ventilator interactions is needed.

Conclusion

The TF developed actionable recommendations for 4 PICO questions, and narrative summaries for 2 other questions. These recommendations are accompanied by discussions of implementation considerations and suggestions for future research (Table 3).

This clinical practice guideline was produced using comprehensive GRADE methodology. Each PICO question was informed by a comprehensive systematic review and certainty of evidence evaluated in order to guide discussion. Recommendation generation was performed using the Evidence-to-Decision process to ensure all relevant considerations were incorporated. One limitation in this guideline is the lack of patient input for PICO questions and outcome prioritization. Despite this, the TF panel specifically tried to focus and prioritize patient-centered outcomes from available literature data, such as dyspnea, quality of sleep and HRQL and use these outcomes to drive recommendation generation. Given the limitations of the evidence, decisions about implementing LTH-NIV in COPD for many patients will depend upon resource constraints— whether or not NIV is funded by insurers, whether acclimation takes place in hospital or a sleep lab, etc. The feasibility of these recommendations may thus vary across health systems.

Our recommendations, based on the best available evidence, can guide the

management of chronic hypercapnic respiratory failure in COPD patients aimed at improving patient outcomes. However, they should be interpreted as conditional recommendations and should be implemented based on patient-related factors, including individual values and preferences. Adequately designed and executed RCTs that properly measure and report all patient-important outcomes are still needed. We anticipate significant progress in the field of LTH-NIV in the forthcoming years and as such these recommendations will require re-evaluation in the future.

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Table 1. Recommendations for PICO (target population-intervention-comparator-outcome) questions.

Question	Recommendation
Should LTH-NIV be used in stable patients with COPD as compared to not using NIV?	The ERS TF suggests LTH-NIV be used for patients with chronic stable hypercapnic COPD (conditional recommendation, low certainty evidence).
Should LTH-NIV be used after an episode of acute hypercapnic respiratory failure in patients with COPD as compared to not using NIV?	The ERS TF suggests LTH-NIV be used in patients with COPD following a life-threatening episode of acute hypercapnic respiratory failure requiring acute NIV, if hypercapnia persists following the episode (conditional recommendation, low certainty evidence).

<p>When using LTH-NIV in COPD patients, should NIV settings be titrated to normalize or at least cause a significant reduction in PaCO₂ as compared to titrating not according to PaCO₂ levels?</p>	<p>The ERS TF suggests titrating LTH-NIV to normalize or reduce PaCO₂ levels in patients with COPD (conditional recommendation, very low certainty evidence).</p>
<p>When using LTH-NIV in COPD patients, should we use fixed pressure modes as compared to adaptive or auto-titrating pressure modes?</p>	<p>The ERS TF suggests using fixed pressure support mode as first-choice ventilator mode in patients with COPD using LTH-NIV (conditional recommendation, very low certainty evidence).</p>

COPD: Chronic obstructive pulmonary disease, LTH-NIV: Long-term home noninvasive ventilation, PaCO₂: Partial pressure of carbon dioxide in arterial blood, ERS TF: European Respiratory Society Task Force.

Table 2. Reproduced from Reference 14.

	Strong recommendation	Weak recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and	Different choices are likely to be appropriate for different patients and therapy should be tailored to the individual patient's circumstances. Those circumstances may include the patient or family's values and preferences.

	preferences.	
For policy-makers	The recommendation can be adapted as policy in most situations including for the use as performance indicators.	Policy making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place.

Table 3. Future high-priority research questions.

<p><i>PICO 1</i> <i>LTH-NIV in chronic stable hypercapnic COPD</i></p>	<p>Strategies for initiating NIV. It is obvious that ventilator setting and acclimatization to NIV are crucial for effectiveness, including better adherence. NIV may be initiated in the hospital or at home. In-hospital initiation can be easily performed in some centers; however, it is more expensive and complex.</p>
	<p>The benefits of NIV in subgroups of patients with COPD. The variability of both adherence and treatment response may vary according to different clinical phenotypes. Indeed, it seems that the response is better in those patients with PaCO₂ > 50mmHg and PaCO₂ reduction to normal following NIV. A phenogrouping strategy of hypercapnic COPD subgroups is needed for better defined the populations to be prioritized in further studies.</p>
	<p>The impact of comorbid conditions in this population e.g. the effect of obesity, OSA-overlap, cardiovascular diseases, and clinical frailty upon clinical outcome.</p>

	<p>Assessment of other underestimated factors, such as lack of social support and patient-ventilator asynchrony, which may impact the effectiveness of LTH-NIV.</p>
	<p>Cost effectiveness studies reporting the health economic value of LTH-NIV in chronic stable COPD.</p>
<p><i>PICO 2</i> <i>LTH-NIV in COPD following an episode of acute hypercapnic respiratory failure</i></p>	<p>Developing more accurate criteria for identifying patients who are likely to benefit from LTH-NIV, such as severity of illness (hypothesis that treatment of higher PaCO₂ at initiation will drive greater clinical benefits), trajectory of hypercapnia recovery after exacerbation (as some patients return to eucapnia more rapidly than others) and treatment response (e.g. early reduction in PaCO₂ level after starting LTH-NIV, with the hypothesis that greater reduction in PaCO₂ will drive greater clinical benefit).</p>

	<p>Physiological and biological mechanisms of action of LTH-NIV: physiological mechanisms determining reduction in PaCO₂; the biological effects of PaCO₂ reduction in chronic hypercapnia upon immune, pulmonary vasculature, and skeletal muscle; biological mechanisms determining reduction in exacerbation; and physiological mechanisms determining enhanced sleep quality.</p>
	<p>The effects of NIV upon mental health and cognition upon patients, including effects upon HRQL and , cognitive function after an acute hypercapnic respiratory failure, the relationship between HRQL and cognitive function upon adherence and acceptability of LTH-NIV.</p>
	<p>Health service delivery research to promote the delivery of LTH-NIV after an acute hypercapnic respiratory failure to the right patient at the right time and prevent the 'overuse' or 'underuse' of the treatment.</p>

	<p>Assessment of novel home treatments, e.g. high flow humidified nasal oxygen, that are capable of reducing PaCO₂ in stable hypercapnic COPD patients.</p>
<p>PICO 3 LTH-NIV to normalize or reduce PaCO₂</p>	<p>The impact of NIV ventilator strategy targeted to maximise PaCO₂ reduction compared to conventional ventilator modes on long-term clinical outcomes (i.e. hyperinflation, exacerbations, cardiovascular complications, hospitalisations, survival, costs, patient's adherence).</p>
<p>PICO 4 Fixed pressure vs new adaptive/auto-titrating modes in LTH-NIV</p>	<p>The role of adaptive/auto-titrating modes to improve the long-term outcome of COPD, acute exacerbation vs chronic stable hypercapnic COPD and optimization of overnight ventilation, especially in specific subgroups in which ventilatory requirements may vary substantially overnight.</p> <p>The assessment of auto-EPAP modes (in addition to adaptive/auto-titrating modes) in the sub-group of patients with COPD-OSA overlap syndrome</p>

	The clinical efficacy and cost effectiveness of of auto-titrating modes in the inpatient vs outpatient settings avoiding the need for hospitalization to initiate NIV, thereby increasing access to NIV.
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COPD: Chronic obstructive pulmonary disease, EPAP: Expiratory positive airway pressure, HRQL : Health related quality of life, LTH-NIV: Long-term home noninvasive ventilation, OSA: Obstructive sleep apnea, PaCO₂: Partial pressure of carbon dioxide in arterial blood, ERS TF: European Respiratory Society Task Force









Appendix. Study comparators in trials included for PICO Question 1.




Trials (Author, year)	Comparator*
Duiverman 2008	Standard of care
Köhnlein 2014	Standard of care (LTOT if indicated)
Eman Shebi 2015	Standard of care
Zhou 2017	Standard of care
Strumpf 1991	Standard of care
Gay 1996	Sham NIV
Kaminski 1999	LTOT alone
Garrod 2000	Standard of care
Casanova 2000	Standard of care
Clini 2002	LTOT alone
Sin 2007	Sham NIV
McEvoy 2009	LTOT alone
Bhatt 2013	Standard of care

*Standard of care consists of pharmacological (inhaled and systematic treatments) and if present, nonpharmacological (pulmonary rehabilitation) therapies for the management of COPD.

LTOT: Long term oxygen therapy, NIV: Noninvasive ventilation.

GRADE Evidence Profile – Q1: NIV vs usual care in stable patients with COPD

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Long-term NIV	usual care	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: range 3 months to 12 months)												
13	randomised trials	serious ^a	not serious	not serious	serious ^b	none	78/422 (18.5%)	101/415 (24.3%)	RR 0.86 (0.58 to 1.27)	34 fewer per 1,000 (from 66 more to 102 fewer)	 LOW	CRITICAL
Number of Hospitalizations (follow up: range 3 months to 12 months)												
3	randomised trials	serious ^a	not serious ^c	not serious	serious ^b	none	154	154	-	MD 1.26 fewer (2.59 fewer to 0.08 more)	 LOW	CRITICAL
Quality of Life (higher is better) (follow up: range 3 months to 12 months; assessed with: Multiple validated scales)												
7	randomised trials	serious ^a	serious ^d	not serious	serious ^b	none	244	244	-	SMD 0.49 SD higher (0.01 lower to 0.98 higher)	 VERY LOW	CRITICAL
Change in Dyspnea Score (assessed with: lower is better)												
5	randomised trials	serious ^a	not serious	not serious	not serious	none	92	96	-	SMD 0.51 SD lower (0.95 lower to 0.06 lower)	 MODERATE	CRITICAL
Change in PaCO2 (follow up: range 3 months to 12 months; assessed with: mmHg)												
12	randomised trials	serious ^a	not serious ^c	not serious	not serious	none	374	373	-	MD 3.37 mmHg lower (5.75 lower to 0.99 lower)	 MODERATE	IMPORTANT
Change in PaO2 (follow up: range 3 months to 12 months; assessed with: mmHg)												
9	randomised trials	serious ^a	not serious	not serious	not serious	none	278	277	-	MD 3.09 mmHg higher (1.45 higher to 4.74 higher)	 MODERATE	IMPORTANT
Change in FEV1 (follow up: range 3 months to 12 months; assessed with: % or L)												
10	randomised trials	serious ^a	not serious	not serious	serious ^e	none	366	374	-	SMD 0.07 SD higher (0.14 lower to 0.27 higher)	 LOW	IMPORTANT
Change in FVC (follow up: range 3 months to 12 months; assessed with: & or L)												
8	randomised trials	serious ^a	not serious	not serious	serious ^e	none	287	296	-	SMD 0.1 SD higher (0.06 lower to 0.26 higher)	 LOW	IMPORTANT
Change in 6 minute walk distance (follow up: range 3 months to 12 months; assessed with: metres)												

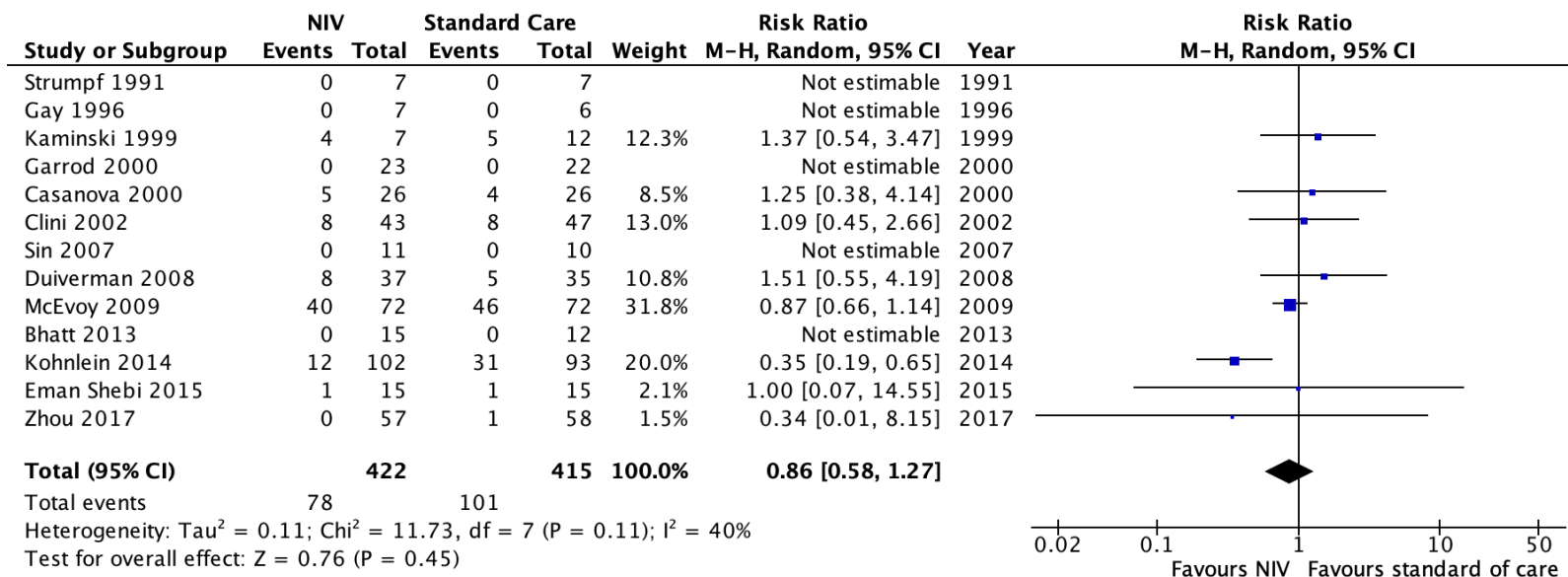
Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Long-term NIV	usual care	Relative (95% CI)	Absolute (95% CI)		
10	randomised trials	serious ^a	not serious	not serious	not serious	none	256	260	-	MD 32.03 metres higher (10.79 higher to 53.26 higher)	 MODERATE	IMPORTANT
Change in Sleep Efficiency (follow up: range 3 months to 12 months)												
3	randomised trials	serious ^a	not serious	not serious	serious ^f	none	61	65	-	SMD 0.55 SD lower (1.13 lower to 0.03 higher)	 LOW	IMPORTANT
Minor Adverse Events (follow up: range 3 months to 12 months; assessed with: discomfort, skin break or rash)												
3	randomised trials	serious ^a	not serious	serious ^a	not serious	none	27/189 (14.3%)	0/175 (0.0%)	RR 10.35 (2.45 to 43.71)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	 LOW	IMPORTANT

CI: Confidence interval; RR: Risk ratio; MD: Mean difference; SMD: Standardised mean difference

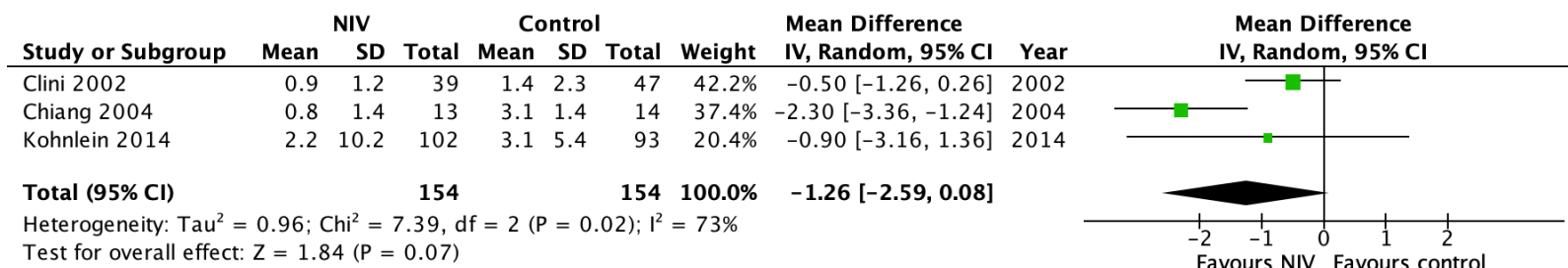
Explanations

- Most trials unblinded, variable lost-to-follow up which was significant in some included trials.
- Wide confidence intervals that do not exclude significant harm.
- High Isquared (>70%) however in most included studies point estimate is on the side of benefit.
- High Isquared (>70%) and variable effects between studies.
- No effect, however confidence intervals don't exclude significant benefit or harm.
- Wide confidence intervals that do not exclude benefit.
- Varying importance and severity of these minor adverse effects.

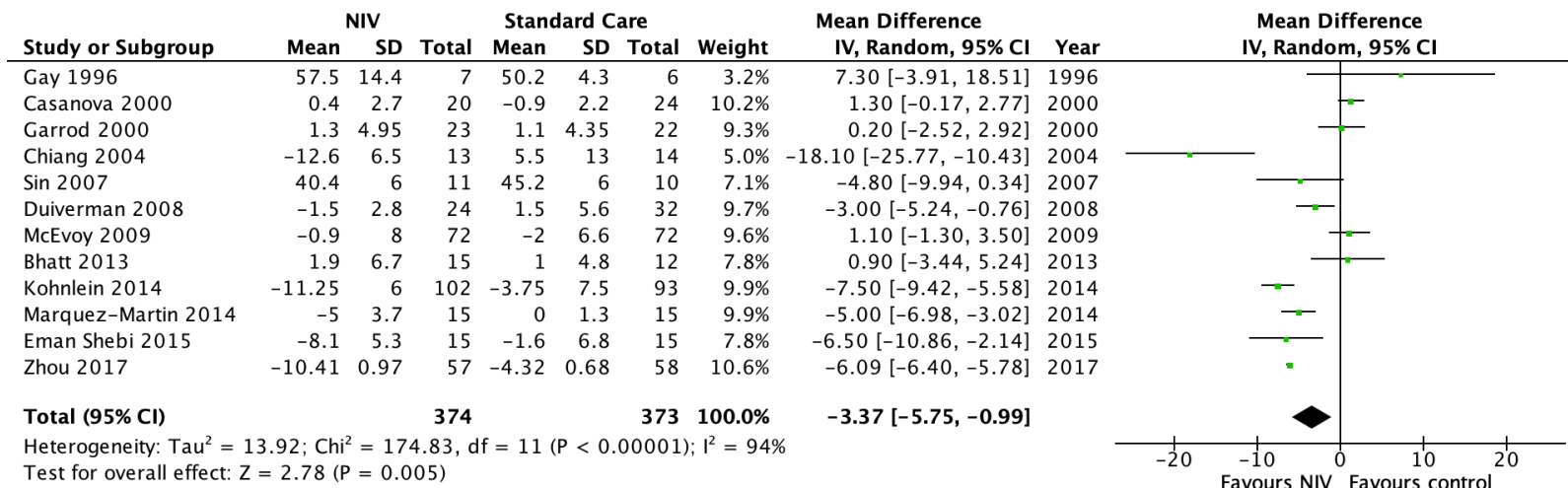
Forest plot 1: Mortality



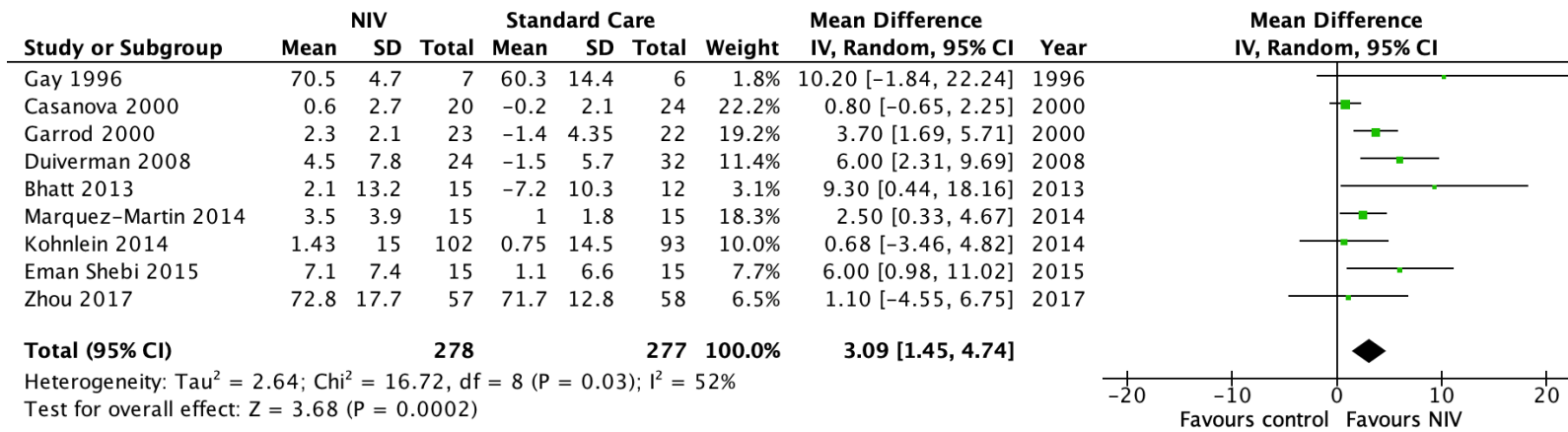
Forest plot 2: Hospitalizations



Forest plot 5: PCO2



Forest plot 6: PO2



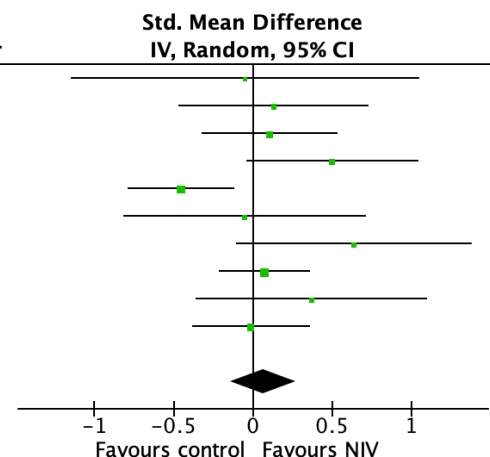
Forest plot 7: FEV1

Study or Subgroup	NIV			Standard Care			Weight	Std. Mean Difference IV, Random, 95% CI	Year
	Mean	SD	Total	Mean	SD	Total			
Gay 1996	-0.02	0.23	7	-0.01	0.1	6	3.1%	-0.05 [-1.14, 1.04]	1996
Casanova 2000	1	8.65	20	0	6.43	24	8.3%	0.13 [-0.46, 0.72]	2000
Clini 2002	0.9	10.2	39	-0.2	10.6	47	12.6%	0.10 [-0.32, 0.53]	2002
Duiverman 2008	-0.03	0.14	24	-0.14	0.26	32	9.5%	0.50 [-0.04, 1.04]	2008
McEvoy 2009	-1.2	9	72	2.4	6.6	72	16.0%	-0.45 [-0.78, -0.12]	2009
Bhatt 2013	0.9	10.1	15	1.4	8	12	5.7%	-0.05 [-0.81, 0.71]	2013
Marquez-Martin 2014	3	7.4	15	-0.5	1.6	15	6.0%	0.64 [-0.10, 1.37]	2014
Kohnlein 2014	0.5	10.3	102	-0.2	9	93	18.1%	0.07 [-0.21, 0.35]	2014
Eman Shebi 2015	2.6	10.7	15	-1.3	9.9	15	6.2%	0.37 [-0.35, 1.09]	2015
Zhou 2017	27.4	19.3	57	27.6	4.8	58	14.6%	-0.01 [-0.38, 0.35]	2017

Total (95% CI) **366** **374** **100.0%** **0.07 [-0.14, 0.27]**

Heterogeneity: Tau² = 0.04; Chi² = 15.01, df = 9 (P = 0.09); I² = 40%

Test for overall effect: Z = 0.63 (P = 0.53)



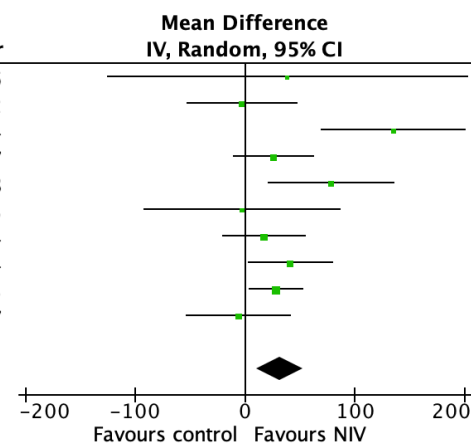
Forest plot 8: Six minute walk distance

Study or Subgroup	NIV			Standard Care			Weight	Mean Difference IV, Random, 95% CI	Year
	Mean	SD	Total	Mean	SD	Total			
Gay 1996	46.39	190.5	7	8	103.6	6	1.6%	38.39 [-125.28, 202.06]	1996
Clini 2002	-18	126.7	39	-15	105.1	47	10.0%	-3.00 [-52.84, 46.84]	2002
Chiang 2004	101.2	81.8	13	-33.8	90.9	14	7.2%	135.00 [69.85, 200.15]	2004
Sin 2007	30	32.2	11	4	49.7	10	13.6%	26.00 [-10.21, 62.21]	2007
Duiverman 2008	-4	44.4	24	-82	155.9	32	8.6%	78.00 [21.14, 134.86]	2008
Bhatt 2013	14	116.3	15	17	117.8	12	4.6%	-3.00 [-91.92, 85.92]	2013
Kohnlein 2014	17.2	117.2	102	0	144.8	93	13.3%	17.20 [-19.99, 54.39]	2014
Marquez-Martin 2014	83	61.9	15	42	42.8	15	13.1%	41.00 [2.92, 79.08]	2014
Eman Shebi 2015	30	35.4	15	2	32.7	15	17.4%	28.00 [3.61, 52.39]	2015
Schneeberger 2017	34	63	15	40	71	16	10.7%	-6.00 [-53.19, 41.19]	2017

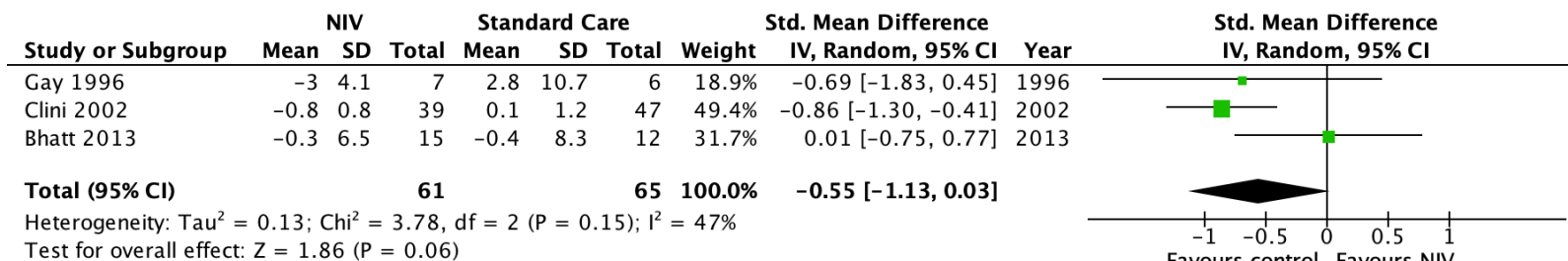
Total (95% CI) **256** **260** **100.0%** **32.03 [10.79, 53.26]**

Heterogeneity: Tau² = 521.24; Chi² = 18.02, df = 9 (P = 0.03); I² = 50%

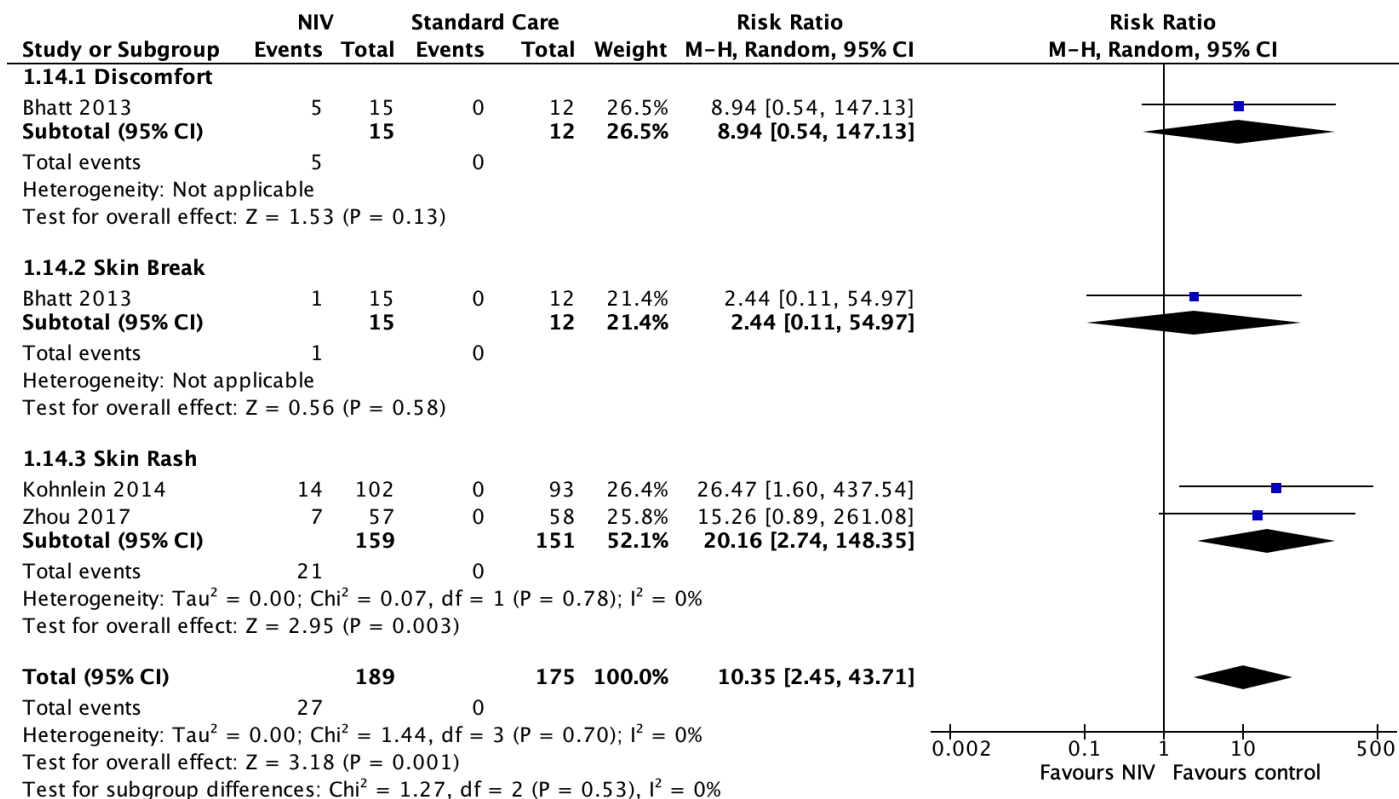
Test for overall effect: Z = 2.96 (P = 0.003)



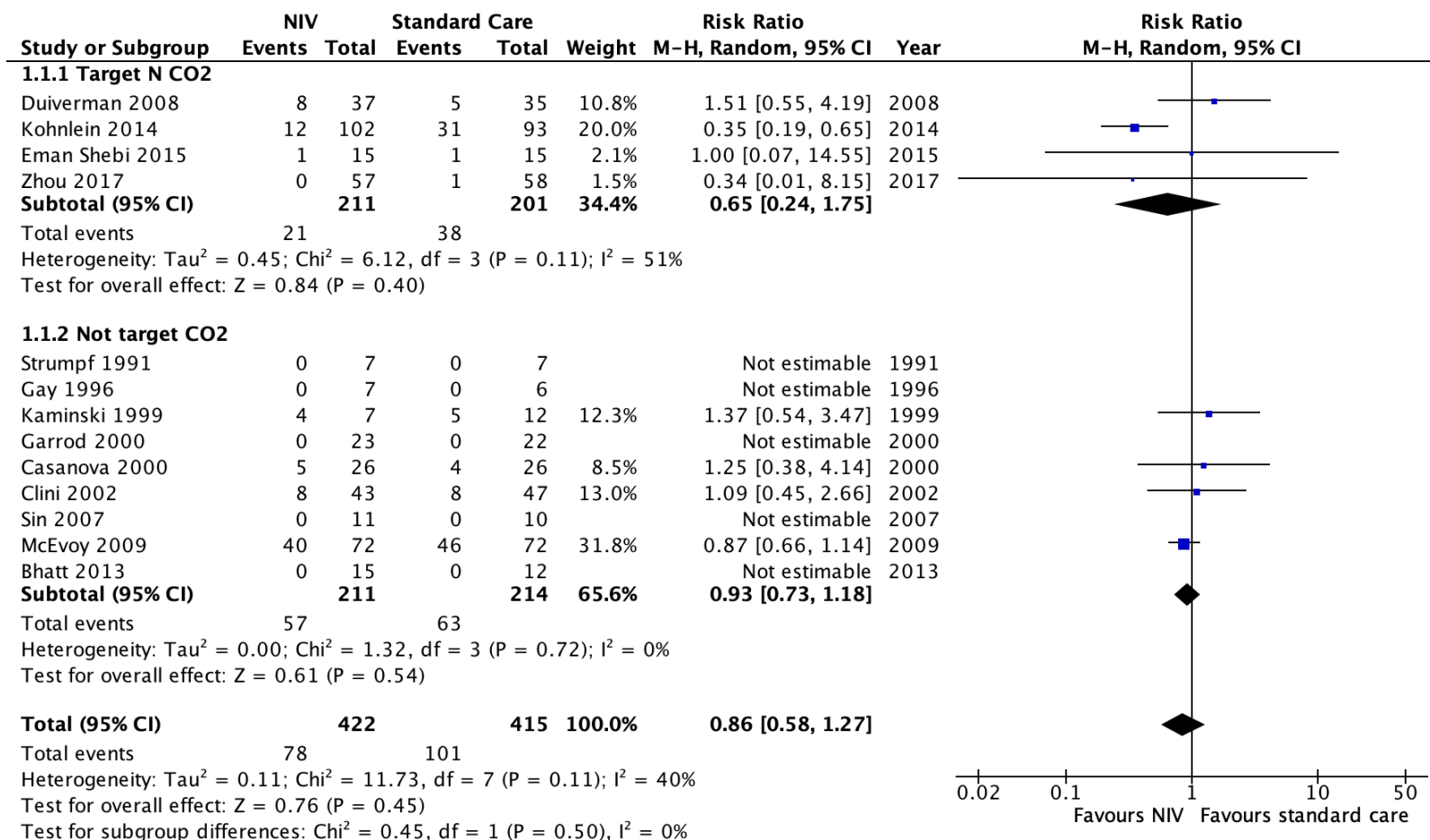
Forest plot 9: Sleep efficiency



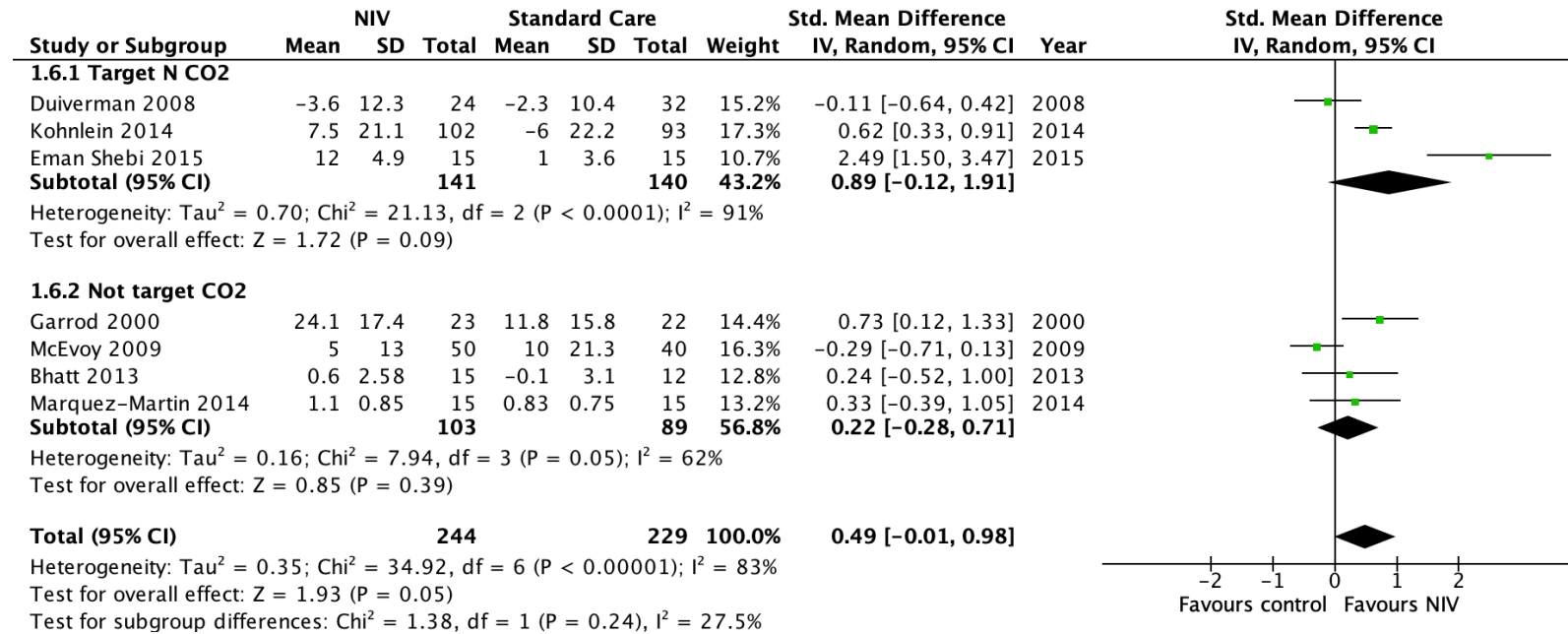
Forest plot 10: Minor adverse events



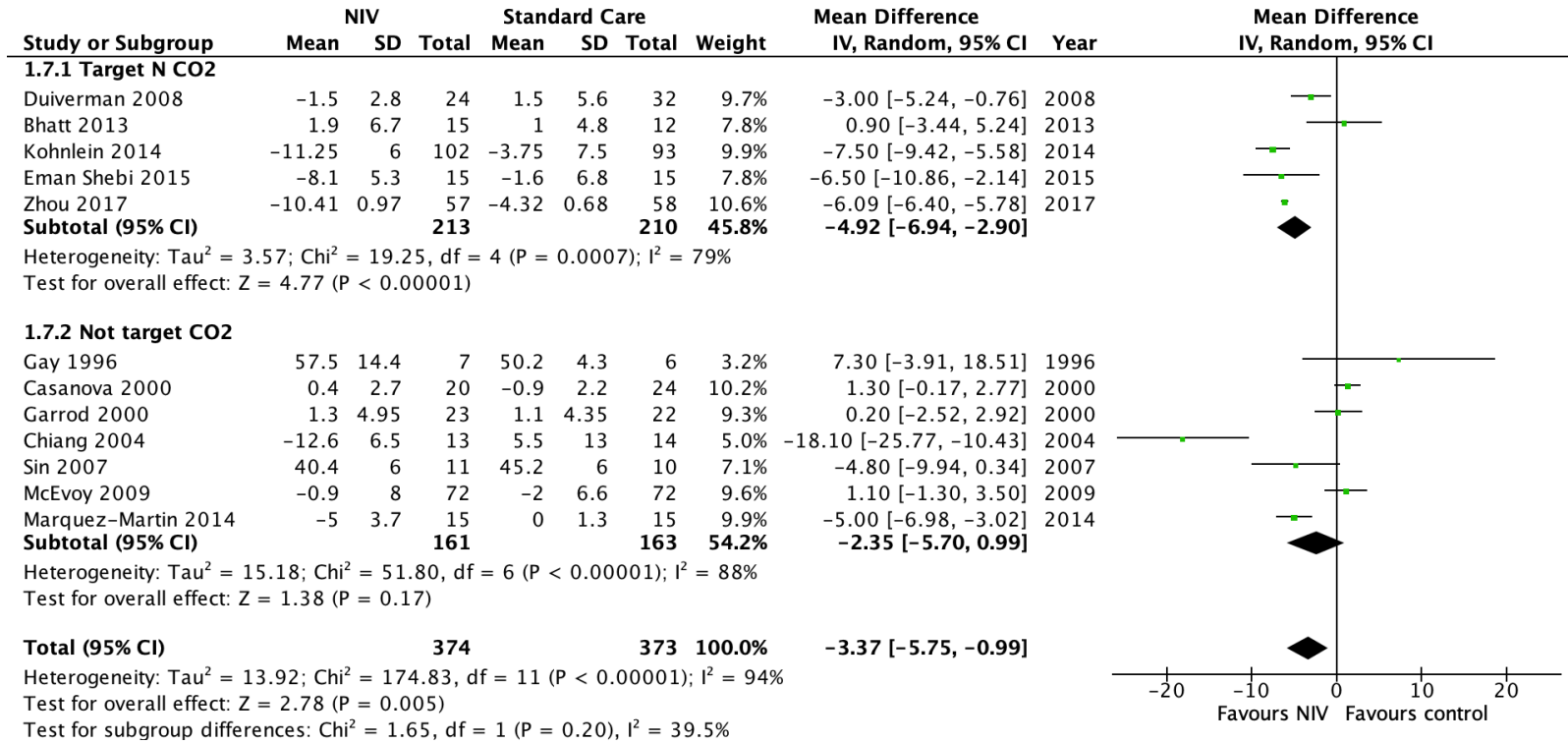
Forest plot 11: Mortality subgroup analysis - targeted PCO2 vs. non-targeted PCO2



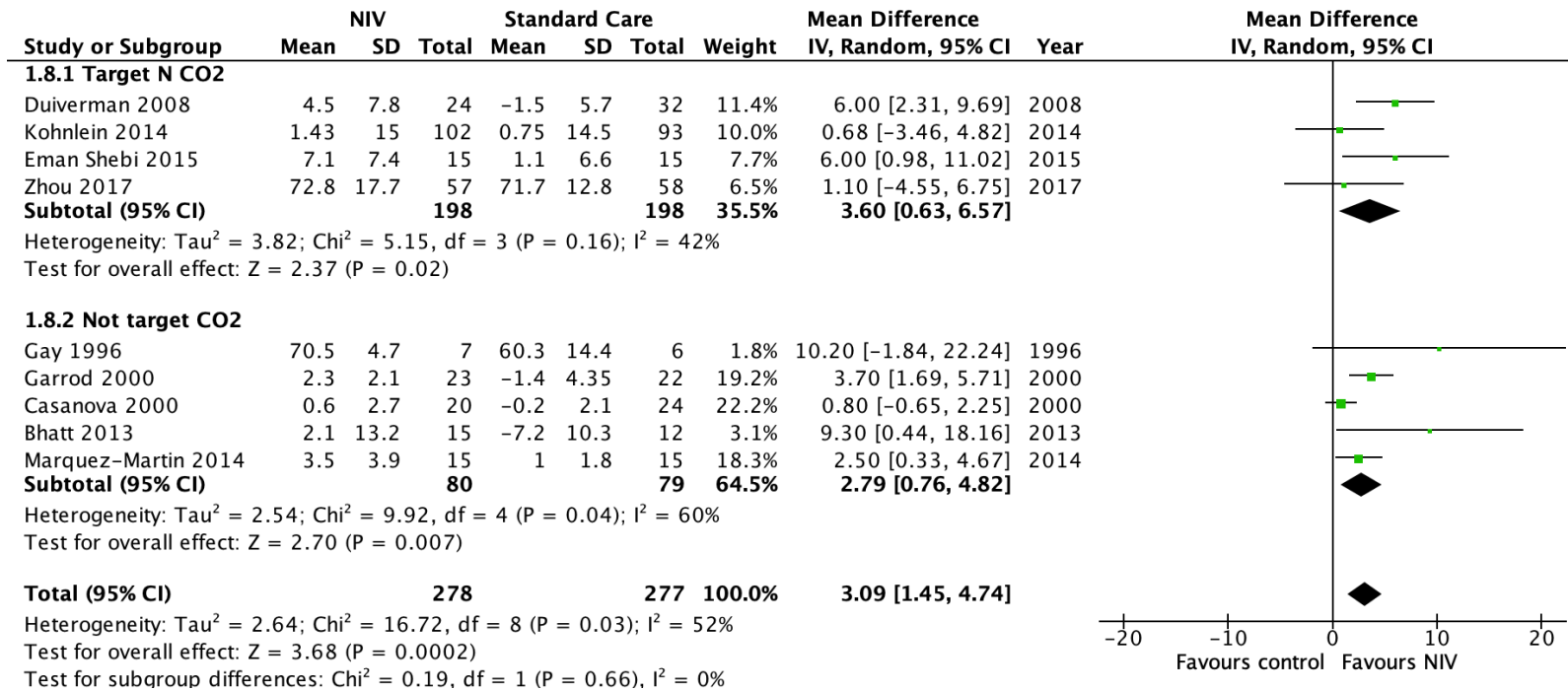
Forest plot 12: Quality of Life subgroup analysis - targeted PCO2 vs. non-targeted PCO2



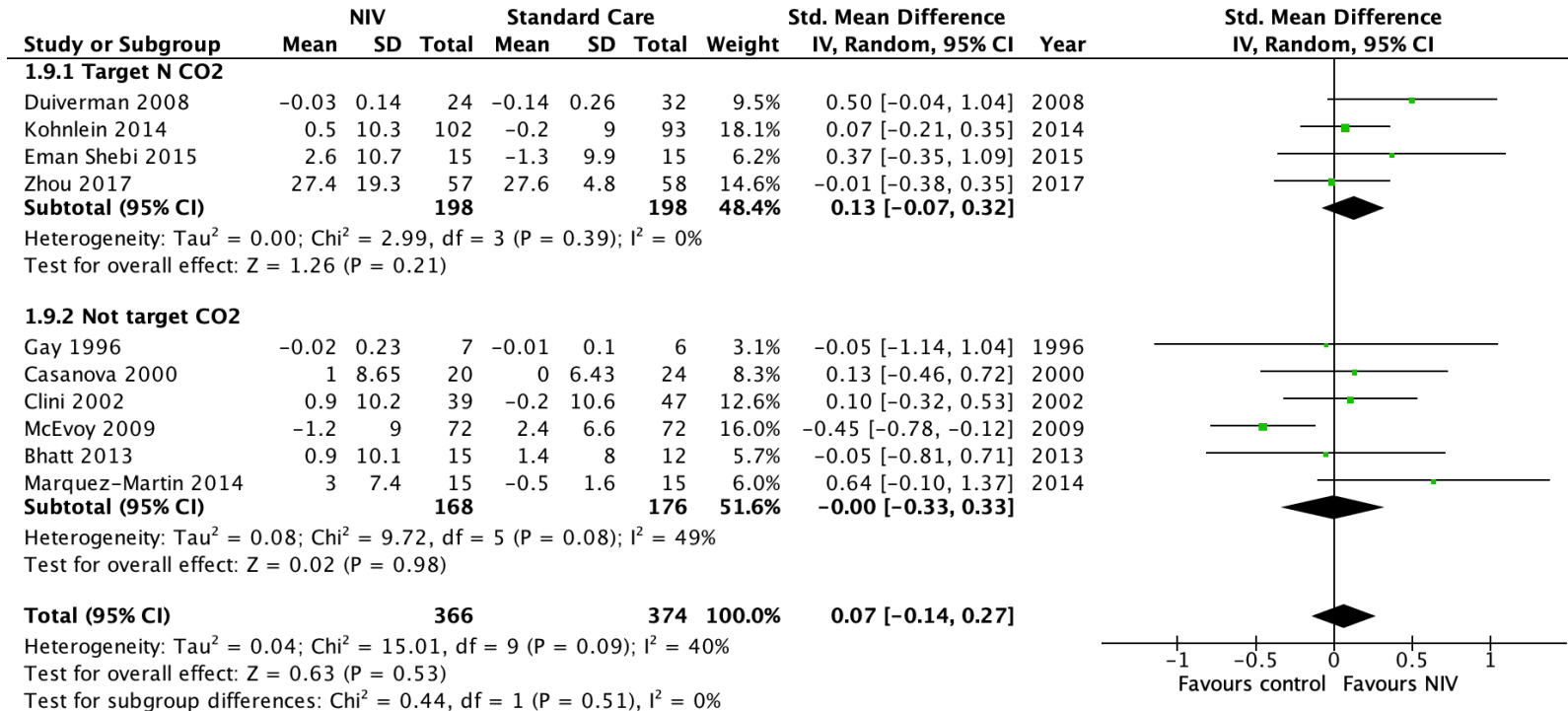
Forest plot 13: PCO2 subgroup analysis - targeted PCO2 vs. non-targeted PCO2



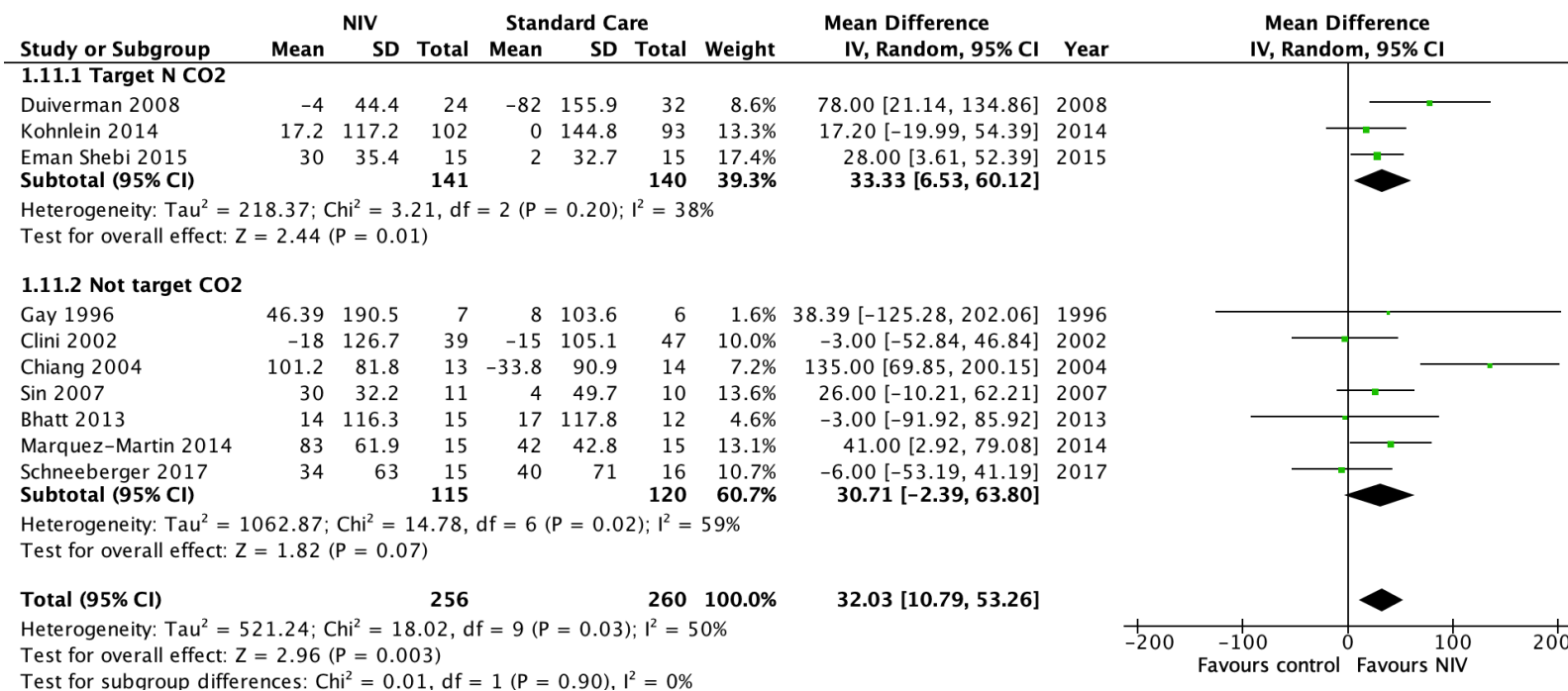
Forest plot 14: PO2 subgroup analysis - targeted PCO2 vs. non-targeted PCO2



Forest plot 15: FEV1 subgroup analysis - targeted PCO2 vs. non-targeted PCO2



Forest plot 16: Six minute walk distance subgroup analysis - targeted PCO2 vs. non-targeted PCO2



GRADE Evidence Profile – Q2: NIV vs usual care after an exacerbation of COPD

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Long-term NIV	Usual care	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: range 1 years to 2 years)												
4	RCTs	serious ^a	not serious	not serious	serious ^b	none	55/201 (27.4%)	62/205 (30.2%)	RR 0.92 (0.67 to 1.25)	24 fewer per 1,000 (from 76 more to 100 fewer)	⊕⊕○○ LOW	CRITICAL
Exacerbations per year (follow up: range 1 years to 2 years)												
3	RCTs	serious ^c	not serious	not serious	serious ^b	none	181	185	-	SMD 0.19 SD lower (0.40 lower to 0.01 higher)	⊕⊕○○ LOW	CRITICAL
Hospitalizations (follow up: range 1 years to 2 years)												
3	RCTs	serious ^a	serious ^d	not serious	serious ^b	none	71/181 (39.2%)	93/185 (50.3%)	RR 0.61 (0.30 to 1.24)	196 fewer per 1,000 (from 121 more to 352 fewer)	⊕○○○ VERY LOW	CRITICAL
Dyspnea score (follow up: range 1 years to 2 years; assessed with: Medical Research Council Dyspnea (MRC) Score)												
2	RCTs	serious ^c	not serious ^e	not serious	serious ^b	none	69	71	-	MD 0.8 lower (2.17 lower to 0.58 higher)	⊕⊕○○ LOW	CRITICAL
Quality of Life (follow up: range 1 years to 2 years; assessed with: Severe Respiratory Insufficiency Questionnaire)												
2	RCTs	serious ^c	not serious ^e	not serious	serious ^b	none	85	77	-	MD 2.89 points higher (6.8 higher to 1.03 lower)	⊕⊕○○ LOW	CRITICAL
PaO ₂ (follow up: range 6 months to 2 years)												
4	RCTs	serious ^c	serious ^d	not serious	serious ^b	none	107	99	-	MD 1.53 mmHg lower (4.24 lower to 1.17 higher)	⊕○○○ VERY LOW	IMPORTANT
PaCO ₂ (follow up: range 6 months to 2 years)												
5	RCTs	serious ^c	not serious	not serious	not serious	none	134	126	-	MD 3.41 mmHg lower (4.09 lower to 2.73 lower)	⊕⊕⊕○ MODERATE	IMPORTANT
Exercise tolerance (follow up: range 6 months to 2 years; assessed with: 6 minute walk test)												

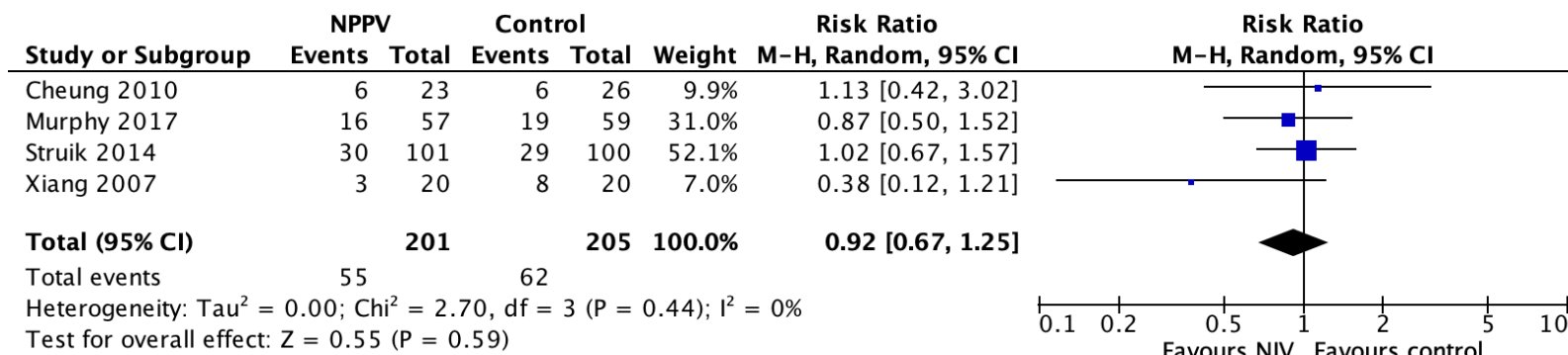
2	RCTs	serious ^c	very serious ^f	not serious	serious ^b	none	30	25	-	MD 8.64 m lower (209 lower to 192 higher)	⊕○○○ VERY LOW	IMPORTANT
FEV1 (follow up: range 6 months to 1 years)												
2	RCTs	serious ^c	not serious	not serious	serious ^b	none	58	51	-	SMD 0.36 SD lower (0.74 lower to 0.03 higher)	⊕⊕○○ LOW	IMPORTANT

CI: Confidence interval; **RCT:** Randomized controlled trial; **RR:** Risk ratio; **MD:** Mean difference; **SMD:** Standardised mean difference

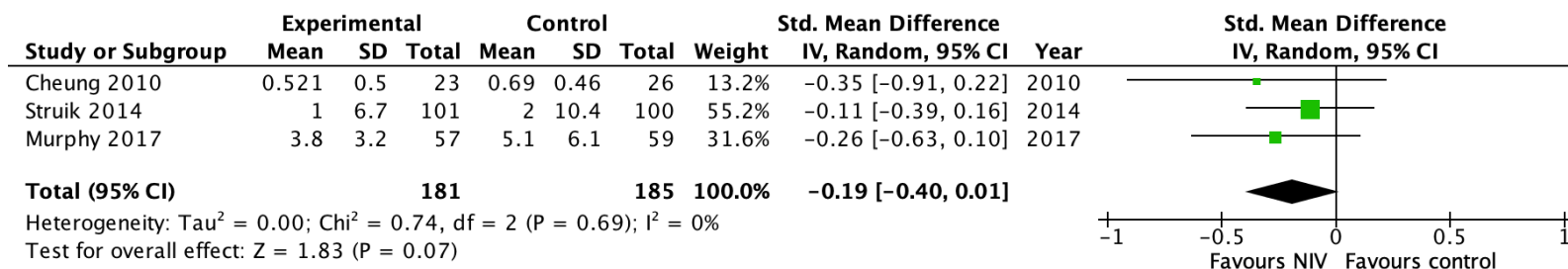
Explanations

- a. Lack of blinding of patients and clinicians which could result in cointervention.
- b. Wide 95% confidence intervals which do not exclude significant benefit nor significant harm.
- c. Lack of blinding of patients and clinicians in most studies which could result in cointervention and/or biased assessment of subjective outcomes, as well as significant loss to follow-up for end-of-study measurements.
- d. I-squared (I²) values high, with individual studies on different sides of the line of no effect.
- e. Though high I-squared (I²) values, all point estimates are on the side of benefit.
- f. Very high I-squared (I²) values with studies on each side of the line of no effect.

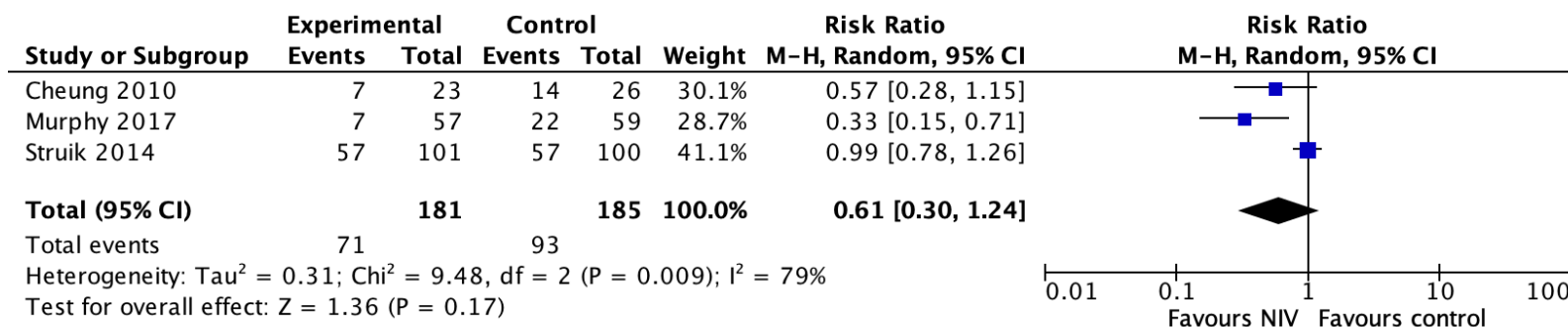
Forest plot 1: Mortality



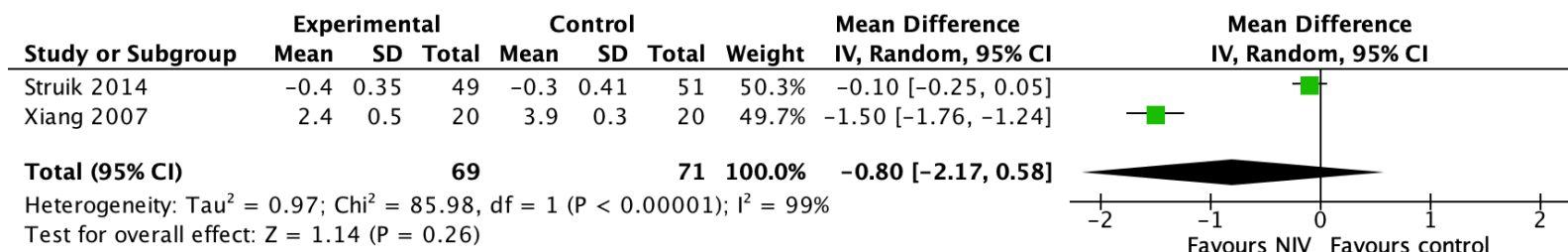
Forest plot 2: Exacerbations



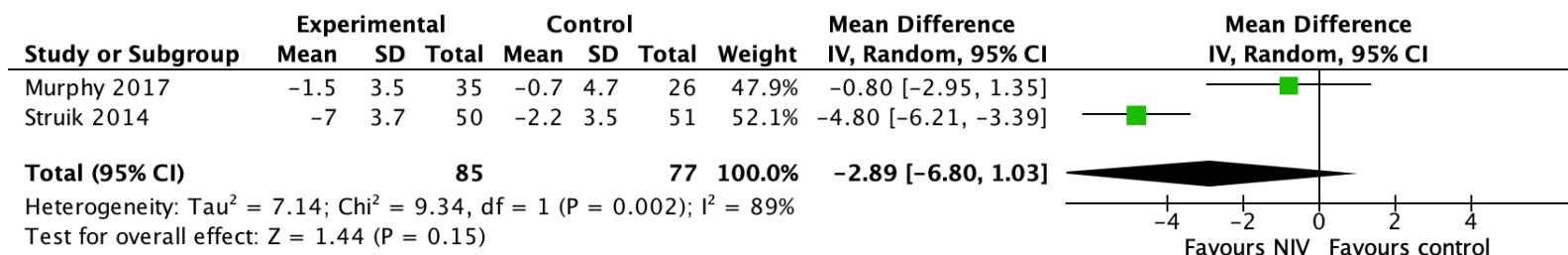
Forest plot 3: Hospitalizations



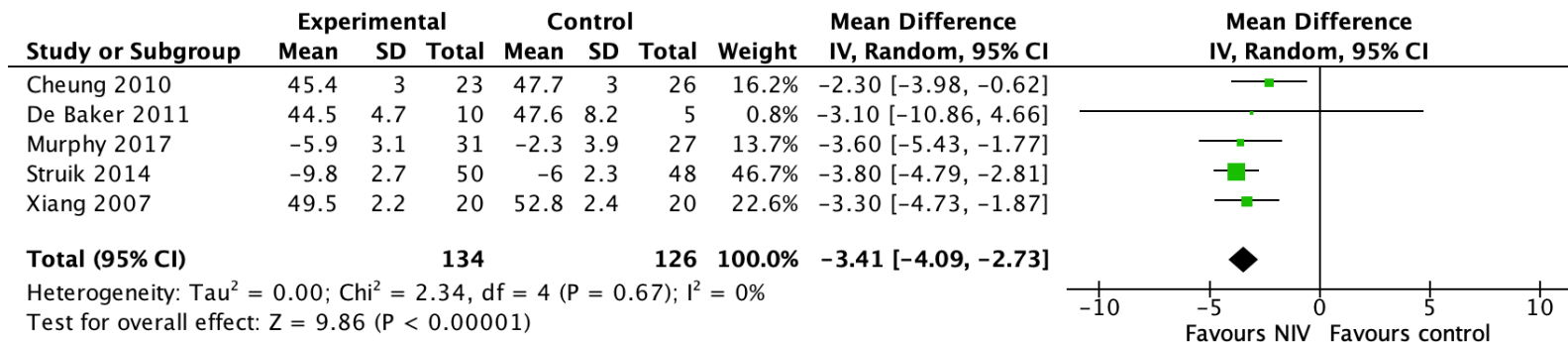
Forest plot 4: Dyspnea



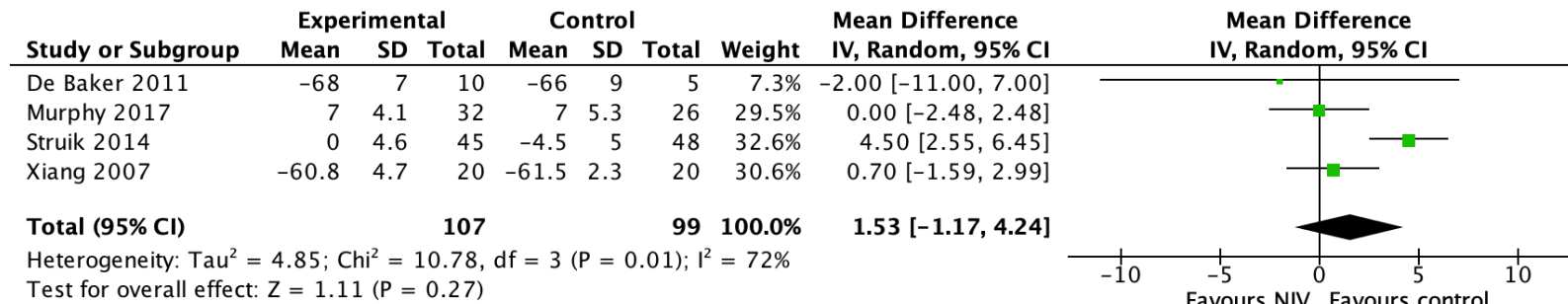
Forest plot 6: Quality of life



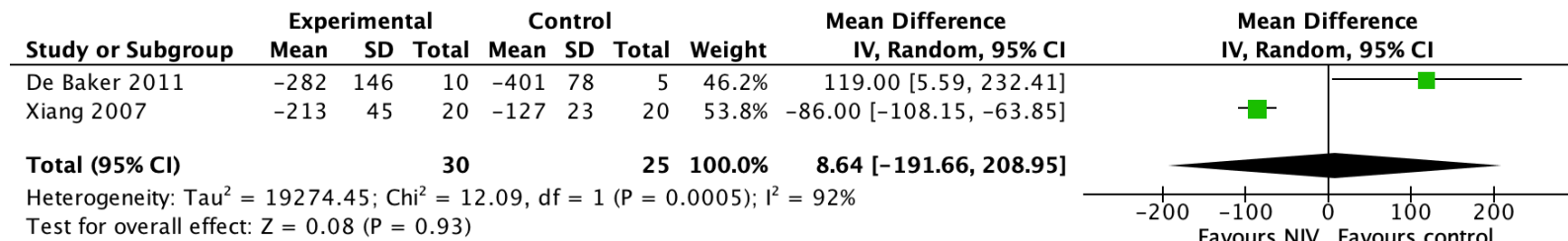
Forest plot 6: PCO2



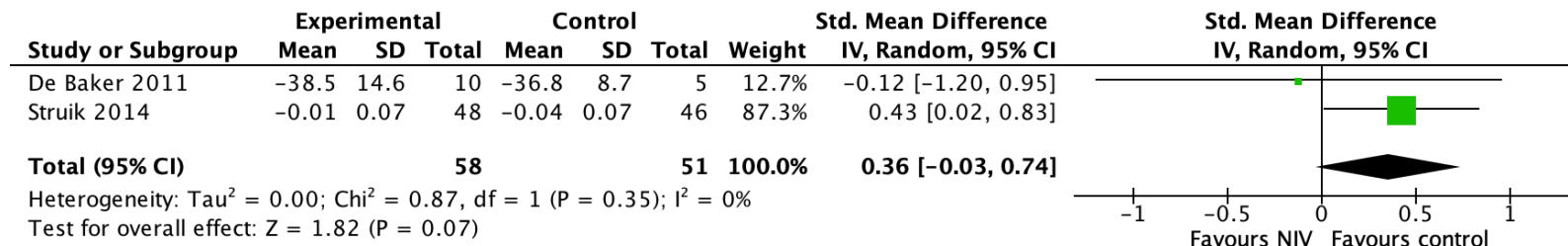
Forest plot 7: PO2



Forest plot 8: Exercise tolerance



Forest plot 9: Pulmonary function- FEV1



GRADE Evidence Profile – Q3: NIV with targeted normalization of PaCO2 levels compared to NIV without targeting normal PaCO2 level for long-term NIV in COPD patients

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NIV with targeted normalization of PaCO2 levels	NIV without targeting normal PaCO2 level	Relative (95% CI)	Absolute (95% CI)		
Quality of Life (follow up: mean 6 weeks; assessed with: SRI-SS score (higher is better))												
3	randomised trials	serious ^a	not serious	not serious	serious ^{b,c}	none	34	36	-	MD 0.95 points lower (8.33 lower to 6.42 higher)	⊕⊕○○ LOW	CRITICAL
Dyspnea (follow up: mean 6 weeks; assessed with: Borg score)												
1	randomised trials	serious ^a	not serious	not serious	serious ^c	none	15	15	-	MD 1.54 points higher (0.56 higher to 2.52 higher)	⊕⊕○○ LOW	CRITICAL
FEV1 (follow up: mean 6 weeks; assessed with: L)												
1	randomised trials	serious ^a	not serious	not serious	serious ^{b,c}	none	11	14	-	MD 0.04 L higher (0.34 lower to 0.42 higher)	⊕⊕○○ LOW	IMPORTANT
PaCO2 (follow up: mean 6 weeks; assessed with: mmHg)												
5	randomised trials	serious ^a	not serious	not serious	serious ^c	none	65	68	-	MD 4.93 mmHg lower (7.43 lower to 2.42 lower)	⊕⊕○○ LOW	IMPORTANT
PaO2 (follow up: mean 6 weeks; assessed with: mmHg)												
3	randomised trials	serious ^a	not serious	not serious	serious ^{b,c}	none	39	39	-	MD 3.4 mmHg higher (2.39 lower to 9.19 higher)	⊕⊕○○ LOW	IMPORTANT
6MWD (follow up: mean 6 weeks; assessed with: metres)												
1	randomised trials	serious ^a	not serious	not serious	serious ^{b,c}	none	15	15	-	MD 14 metres higher (70.42 lower to 98.42 higher)	⊕⊕○○ LOW	IMPORTANT
Sleep Comfort (follow up: mean 6 weeks; assessed with: VAS scale)												
1	randomised trials	serious ^a	not serious	not serious	very serious ^{b,c}	none	8	7	-	MD 1 cm higher (28.42 lower to 30.42 higher)	⊕○○○ VERY LOW	IMPORTANT

CI: Confidence interval; MD: Mean difference

Explanations

- a. Unblinded intervention may affect co-intervention use. Crossover study with potential for carryover effect.
- b. Wide confidence intervals don't exclude significant harm or significant benefit.
- c. Small number of patients limit precision.

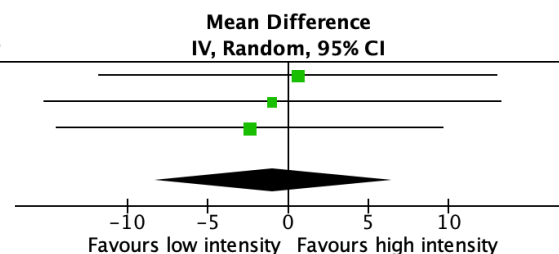
Forest plot 1: Quality of Life

Study or Subgroup	High Intensity			Low Intensity			Weight	Mean Difference		Year
	Mean	SD	Total	Mean	SD	Total		IV, Random, 95% CI		
Dreher 2010	63.22	16.9	15	62.6	17.7	15	35.4%	0.62	[-11.76, 13.00]	2010
Murphy 2012	66	16	8	67	12	7	26.9%	-1.00	[-15.21, 13.21]	2012
Duiverman 2017	51.3	15	11	53.7	15.5	14	37.6%	-2.40	[-14.42, 9.62]	2017

Total (95% CI) **34** **36** **100.0%** **-0.95 [-8.33, 6.42]**

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.12$, $df = 2$ ($P = 0.94$); $I^2 = 0\%$

Test for overall effect: $Z = 0.25$ ($P = 0.80$)



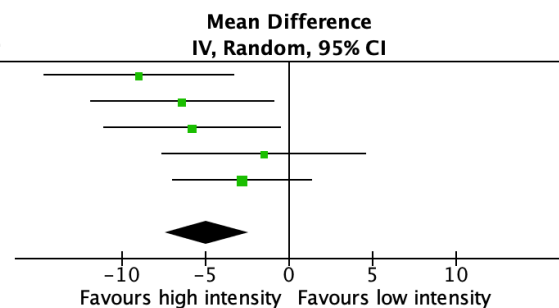
Forest plot 2: PCO2

Study or Subgroup	High Intensity			Low Intensity			Weight	Mean Difference		Year
	Mean	SD	Total	Mean	SD	Total		IV, Random, 95% CI		
Dreher 2010	47.8	7.2	15	56.8	8.6	15	17.3%	-9.00	[-14.68, -3.32]	2010
Dreher 2011	50.2	6.2	16	56.6	9.6	17	18.4%	-6.40	[-11.88, -0.92]	2011
Lukacsovits 2012	49.4	7.8	15	55.2	6.9	15	19.7%	-5.80	[-11.07, -0.53]	2012
Murphy 2012	52.5	6	8	54	6	7	15.3%	-1.50	[-7.59, 4.59]	2012
Duiverman 2017	45.3	5.33	11	48.1	5.18	14	29.4%	-2.80	[-6.96, 1.36]	2017

Total (95% CI) **65** **68** **100.0%** **-4.93 [-7.43, -2.42]**

Heterogeneity: $\tau^2 = 1.05$; $\chi^2 = 4.58$, $df = 4$ ($P = 0.33$); $I^2 = 13\%$

Test for overall effect: $Z = 3.86$ ($P = 0.0001$)



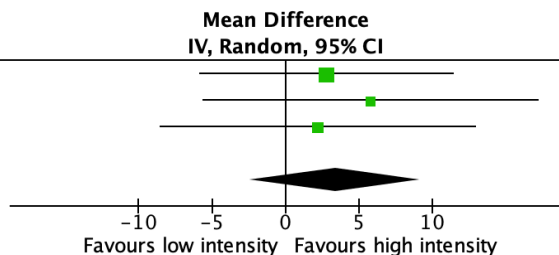
Forest plot 3: PO2

Study or Subgroup	High Intensity			Low Intensity			Weight	Mean Difference		Year
	Mean	SD	Total	Mean	SD	Total		IV, Random, 95% CI		
Dreher 2011	71.7	10.8	16	68.9	14.3	17	45.1%	2.80	[-5.81, 11.41]	2011
Lukacsovits 2012	71.6	19.1	15	65.8	11.9	15	25.8%	5.80	[-5.59, 17.19]	2012
Murphy 2012	61.5	9.75	8	59.3	11.25	7	29.1%	2.20	[-8.53, 12.93]	2012

Total (95% CI) **39** **39** **100.0%** **3.40 [-2.39, 9.19]**

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.24$, $df = 2$ ($P = 0.89$); $I^2 = 0\%$

Test for overall effect: $Z = 1.15$ ($P = 0.25$)



Question 4: Adaptive ventilatory modes in long-term NIV for COPD

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adaptive NIV	Conventional NIV	Relative (95% CI)	Absolute (95% CI)		
Quality of Life (follow up: range 2 months to 3 months; assessed with: Severe Respiratory Insufficiency Questionnaire (1 study); St. George's Respiratory Questionnaire (2 studies))												
3	RCTs	serious ^a	not serious	not serious	serious ^b	none	54	54	-	SMD 0.28 SD higher (0.66 higher to 0.1 lower)	⊕⊕○○ LOW	CRITICAL
Sleep quality (follow up: range 1 days to 3 months; assessed with: Visual analogue scale (2 studies); unvalidated questionnaire (2 studies); Epworth Sleepiness Scale (1 study))												
5	RCTs	serious ^a	not serious	serious ^c	serious ^b	none	80	80	-	SMD 0.14 lower (0.53 lower to 0.26 higher)	⊕○○○ VERY LOW	IMPORTANT
Exercise tolerance (follow up: range 2 months to 3 months; assessed with: Shuttle walk test (2 studies); 6 minute walk test (1 study))												
3	RCTs	serious ^a	not serious	not serious	serious ^b	none	47	47	-	SMD 0.1 lower (0.51 lower to 0.3 higher)	⊕⊕○○ LOW	IMPORTANT
PaCO ₂ (follow up: range 1 days to 3 months)												
6	RCTs	serious ^a	not serious	not serious	serious ^b	none	91	91	-	MD 1.95 mmHg lower (4.29 lower to 0.4 higher)	⊕⊕○○ LOW	IMPORTANT
Oxygenation (follow up: range 1 days to 3 months; assessed with: PaO ₂ , or SaO ₂ oximetry)												
6	RCTs	serious ^a	not serious	not serious	serious ^b	none	91	91	-	SMD 0.04 lower (0.33 lower to 0.26 higher)	⊕⊕○○ LOW	IMPORTANT

CI: Confidence interval; SMD: Standardised mean difference; MD: Mean difference

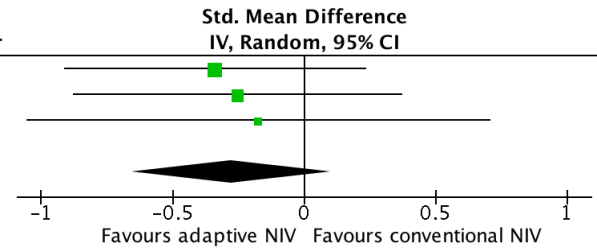
Explanations

- a. Lack of blinding which could result in cointervention, or affect judgement of subjective outcomes.
- b. Wide 95% confidence interval which fails to exclude significant benefit or harm.
- c. Most studies did not use a validated instrument to assess sleep quality.

Forest plot 1: Quality of Life

Study or Subgroup	Hybrid NIV			Pressure NIV			Weight	Std. Mean Difference IV, Random, 95% CI	Year
	Mean	SD	Total	Mean	SD	Total			
Oscroft 2010	55	13	24	59	10	24	44.2%	-0.34 [-0.91, 0.23]	2010
Oscroft 2014	59.7	20.8	20	64.4	15.1	20	37.1%	-0.25 [-0.88, 0.37]	2014
Storre 2014	-62.4	18.9	10	-59.3	14.8	10	18.6%	-0.17 [-1.05, 0.70]	2014
Total (95% CI)			54			54	100.0%	-0.28 [-0.66, 0.10]	

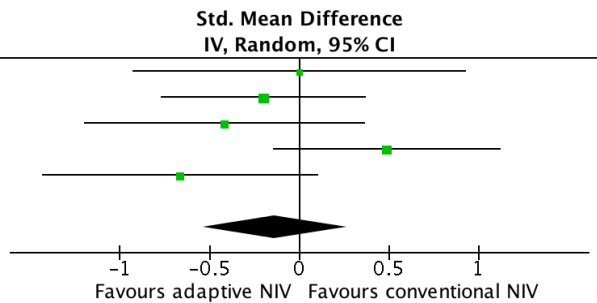
Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 2 (P = 0.95); I² = 0%
 Test for overall effect: Z = 1.43 (P = 0.15)



Forest plot 2: Sleep quality

Study or Subgroup	Hybrid NIV			Pressure NIV			Weight	Std. Mean Difference IV, Random, 95% CI	Year
	Mean	SD	Total	Mean	SD	Total			
Crisafulli 2009	5.1	2	9	5.1	1.7	9	14.0%	0.00 [-0.92, 0.92]	2009
Oscroft 2010	-78	22	24	-73	27	24	26.3%	-0.20 [-0.77, 0.37]	2010
Ekkenkamp 2014	-81	7.4	13	-77	10.8	13	17.9%	-0.42 [-1.20, 0.36]	2014
Oscroft 2014	-6.2	4.1	20	-8.9	6.5	20	23.4%	0.49 [-0.14, 1.12]	2014
Nilius 2017	7	3.6	14	9.3	3.1	14	18.4%	-0.66 [-1.43, 0.10]	2017
Total (95% CI)			80			80	100.0%	-0.14 [-0.53, 0.26]	

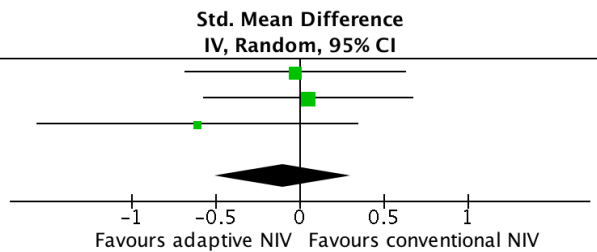
Heterogeneity: Tau² = 0.07; Chi² = 6.22, df = 4 (P = 0.18); I² = 36%
 Test for overall effect: Z = 0.67 (P = 0.51)



Forest plot 3: Exercise tolerance

Study or Subgroup	Hybrid NIV			Pressure NIV			Weight	Std. Mean Difference IV, Random, 95% CI	Year
	Mean	SD	Total	Mean	SD	Total			
Oscroft 2010	-173	97	18	-170	107	18	38.7%	-0.03 [-0.68, 0.62]	2010
Oscroft 2014	-129	90	20	-133	71	20	43.0%	0.05 [-0.57, 0.67]	2014
Storre 2014	-311	115	9	-238	113	9	18.3%	-0.61 [-1.56, 0.34]	2014
Total (95% CI)			47			47	100.0%	-0.10 [-0.51, 0.30]	

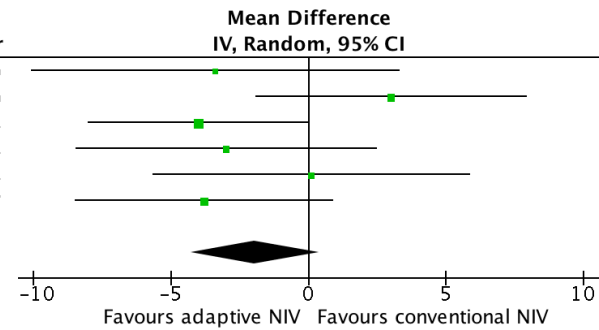
Heterogeneity: Tau² = 0.00; Chi² = 1.37, df = 2 (P = 0.50); I² = 0%
 Test for overall effect: Z = 0.49 (P = 0.62)



Forest plot 4: PCO2

Study or Subgroup	Hybrid NIV			Pressure NIV			Weight	Mean Difference		Year
	Mean	SD	Total	Mean	SD	Total		IV, Random, 95% CI	Year	
Crisafulli 2009	59.8	7.7	9	63.2	6.7	9	10.7%	-3.40	[-10.07, 3.27]	2009
Oscroft 2010	50.3	8.3	24	47.3	9	24	17.7%	3.00	[-1.90, 7.90]	2010
Oscroft 2014	50.4	3.8	20	54.4	8.3	20	23.9%	-4.00	[-8.00, 0.00]	2014
Ekkenkamp 2014	40.6	7.6	14	43.6	7.1	14	15.0%	-3.00	[-8.45, 2.45]	2014
Storre 2014	47.2	3.9	10	47.1	8.4	10	13.7%	0.10	[-5.64, 5.84]	2014
Nilius 2017	49.1	6.4	14	52.9	6.2	14	19.1%	-3.80	[-8.47, 0.87]	2017
Total (95% CI)	91			91			100.0%	-1.95	[-4.29, 0.40]	

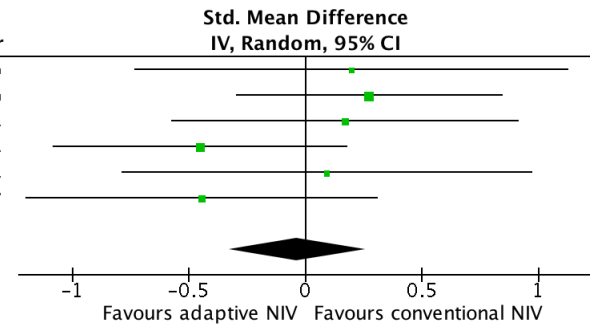
Heterogeneity: Tau² = 1.82; Chi² = 6.35, df = 5 (P = 0.27); I² = 21%
 Test for overall effect: Z = 1.63 (P = 0.10)



Forest plot 5: PO2

Study or Subgroup	Hybrid NIV			Pressure NIV			Weight	Std. Mean Difference		Year
	Mean	SD	Total	Mean	SD	Total		IV, Random, 95% CI	Year	
Crisafulli 2009	-70.2	9.2	9	-72.7	14.4	9	10.0%	0.20	[-0.73, 1.12]	2009
Oscroft 2010	-58.5	9	24	-60.8	7.5	24	26.5%	0.27	[-0.30, 0.84]	2010
Ekkenkamp 2014	-73.4	15.6	14	-76	14	14	15.5%	0.17	[-0.57, 0.91]	2014
Oscroft 2014	-65	12.8	20	-59.1	12.8	20	21.7%	-0.45	[-1.08, 0.18]	2014
Storre 2014	-77.6	18.2	10	-79.1	12.5	10	11.1%	0.09	[-0.79, 0.97]	2014
Nilius 2017	-92.6	3.5	14	-90.9	3.9	14	15.2%	-0.45	[-1.20, 0.31]	2017
Total (95% CI)	91			91			100.0%	-0.04	[-0.33, 0.26]	

Heterogeneity: Tau² = 0.00; Chi² = 4.58, df = 5 (P = 0.47); I² = 0%
 Test for overall effect: Z = 0.25 (P = 0.81)



QUESTION

Should Long-term NIV vs. usual care be used for stable patients with COPD?

POPULATION:	stable patients with COPD
INTERVENTION:	Long-term NIV
COMPARISON:	usual care
MAIN OUTCOMES:	Mortality; Number of Hospitalizations; Quality of Life (higher is better); Change in Dyspnea Score ; Change in PaCO ₂ ; Change in PaO ₂ ; Change in FEV ₁ ; Change in FVC; Change in 6 minute walk distance; Change in Sleep Efficiency; Minor Adverse Events;
SETTING:	
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know		The panel decided on these PICO questions in advance of the guideline meeting on the basis of their importance to clinical practice.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> Trivial <input type="radio"/> Small <input type="radio"/> Moderate <input checked="" type="radio"/> Large <input type="radio"/> Varies <input type="radio"/> Don't know	<p>Desirable Quality of life increased (0.49 SD higher) Reduced dyspnea score (0.51 SD lower). Really key-- this is a critical outcome for patients. Small improvement in 6 minute walk test (~30 m longer)</p> <p>Undesirable Slightly lower sleep efficiency (0.55 SD lower)</p>	<p>Significant concerns raised about the heterogeneity of ventilatory settings-- do studies with higher CO₂ clearance or settings demonstrate a greater effect?</p> <p>Further analysis requested on settings and whether or not there are other effects. Sensitivity analysis done looking at high-vs-low CO₂ targeting.</p>

Increase in minor adverse events eg skin breakdown etc. (10 fold increase)

Neutral/little effect

Reduced mortality with NIV (14%) -not explicitly respiratory causes; and potentially high rate of dropouts, but imprecise with wide 95% CI.
Reduced hospitalizations (mean 1.26 fewer), but imprecise with wide 95% CI
No significant effect upon FEV1 or FVC.

Studies targeting normal CO2 had stronger signal for benefit of NIV.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"><input type="radio"/> Large<input type="radio"/> Moderate<input checked="" type="radio"/> Small<input type="radio"/> Trivial<input type="radio"/> Varies<input type="radio"/> Don't know	<p>Desirable Quality of life increased (0.49 SD higher) Reduced dyspnea score (0.51 SD lower). Really key-- this is a critical outcome for patients. Small improvement in 6 minute walk test (~30 m longer)</p> <p>Undesirable Slightly lower sleep efficiency (0.55 SD lower) Increase in minor adverse events eg skin breakdown etc. (10 fold increase)</p> <p>Neutral/little effect Reduced mortality with NIV (14%) -not explicitly respiratory causes; and potentially high rate of dropouts, but imprecise with wide 95% CI. Reduced hospitalizations (mean 1.26 fewer), but imprecise with wide 95% CI No significant effect upon FEV1 or FVC.</p>	<p>Dropout is also a concern here. Those that did not tolerate NIV fell out and therefore not exposed to benefit. (getting at lack of adherence as well) Meecham-Jones study data missing for sleep quality, though unlikely to change effects.</p>

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"><input type="radio"/> Very low<input checked="" type="radio"/> Low<input type="radio"/> Moderate<input type="radio"/> High<input type="radio"/> No included studies	<p>Moderate certainty for dyspnea scores, changes in PaO2, PCO2. Low or very low certainty evidence for all other outcomes</p>	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Important uncertainty or variability <input checked="" type="radio"/> Possibly important uncertainty or variability <input type="radio"/> Probably no important uncertainty or variability <input type="radio"/> No important uncertainty or variability 	<p>Exacerbations, dyspnea, and quality of life are among the most important outcomes in patients with COPD. Symptom relief was generally found to be more important than adverse events. PMID: 30002103</p>	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input checked="" type="radio"/> Probably favors the intervention <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input type="radio"/> Don't know 		<p>The onyl negative effects see were sleep efficiency and minor adverse events; most other outcomes were positive (QOL, dyspnea, exercise tolerance) or neutral. Of note, mortality and hospitalizations the signal is towards benefit, which is reassuring.</p>

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Large costs <input checked="" type="radio"/> Moderate costs <input type="radio"/> Negligible costs and savings <input type="radio"/> Moderate savings <input type="radio"/> Large savings <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>The estimated costs of providing a domiciliary NIV service are reported in Table 34 and for NIV were £2373 in the first year and £1536 in subsequent years. This estimate was in between cost estimates reported in the two studies identified in the clinical review. Tuggey et al. (2003)⁴⁰ estimate domiciliary NIV to cost £1060 per year in 2003 prices, which converts to £1344 in 2012 prices (assuming a 3% inflation rate), and Clini et al. (2009)¹³⁴ estimated NIV to cost €1920 in 2008 prices, which converts to £2727 (converting to GBP at the mid-year conversion rate of 1.263168 and inflating to 2012 prices at a rate of 3%).</p>	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Very low <input checked="" type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input type="radio"/> No included studies 		<p>Low certainty as the cost and availability of resources for NIV may vary greatly across settings.</p>

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input checked="" type="radio"/> Probably favors the intervention <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input type="radio"/> No included studies 	<p>Economic modelling suggested that NIV may be cost-effective in a stable population at a threshold of £30,000 per quality-adjusted life-year (QALY) gained (incremental cost-effectiveness ratio £28,162), but this is associated with uncertainty. In the case of the post-hospital population, results for three separate base cases ranged from usual care dominating to NIV being cost-effective, with an incremental cost-effectiveness ratio of less than £10,000 per QALY gained. All estimates were sensitive suggested that reductions in the rate of hospital admissions per patient per year of 24% and 15% in the stable and post-hospital populations, respectively, are required for NIV to be cost-effective.</p>	<p>The group vacillated between "Favours the intervention" vs. "Probably favours the intervention." All agreed towards the side of cost effectiveness of NIV vs. comparison.</p>

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Reduced <input type="radio"/> Probably reduced <input type="radio"/> Probably no impact <input type="radio"/> Probably increased <input type="radio"/> Increased <input type="radio"/> Varies <input type="radio"/> Don't know 		<p>COPD patients disproportionately come from disadvantaged populations, so treating COPD may improve equity. In low or middle income countries/populations, home NIV may not be feasible and a recommendation for NIV may exacerbate health equity vs. more financially advantageous regions.</p>

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know		Many clinicians would find NIV acceptable due to its use in acute exacerbations-- it is a familiar therapy to those who treat COPD. Patients may vary with regard to acceptability of NIV in the long-term settings, however if it improves dyspnea and quality of life it may be acceptable.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input type="radio"/> Yes <input checked="" type="radio"/> Varies <input type="radio"/> Don't know		Some regions may not have infrastructure to support this; however there is widespread use of NIV in other countries which can provide practice models to guide practice. This will vary depending on the health care system, resources, and patient location.

SUMMARY OF JUDGEMENTS

PROBLEM	JUDGEMENT						
	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know

RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention <input type="radio"/>	Conditional recommendation against the intervention <input type="radio"/>	Conditional recommendation for either the intervention or the comparison <input type="radio"/>	Conditional recommendation for the intervention <input checked="" type="radio"/>	Strong recommendation for the intervention <input type="radio"/>
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CONCLUSIONS

Recommendation

The ERS TF suggests long-term NIV be used for patients with chronic stable hypercapnic COPD (conditional recommendation, low certainty evidence).

Justification

Most outcomes favour NIV, including patient-important outcomes of dyspnea, QOL, exercise tolerance, with reassuring signal for mortality and exacerbations (towards benefit of NIV), and few harms (minor reduction in sleep efficacy and minor adverse events). Factors such as cost, acceptability, feasibility probably in favour though could vary between patients and settings. Overall balance of effects favour NIV though certainty of evidence is low, hence the panel chose a conditional/weak recommendation for NIV only; this allows a tailored approach to patient and setting-specific conditions as well.

Subgroup considerations

We examined the subgroup of studies which targeted normal CO₂ (generally newer studies). The signal if anything was for more benefit of NIV if lower CO₂ targeted, again suggesting hypercapnic patients derive the most benefit from NIV.

Implementation considerations

The panel recognized that the acceptability, feasibility, and costs of NIV vary greatly. For some patients and clinicians, the potential benefits (dyspnea, QOL, exercise tolerance; possible reduction in hospitalizations, though imprecise evidence) may not be worth it. This is consistent with a conditional recommendation in GRADE.

Monitoring and evaluation

See research priorities, below.

Research priorities

- 1) Strategies for initiating NIV. It is obvious that ventilator setting and acclimatization to NIV are crucial for effectiveness, including better adherence. NIV may be initiated in the hospital or at home. In-hospital initiation can be easily performed in some centers; however, it is more expensive and complex.
- 2) The benefits of NIV in subgroups of patients with COPD. The variability of both adherence and treatment response may vary according to different clinical phenotypes. Indeed, it seems that the response is better in those patients with PaCO₂ > 50mmHg and PaCO₂ reduction to normal following NIV. A phenotyping strategy of hypercapnic COPD subgroups is needed for better defined the populations to be prioritized in further studies.
- 3) The impact of comorbid conditions in this population e.g. the effect of obesity, OSA-overlap, cardiovascular diseases, and clinical frailty upon clinical outcome.
- 4) Assessment of other underestimated factors, such as lack of social support and patient-ventilator asynchrony, which may impact the effectiveness of long-term NIV.
- 5) Cost effectiveness studies reporting the health economic value of long-term NIV in chronic stable COPD.

QUESTION

Should Long-term NIV vs. usual care be used for patients with COPD after an acute hypercapnic respiratory failure episode?

POPULATION:	patients with COPD after an acute hypercapnic respiratory failure episode
INTERVENTION:	Long-term NIV
COMPARISON:	usual care
MAIN OUTCOMES:	Mortality; Exacerbations; Hospitalizations; Dyspnea score; Quality of Life; PaO ₂ ; PaCO ₂ ; Exercise tolerance; FEV ₁ ;
SETTING:	
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem		
Is the problem a priority?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know		The panel decided on these PICO questions in advance of the guideline meeting on the basis of their importance to clinical practice.
Desirable Effects		
How substantial are the desirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> Trivial <input type="radio"/> Small <input checked="" type="radio"/> Moderate <input type="radio"/> Large <input type="radio"/> Varies <input type="radio"/> Don't know	Desirable effect Exacerbations-- small reduction, but imprecise (SMD -0.19 exacerbations, -0.4 to 0.01) Hospitalizations-- small reduction, but imprecise (RR 0.61, 95%CI 0.30 to 1.24) Reduction in PCO ₂ (-3.41 mmHg) Dyspnea (MD -0.80)	Limited evidence based for this discussion. Small sample size and number of trials limit precision. May be a reduction in exacerbations and hospitalizations but limited by imprecision; other patient important outcomes likely also favour NIV but again issues with imprecision.

Quality of life (MD -2.89 measured using SRI)

Undesirable effect

PO2 MD 1.53 mmHg

Little to no effect

Mortality RR 0.92

Exercise tolerance MD 8.64

Inclusion of Chung study which is considered to be at high risk of bias may limit interpretation of some outcome (eg. exacerbations). Sensitivity analysis including and excluding Chung has minimal impact upon point estimates; including increases precision slightly.

Timing of initiation is also an important consideration-- HOT-HMV demonstrated reduction in exacerbations in select population of patients who remain hypercapnic ~2-4 weeks after their exacerbation; this is the subgroup most likely to benefit and possibly why smaller benefits seen with Struik. Sensitivity analysis excluding RESCUE trial demonstrates statistical significance for reduction in events; unfortunately no subgroup of persistent hypercapnia from Struik et al to compare.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Large <input type="radio"/> Moderate <input checked="" type="radio"/> Small <input type="radio"/> Trivial <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>Desirable effect Exacerbations-- small reduction, but imprecise (SMD -0.19 exacerbations, -0.4 to 0.01) Hospitalizations-- small reduction, but imprecise (RR 0.61, 95%CI 0.30 to 1.24) Reduction in PCO2 (-3.41 mmHg) Dyspnea (MD -0.80) Quality of life (MD -2.89 measured using SRI)</p> <p>Undesirable effect PO2 MD 1.53 mmHg</p> <p>Little to no effect Mortality RR 0.92 Exercise tolerance MD 8.64</p>	<p>Even though not reflected in this evidence base, adverse events from Q1 also apply here as indirect evidence as presumably the mask and interfaces have the same effects whether used early after exacerbation or later in stable phase.</p> <p>Its possible that newer techniques and newer interfaces have less side effects.</p>

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Very low <input checked="" type="radio"/> Low 	<p>Low for almost all outcomes due to imprecision.</p>	

<input type="radio"/> Moderate <input type="radio"/> High <input type="radio"/> No included studies		
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Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> Important uncertainty or variability <input checked="" type="radio"/> Possibly important uncertainty or variability <input type="radio"/> Probably no important uncertainty or variability <input type="radio"/> No important uncertainty or variability	Exacerbations, dyspnea, and quality of life are among the most important outcomes in patients with COPD. Symptom relief was generally found to be more important than adverse events. PMID: 30002103	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input checked="" type="radio"/> Probably favors the intervention <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input type="radio"/> Don't know		<p>Probably favors the intervention, especially in subgroup of patients with persistent hypercapnia 2-4 weeks post exacerbation as seen in HOT-HMV trial. Reduction of events is of great importance to patients. Possibly improvements in QOL and dyspnea as well. All outcomes limited by imprecision.</p> <p>ALSO, little evidence of harm from NIV-- suspect that still occurs-- will assume similar rates of minor adverse reactions as in PICO 1, as mask fit etc. likely similar in post-exacerbation as chronic stable population.</p>

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> Large costs <input checked="" type="radio"/> Moderate costs <input type="radio"/> Negligible costs and savings	The estimated costs of providing a domiciliary NIV service are reported in Table 34 and for NIV were £2373 in the first year and £1536 in subsequent years. This estimate was in between cost estimates reported in the two	

<ul style="list-style-type: none"> <input type="radio"/> Moderate savings <input type="radio"/> Large savings <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>studies identified in the clinical review. Tuggey et al. (2003)⁴⁰ estimate domiciliary NIV to cost £1060 per year in 2003 prices, which converts to £1344 in 2012 prices (assuming a 3% inflation rate), and Clini et al. (2009)¹³⁴ estimated NIV to cost €1920 in 2008 prices, which converts to £2727 (converting to GBP at the mid-year conversion rate of 1.263168 and inflating to 2012 prices at a rate of 3%).</p>	
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Certainty of evidence of required resources
 What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Very low <input checked="" type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input type="radio"/> No included studies 		<p>Low certainty as the cost and availability of resources for NIV may vary greatly across settings</p>

Cost effectiveness
 Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input checked="" type="radio"/> Probably favors the intervention <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input type="radio"/> No included studies 	<p>Economic modelling suggested that NIV may be cost-effective in a stable population at a threshold of £30,000 per quality-adjusted life-year (QALY) gained (incremental cost-effectiveness ratio £28,162), but this is associated with uncertainty. In the case of the post-hospital population, results for three separate base cases ranged from usual care dominating to NIV being cost-effective, with an incremental cost-effectiveness ratio of less than £10,000 per QALY gained. All estimates were sensitive to effectiveness estimates, length of benefit from NIV (currently unknown) and some costs. Modelling suggested that reductions in the rate of hospital admissions per patient per year of 24% and 15% in the stable and post-hospital populations, respectively, are required for NIV to be</p>	<p>Probably favours NIV in hypercapnic, "frequent flyer" population with recurrent hospitalizations and exacerbations.</p>

DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention <input type="radio"/>	Conditional recommendation against the intervention <input type="radio"/>	Conditional recommendation for either the intervention or the comparison <input type="radio"/>	Conditional recommendation for the intervention <input checked="" type="radio"/>	Strong recommendation for the intervention <input type="radio"/>
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CONCLUSIONS

Recommendation

The ERS TF suggests long-term NIV be used in patients with COPD following a life-threatening episode of acute hypercapnic respiratory failure requiring acute NIV, if hypercapnia persists beyond 2-4 weeks following the episode (conditional recommendation, low certainty evidence).

Justification

Generally low certainty of evidence, but most important outcomes are neutral (mortality, exercise tolerance) or favour NIV (exacerbations, hospitalizations, HRQOL measured using SRI) without any major harms seen. Reduction in events seen in HOT-HMV trial likely because that trial included patients with persistent hypercapnia some time (2-4 weeks) after event; unfortunately subgroup data from Struik/RESCUE study does not have equivalent subgroup data; NIV appears to result in statistically significant reduction in exacerbations in the persistent hypercapnic subgroup. Subgroup analysis excluding Cheung et al study (thought to be high risk of bias) does not significantly affect estimates. Overall less certainty of effects but desirable effects likely outweigh undesirable effects; given low certainty of evidence only conditional/week recommendation could be made, and this after considering patient values & preferences; acceptability, feasibility and cost of NIV in local setting. Future evidence could change this recommendation in the future.

Subgroup considerations

Major issue is that subgroup of persistently hypercapnic patients from HOT-HMV appear to be most likely to benefit; this subgroup has statistically significant reduction in hospitalizations compared to Struik/RESCUE data.

Implementation considerations

Patients who are started early may not remain hypercapnic; suggest that the group most likely to benefit from NIV is the group who remains hypercapnic 2-4 weeks after the episode, as seen in HOT-HMV. The panel recognized that the acceptability, feasibility, and costs of NIV vary greatly. For some patients and clinicians, the potential benefits (dyspnea, QOL, exercise tolerance; possible reduction in hospitalizations, though imprecise evidence) may not be worth it. This is consistent with a conditional recommendation in GRADE.

Monitoring and evaluation

Research priorities

1. Developing more accurate criteria for identifying patients who are likely to benefit from long-term NIV, such as severity of illness (hypothesis that treatment of higher PaCO₂ at initiation will drive greater clinical benefits), trajectory of hypercapnia recovery after exacerbation (as some patients return to eucapnia more rapidly than others) and treatment response (e.g. early reduction in PaCO₂ level after starting home NIV, with the hypothesis that greater reduction in PaCO₂ will drive greater clinical benefit).

2. Physiological and biological mechanisms of action of long-term NIV: physiological mechanisms determining reduction in PaCO₂; the biological effects of PaCO₂ reduction in chronic hypercapnia upon immune, pulmonary vasculature, and skeletal muscle; biological mechanisms determining reduction in exacerbation; and physiological mechanisms determining enhanced sleep quality.
3. The effects of NIV upon mental health and cognition upon patients, including effects upon HRQL post ARF, cognitive function post-AHRF, the relationship between HRQL and cognitive function upon adherence and acceptability of home NIV.
4. Health service delivery research to promote the delivery of post-acute NIV to the right patient at the right time and prevent the 'overuse' or 'underuse' of the treatment.
5. Assessment of novel home treatments, e.g. high flow humidified nasal oxygen, that are capable of reducing PaCO₂ in stable hypercapnic COPD patients.

QUESTION

Should NIV with targeted normalization of PaCO₂ levels vs. NIV without targeting normal PaCO₂ level be used for long-term NIV in COPD patients?

POPULATION:	long-term NIV in COPD patients
INTERVENTION:	NIV with targeted normalization of PaCO ₂ levels
COMPARISON:	NIV without targeting normal PaCO ₂ level
MAIN OUTCOMES:	Quality of Life; Dyspnea; FEV ₁ ; PaCO ₂ ; PaO ₂ ; 6MWD; Sleep Comfort;
SETTING:	
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem		
Is the problem a priority?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know		The panel chose the PICO questions based upon their apparent relevance to clinical practice.
Desirable Effects		
How substantial are the desirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> Trivial <input checked="" type="radio"/> Small <input type="radio"/> Moderate <input type="radio"/> Large <input type="radio"/> Varies <input type="radio"/> Don't know	<p>Desirable effects Reduction in PaCO₂, generally at rest (reduction 5 mmHg)</p> <p>Undesirable effects Slightly higher dyspnea scores in only 1 RCT</p>	Consider sensitivity analysis excluding Lukacsovits 2012 as measurements for PaO ₂ and PaCO ₂ were measured during NIV. Murphy looked at high-intensity vs. high-pressure. Thus substantial questions therefore raised about the directness of the evidence.

	<p>Minimal effect Quality of life measured with SRI Sleep quality Exercise tolerance</p>	<p>The panel examined the studies from PICO 1 and the subgroup of studies which targeted normalization of CO2 vs. studies which did not target normalization. The subgroup which targeted normal CO2 demonstrated more benefit for NIV (ie effect sizes were larger in studies which targeted normal CO2).</p> <p>The panel judged overall there may be a small benefit to targeting normal CO2.</p>
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Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Large <input type="radio"/> Moderate <input type="radio"/> Small <input checked="" type="radio"/> Trivial <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>Desirable effects Reduction in PaCO2, generally at rest (reduction 5 mmHg)</p> <p>Undesirable effects Slightly higher dyspnea scores in only 1 RCT</p> <p>Minimal effect Quality of life measured with SRI Sleep quality Exercise tolerance</p>	<p>Trivial undesirable effects-- slightly higher dypnea scores in a single study.</p>

Certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input checked="" type="radio"/> Very low <input type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input type="radio"/> No included studies 	<p>Very low certainty evidence. Less certainty as well because studies were generally short-term, without measuring effects upon mortality, hospitalizations, exacerbations.</p>	

Values
Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Important uncertainty or variability <input checked="" type="radio"/> Possibly important uncertainty or variability <input type="radio"/> Probably no important uncertainty or variability <input type="radio"/> No important uncertainty or variability 	<p>Exacerbations, dyspnea, and quality of life are among the most important outcomes in patients with COPD. Symptom relief was generally found to be more important than adverse events. PMID: 30002103</p>	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input checked="" type="radio"/> Probably favors the intervention <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input type="radio"/> Don't know 		<p>While very low certainty of evidence of a small benefit, the anticipated harms are trivial, meaning the evidence probably favours the intervention.</p>

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Large costs <input type="radio"/> Moderate costs <input checked="" type="radio"/> Negligible costs and savings <input type="radio"/> Moderate savings <input type="radio"/> Large savings <input type="radio"/> Varies <input type="radio"/> Don't know 		<p>Implimenting higher intensity CO2 reduction required more time in hospital in one study, though admittedly limited evidence. No formal analysis of cost in any studies.</p>

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
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<ul style="list-style-type: none"> <input checked="" type="radio"/> Very low <input type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input type="radio"/> No included studies 		
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Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input type="radio"/> Probably favors the intervention <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input checked="" type="radio"/> No included studies 		<p>Given lack of certainty of benefits, lack of evidence for costs, the task force could not provide a judgement of the cost-effectiveness of targeting normalization of CO2 levels. If targeting normal CO2 was technically challenging in a given setting, it may not be cost-effective.</p>

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Reduced <input type="radio"/> Probably reduced <input checked="" type="radio"/> Probably no impact <input type="radio"/> Probably increased <input type="radio"/> Increased <input type="radio"/> Varies <input type="radio"/> Don't know 		<p>Probably no impact upon equity when implementing in a patient population already receiving NIV.</p>

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know		<p>This approach is probably acceptable to clinicians, who appreciate having a clear "target" for CO2. It makes physiologic sense to clinicians as well.</p> <p>Patients probably have no issues with acceptability unless settings need to be very high to achieve normal CO2; in such cases high-intensity NIV may not be acceptable.</p>

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know		<p>In situations where NIV is planned, more targeting a significant reduction of CO2 is feasible, though actual normalization of CO2 levels is unlikely to be achieved for many patients, based upon the results of the included studies, which did not demonstrate complete normalization of CO2.</p>

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ●	Strong recommendation for the intervention ○
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CONCLUSIONS

Recommendation

The ERS TF suggests titrating long-term NIV to normalize or reduce PaCO₂ levels in patients with COPD (conditional recommendation, very low certainty evidence).

Justification

We make a conditional recommendation due to the minimal potential harms of targeted normalization of CO₂ and it is recognized that this is unlikely to be achieved in many patients. While high-intensity NIV may or may not have benefits, this is the approach most commonly used in many centres, and thus this is probably the most acceptable approach for many clinicians. Setting NIV to target a reduction in PaCO₂ may require more time spent in hospital and therefore possibly increase costs and decrease feasibility of NIV. Recognizing the lack of compelling evidence, the panel made a conditional recommendation for high-intensity NIV, but low-intensity approaches may also be acceptable and useful in many patients.

Subgroup considerations

Implementation considerations

It is likely reasonable for initially aim for a normal CO₂ in most patients, given the lack of harms and the possible, though very small, benefits with such an approach. If achieving normal CO₂ was very difficult or the settings very high and uncomfortable for the patient, targeting normal CO₂ may not worth lots of effort to achieve.

Monitoring and evaluation

Research priorities

1) The impact of NIV ventilator strategy targeted to maximise PaCO₂ reduction compared to conventional ventilator modes on long-term clinical outcomes (i.e. hyperinflation, exacerbations, cardiovascular complications, hospitalisations, survival, costs, patient's adherence).

QUESTION

Should Adaptive volume-targeted NIV vs. conventional NIV be used for long-term NIV in patients with COPD?

POPULATION:	long-term NIV in patients with COPD
INTERVENTION:	Adaptive volume-targeted NIV
COMPARISON:	conventional NIV
MAIN OUTCOMES:	Quality of Life; Sleep quality; Exercise tolerance; PaCO ₂ ; Oxygenation;
SETTING:	
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input checked="" type="radio"/> Don't know		<p>Question about variable modes is clearly important, however most modes are not studied,</p> <p>All studies in the systematic reviewer compared volume-targeted ventilator modes. The number of studies looking at these modes may reflect the desire of industry to find evidence to support these modes, rather than patient or clinician needs. Safety is the priority question given that these modes could result in hypoventilaion or result in large leaks.</p> <p>The studies included in PICOs 1-3 generally used fixed-pressure modes, making the applicability of evidence for these questions uncertain for auto-titrating modes: there is no long-term evidence of the impact of these modes upon mortality, hospitalizations etc.</p>

Desirable Effects

How substantial are the desirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input checked="" type="radio"/> Trivial <input type="radio"/> Small <input type="radio"/> Moderate <input type="radio"/> Large <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>Desirable effects Small improvement in short-term (~2-3 months) QoL PCO2</p> <p>Undesirable effects</p> <p>Little to no effect Sleep quality Exercise tolerance</p> <p>Unknown Mortality Hospitalizations Exacerbations</p>	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Large <input type="radio"/> Moderate <input type="radio"/> Small <input checked="" type="radio"/> Trivial <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>Desirable effects Small improvement in short-term (~2-3 months) QoL PCO2</p> <p>Undesirable effects</p> <p>Little to no effect Sleep quality Exercise tolerance</p> <p>Unknown Mortality Hospitalizations Exacerbations</p>	<p>Potential harms not included in short-term studies included in meta-analysis.</p> <p>Theoretical risk of large leaks and hypoventilation with auto-titrating modes which may not be evident in short-term studies. Risks of impacting mortality, hospitalizations, and exacerbations.</p>

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Very low <input checked="" type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input type="radio"/> No included studies 	<p>Generally low certainty of pooled evidence.</p>	<p>Substantial uncertainty about the effectiveness across algorithms, machines, makes and models.</p>

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"><input type="radio"/> Important uncertainty or variability<input checked="" type="radio"/> Possibly important uncertainty or variability<input type="radio"/> Probably no important uncertainty or variability<input type="radio"/> No important uncertainty or variability	Exacerbations, dyspnea, and quality of life are among the most important outcomes in patients with COPD. Symptom relief was generally found to be more important than adverse events. PMID: 30002103	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"><input type="radio"/> Favors the comparison<input type="radio"/> Probably favors the comparison<input checked="" type="radio"/> Does not favor either the intervention or the comparison<input type="radio"/> Probably favors the intervention<input type="radio"/> Favors the intervention<input type="radio"/> Varies<input type="radio"/> Don't know		<p>Auto-titrating modes may be more beneficial in those in the setting of exacerbation or in the time of titration when trying to decide on levels of support.</p> <p>Despite possible improvement in short-term QOL, there is no clear benefit to use overall, and ongoing safety concerns about leaks and hypoventilation in the long-term.</p>

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"><input type="radio"/> Large costs<input type="radio"/> Moderate costs<input type="radio"/> Negligible costs and savings<input type="radio"/> Moderate savings<input type="radio"/> Large savings<input checked="" type="radio"/> Varies<input type="radio"/> Don't know		It will cost more to upgrade from an existing machine. For a new machine, the price of a ventilator with these capabilities will vary, but could be anything from no extra cost to expensive depending on make, model, funding strategy, etc.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"><input type="radio"/> Very low<input type="radio"/> Low<input type="radio"/> Moderate<input type="radio"/> High<input checked="" type="radio"/> No included studies		No real evidence to address cost.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"><input type="radio"/> Favors the comparison<input type="radio"/> Probably favors the comparison<input type="radio"/> Does not favor either the intervention or the comparison<input type="radio"/> Probably favors the intervention<input type="radio"/> Favors the intervention<input type="radio"/> Varies<input checked="" type="radio"/> No included studies		Given lack of evidence for benefits and harms, lack of certainty around costs it is difficult to assess cost-effectiveness.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"><input type="radio"/> Reduced<input type="radio"/> Probably reduced<input type="radio"/> Probably no impact		Cost is higher so implementing these modes may increase inequity, heightening disparities between those with financial resources and those without. May reduce inequity as patients who do not have

<input type="radio"/> Probably increased <input type="radio"/> Increased <input checked="" type="radio"/> Varies <input type="radio"/> Don't know	access to a sleep laboratory to titrate NIV may benefit from some titration of NIV settings, though this question has not been studied in the existing clinical trials.
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Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know	Compliance between adaptive VTPCV and conventional NIV were not significantly different in 5 studies (Crisafulli 2009, Oscroft 2010, Oscroft 2014, Ekkernkamp 2014, Storre 2014) which used data directly from the NIV devices. Patient self-reported tolerance was not significantly different in 2 studies (Oscroft 2010, Storre 2014). Self-reported comfort was not different in 2 studies (Crisafulli 2009, Oscroft 2010). One study (Nilius 2017) used a questionnaire to assess acceptability, again finding no differences.	Overall doesn't seem to be any differences in acceptability of these modes vs. conventional fixed pressure modes.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know		Probably feasible, if ventilators already have these modes included. If not, would be less feasible.

SUMMARY OF JUDGEMENTS

PROBLEM	JUDGEMENT						
	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
			Does not favor				

BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention <input type="radio"/>	Conditional recommendation against the intervention <input checked="" type="radio"/>	Conditional recommendation for either the intervention or the comparison <input type="radio"/>	Conditional recommendation for the intervention <input type="radio"/>	Strong recommendation for the intervention <input type="radio"/>
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CONCLUSIONS

Recommendation

The ERS TF suggests using fixed pressure support mode as first-choice ventilator mode in patients with COPD using long-term NIV (conditional recommendation, very low certainty evidence).

Justification

While there may be benefits based upon the included short-term studies, further research is needed to demonstrate safety, especially given potential safety concerns

about dynamic auto-changes of the ventilator resulting in leaks or hypoventilation. Given that virtually all studies in other questions (PICO 1, 2, 3) used fixed-pressure modes, and that the PICO recommendations are thus based upon studies using this mode, it is unclear if the existing evidence would also apply to ventilators using these auto-titrating modes. Lastly, changing to these auto-modes may require purchase or exchange of new ventilators, reducing feasibility. While these modes may theoretically be useful to titrate without monitoring, until the safety of such approach is demonstrated the risks of unmonitored titration are unclear and this is not recommended.

Overall, given the uncertainty of long-term benefits, difficulty applying the evidence and recommendations from PICOs 1-3, the panel made a conditional recommendation against using auto-titrating modes as the initial mode of ventilation. However, conditional recommendation also means there may be some circumstances where these modes are considered for use, though the panel did not identify any such situations.

Subgroup considerations

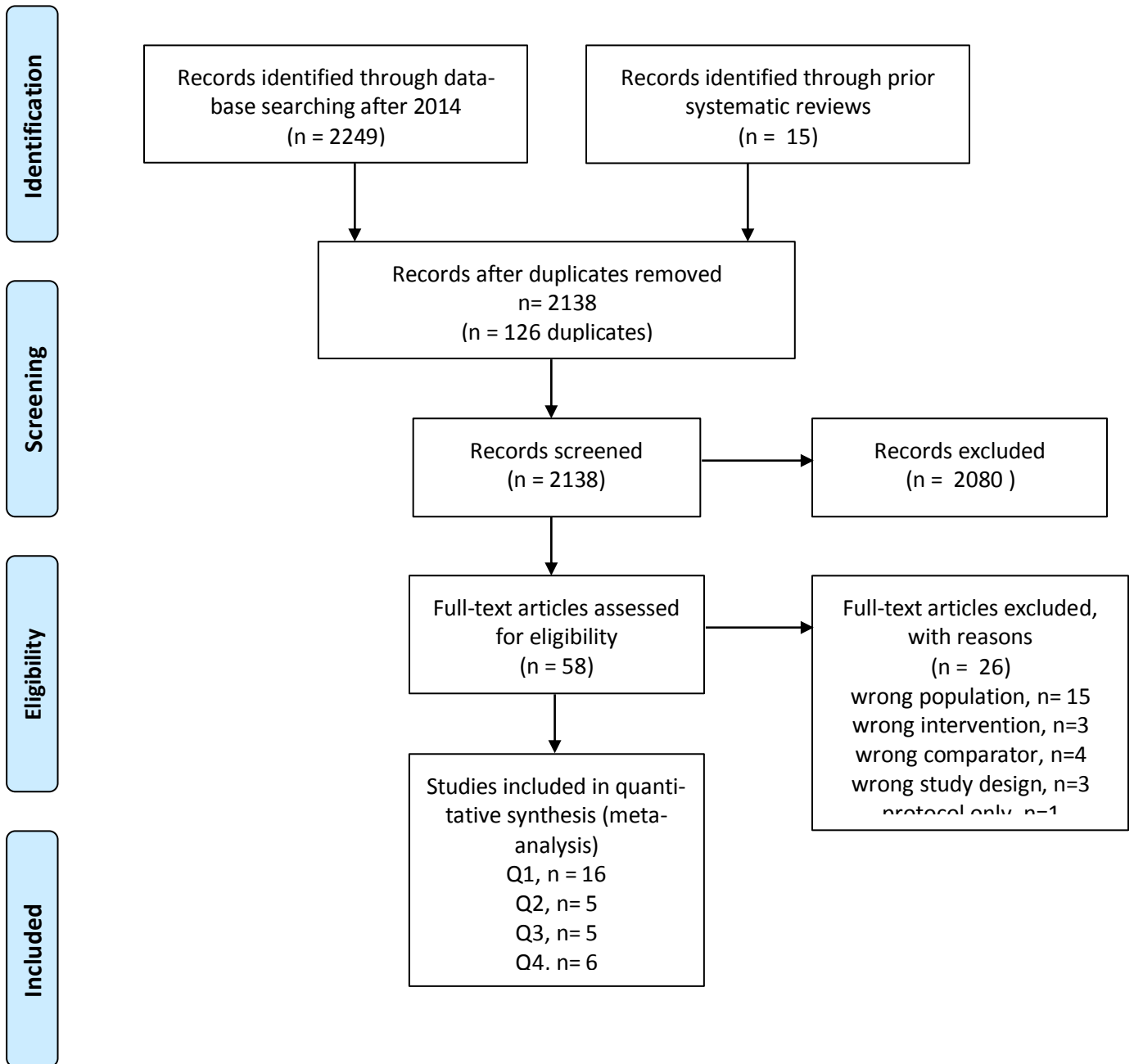
Implementation considerations

Monitoring and evaluation

Research priorities

- 1) The role of adaptive/auto-titrating modes to improve the long-term outcome of COPD, acute exacerbation vs chronic stable hypercapnic COPD and optimization of overnight ventilation, especially in specific subgroups in which ventilatory requirements may vary substantially overnight.
- 2) The assessment of auto-EPAP modes (in addition to adaptive/auto-titrating modes) in the sub-group of patients with COPD-OSA overlap syndrome
- 3) The clinical efficacy and cost effectiveness of auto-titrating modes in the inpatient vs outpatient settings avoiding the need for hospitalization to initiate NIV, thereby increasing access to NIV.

Supplementary Figure 1: PRISMA Diagram of Included Studies



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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