ERS Clinical Practice Guidelines: High-flow nasal cannula in acute respiratory failure

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Early View

Task force report

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ERS Clinical Practice Guidelines: High-flow nasal cannula in acute respiratory failure

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Abstract

Background

High-flow nasal cannula (HFNC) has become a frequently used non-invasive form of respiratory support in acute settings, however evidence supporting its use has only recently emerged. These guidelines provide evidence-based recommendations for the use of HFNC alongside other noninvasive forms of respiratory support in adults with acute respiratory failure (ARF).

Materials and methodology

The European Respiratory Society Task Force panel included expert clinicians and methodologists in pulmonology and intensive care medicine. The Task Force used the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) methods to summarize evidence and develop clinical recommendations for the use of HFNC alongside conventional oxygen therapy (COT) and non-invasive ventilation (NIV) for the management of adults in acute settings with ARF.

Results

The Task Force developed 8 conditional recommendations, suggesting using: 1) HFNC over COT in hypoxemic ARF, 2) HFNC over NIV in hypoxemic ARF, 3)HFNC over COT during breaks from NIV, 4) either HFNC or COT in post-operative patients at low risk of pulmonary complications, 5) either HFNC or NIV in post-operative patients at high risk of pulmonary complications, 6) HFNC over COT in non-surgical patients at low risk of extubation failure, 7) NIV over HFNC for patients at high risk of extubation failure unless there are relative or absolute contraindications to NIV, 8) trialling NIV prior to use of HFNC in patients with chronic obstructive pulmonary disease (COPD) and hypercapnic ARF.

Conclusions

HFNC is a valuable intervention in adults with ARF. These conditional recommendations can assist clinicians in choosing the most appropriate form of non-invasive respiratory support to provide to patients in different acute settings.

Introduction

HFNC is a respiratory support device, which is used during early non-invasive management of acute respiratory failure (ARF), alongside conventional oxygen therapy (COT), and non-invasive ventilation (NIV). Benefits of HFNC, which are both clinical (e.g., patient comfort and ease of use) and physiological (e.g., high oxygenation, alveolar recruitment, humidification and heating, increased secretion clearance, reduction of dead space) (1), can prevent deterioration of lung function and endotracheal intubation (2-4).

However, there is limited evidence on the most appropriate form of non-invasive respiratory support in the different ARF scenarios. While HFNC is more comfortable and tolerated when compared to COT and to NIV, its ability to unload respiratory muscles in ARF may be lower than that provided by NIV. Moreover, prolonging non-invasive respiratory support in patients failing with either HFNC and NIV may result in delayed intubation and worsen hospital mortality (2, 5). Risks and benefits may vary in different scenarios (e.g., hypoxemic and hypercapnic ARF, post-operative and post-extubation ARF, coronavirus disease 2019 [COVID-19] pneumonia).

The European Respiratory Society (ERS) created a Task Force (TF) to provide evidence-based recommendations on HFNC in adults with ARF.

Materials and Methods

Scope and purpose of the document

This document is intended to help clinicians, policy-makers and patients in making evidence-based decisions on HFNC in adults with ARF in different settings. For the most part, the perspective of individual clinicians in high-resourced settings was considered, being reflective of the ERS membership. Nevertheless, feasibility of HFNC in lower-resourced countries has been considered **(Table 1)** (6). Due to limitations in the certainty of evidence and the variation in available resources, all recommendations were weak/conditional.

Composition of the TF panel

The TF consisted of 18 clinicians with expertise in respiratory and acute care medicine. The leadership team consisted of clinical chairs (B. Ergan, R. Scala) along with the methodology team (S. Oczkowski, G. Sotgiu) and ERS methodologist (T. Tonia) who had experience in guidelines development using Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology. The European Lung Foundation (ELF) provided a representative to give a patient perspective.

Conflict of interest declaration and management

All TF members were required to disclose any financial conflicts and sign a confidentiality agreement in accordance with the ERS policy.

Formulation of questions

An initial list of eight questions was developed by the TF chairs (BE, RS) and submitted to ERS for approval. The questions were structured in PICO (population; intervention; comparison; outcomes) format and, together with a list of outcomes, were approved by the TF panelists and the methodology team **(Table 2).** The TF planned two *a priori* subgroups: for PICO questions on hypoxemic respiratory failure: immunocompetent and immunocompromised patients. With the advent of the COVID-19 pandemic in March 2020, the TF included a third subgroup: COVID-19 patients.

Literature searches

With the assistance of a medical librarian, the methodology team conducted systematic searches of the medical literature. We searched up to January 2021 in MEDLINE, Embase (database inception onwards) and Cochrane CENTRAL (2006 onwards) for relevant observational studies and randomized clinical trials (RCTs). **(supplementary material - search strategy and results)**

The retrieved references were screened in duplicate using Covidence reference management software.(7) We included English-language RCTs and observational studies comparing HFNC to COT or NIV. **(supplemental Figure S1)** Data was extracted into a pilot-tested data extraction form, and entered into Revman v.5.3 software for meta-analysis.(8) For each PICO question the methodology team, with input from the TF chairs, rated the certainty of evidence for each outcome using standard GRADE methods and created evidence summaries.(9, 10) Certainty of evidence was rated as "high," "moderate," "low," or "very low" with RCTs starting as "high" certainty and observational evidence as "low" certainty.(11) Evidence could be rated down one or two levels based upon whether the included studies were judged to be at high risk of bias,(12) results were inconsistent between studies,(13) the evidence was indirect,(14) imprecise,(15), or at high risk of publication bias.(16)

The TF was asked to prioritize the initial list of outcomes, rating their clinical importance from 1-9, with mean scores of 1-3 indicating "low importance", 4-6 "important but not critical," and 7-9 as "critical".(17) The panel prioritized as "critical" mortality, intubation, and escalation of treatment.

A virtual meeting was held during the ERS Congress in September 2020 to discuss PICOs and the literature search results. The leadership team met virtually in November 2020 to work through the GRADE evidence-to-decision (EtD) framework and develop draft recommendations. The EtD framework considers balance of desirable and undesirable effects, certainty of effects, patient values and preferences, resource use, cost-effectiveness, health equity, and acceptability and feasibility of an intervention in order to develop an overall recommendation.(18) Recommendations were designated as "weak/conditional" or "strong," using the wording "we suggest" and "we recommend," respectively.(19)

The TF panel reviewed the evidence and draft recommendations, and voted on both using the GRADEPro PanelVoice system between December 2020 and January 2021.(20) For a weak/conditional recommendation a majority vote was sufficient to approve the recommendation; for a strong recommendation, stronger agreement (>70%) was required.

Questions for which consensus were not reached were re-evaluated by the leadership team based upon feedback from the TF, revised, and had additional rounds of voting to reach consensus.

Results

All recommendations had consensus except for PICO questions #7 and #8, for which a second round of voting was conducted. Evidence summaries (including forest plots from meta-analyses) and Evidence-to-Decision Framework summaries for each PICO can be found in the supplementary material.

HFNC FOR HYPOXEMIC ACUTE RESPIRATORY FAILURE

PICO Question 1 : *Should HFNC or COT be used in patients with acute hypoxemic respiratory failure?*

1.

Recommendation 1: *We suggest the use of HFNC over COT in adults acute hypoxemic respiratory failure (conditional recommendation, moderate certainty of evidence).*

Background

Acute hypoxemic respiratory failure (AHRF) is caused by a wide range of etiologies including pulmonary infection, inflammation, or exacerbation of chronic heart or lung disease. The clinical spectrum of AHRF ranges from mild hypoxemia to full-blown acute respiratory distress syndrome (ARDS). In this question de-novo AHRF was addressed, rather than established ARDS, as there is not yet consensus on whether non-intubated patients can be diagnosed with ARDS.(21) Non-invasive respiratory support aims to improve hypoxemia, reduce work of breathing, enhance comfort, avoid intubation, and provide time to effectively treat the triggering condition, thereby reducing mortality.(22) Unfortunately, many patients with AHRF require escalation to invasive mechanical ventilation (IMV). (23) The most

common non-invasive respiratory treatment in AHRF is COT, which increases the fraction of inspired oxygen (FiO_2), using simple interfaces including nasal prongs, facemask with reservoirs, or Venturi mask. Potential mechanisms of COT failure include ineffective support matching patient ventilatory needs due to altered respiratory mechanics, unreliable FiO_2 delivery, lack of humidification, and patient self-inflicted lung injury (P-SILI).(24, 25) HFNC is a non-invasive, high concentration oxygen delivery interface which addresses some of the limitations of COT. By providing airflows as high as 50–60 litres/minute, HFNC closely matches the inspiratory demands of dyspneic patients with AHRF, and reliably achieves an FiO_2 as high as 100%, while also providing a low level of positive end-expiratory pressure (PEEP) in the upper airways, facilitating alveolar recruitment. (2) Other potential benefits of HFNC over COT include decreased risk of P-SILI avoiding harmful changes in trans-pulmonary pressure, carbon dioxide (CO_2) washout of upper airways, improved ventilation; and provision of reliable humidification, which may result in increased patient comfort and enhanced secretion clearance.(1, 26-28) These clinical and physiologic benefits constitute a strong rationale for early use of HFNC to prevent the need of non-invasive and invasive positive-pressure ventilation, and to reduce the risk of mortality mostly correlated with ventilator-associated complications. This is particularly true for immunocompromised patients who are more likely to develop complications correlated to IMV, such as ventilator-associated pneumonia (VAP).(29, 30)

Evidence Summary

12 parallel-group RCTs (31-42) and 4 cross-over RCTs (27, 43-45) comparing HFNC to COT were selected. In general, the evidence is limited by imprecision. Mortality is similar in the short term (hospital, intensive care unit [ICU], or 28 days) (RR 0.99, 95% CI 0.84-1.17; RD -0.3% 95%CI -4.1 to 4.3; moderate certainty) or 90 days (RR 0.97, 95% CI 0.83-1.13; RD -1.0, 95%CI -5.7 to 4.4; moderate certainty). 11 studies evaluated the effect of HFNC on intubation, finding that HFNC may reduce intubation (RR 0.89, 95% CI 0.77-1.02; RD -3.1%,

95% CI -6.4 to 0.6; moderate certainty) and escalation to NIV (RR 0.76, 95%CI 0.43 to 1.34; RD -2.9%, 95%CI -6.9 to 4.1, moderate certainty).(32-38, 40-42) HFNC reduces patient discomfort (SMD 0.54 lower, 95% CI 0.86 lower to 0.23 lower; high certainty), dyspnea (SMD 0.32 lower, 95% CI 0.66 lower to 0.03 higher; moderate certainty), and slightly lowers respiratory rate (MD 2.25 RPM, 95%CI 3.24 lower to 1.25 lower; high certainty). The impact of HFNC upon gas exchange is generally small, with HFNC increasing partial pressure of oxygen in arterial blood (PaO_2) values (MD 16.72 mmHg, 95% CI 5.74 higher to 27.71 higher; high certainty) and, possibly, the ratio of partial pressure of oxygen in arterial blood to fraction of inspired oxygen (PaO_2/FiO_2) (MD 25.01 mmHg, 95% CI 14.21 lower to 64.24 higher; low certainty); without a substantial effect on $PaCO_2$ values (MD 0.01 mmHg, 95% CI 1.17 lower to 1.2 higher, high certainty).

Impact upon length of stay is inconsistent, suggesting an increased ICU stay by 1.97 days (95% CI 1.02 higher to 2.93 higher, moderate certainty), with a small overall reduction in hospital length of stay of 0.72 days (95% CI 1.54 lower to 0.1 higher, moderate certainty).

For the subgroup of immunocompromised patients, effects are similar, with no impact upon mortality, (33, 34, 38, 42) although without the reduced intubation rate between HFNC and COT. No RCTs evaluating HFNC vs. COT in patients with COVID-19 were found.

Justification

The guideline TF panel makes a conditional recommendation for HFNC over COT as the evidence suggested that the balance of effects, particularly a reduction in intubation, likely favors HFNC over COT. However, the panel's certainty is limited by imprecision. The impact on mortality is likely small (<1%). Thus, HFNC is most likely to benefit patients who are at high risk of intubation; its use should be favored in patients with more severe disease rather than patients requiring low oxygen flow rates, or in those with severe symptoms, given the improvements in patient comfort, dyspnea, respiratory rate, and gas exchange. The panel

notes that AHRF, particularly ARDS, is heterogenous: identifying patients most likely to benefit from HFNC requires clinician judgment.(46)

The TF does not identify any major tradeoffs in which patient values would likely play a role, as both the increased comfort of HFNC along with lower intubation rates would likely be preferred by most patients.

There is limited evidence on resource utilization. While material cost, set-up, and oxygen use of HFNC are likely higher than COT, avoiding intubation may save money and ancillary costs (ie, sedation, ventilators, monitors). On the other hand, during times of resource scarcity other considerations (avoiding intubation vs. limiting oxygen vs. human resources) may influence the choice of HFNC versus. COT. While the existing evidence suggests an increased ICU length of stay, the panel is uncertain as hospital policies differ whether or not HFNC requires ICU, intermediate care and respiratory high-dependency unit (step-down/step-up unit), or general ward. (47) Overall hospital length of stay may be unaffected by use of HFNC. TF identified one study evaluating cost-effectiveness of HFNC in the pre-intubation phase in the UK.(48) It found that HFNC resulted in overall cost-savings of £156 compared to COT, and higher savings of £727 in high-risk patients. In low-income countries HFNC may reduce health equity (e.g., the device may not be available to all persons, and high oxygen use by HFNC may limit availability of oxygen to other patients). Widespread use of HFNC in ICUs demonstrates feasibility of the device, even in resource-constrained settings during a pandemic.(49)

Subgroup considerations

Data for both immunocompetent and immunocompromised subgroups were estimated and similar for mortality, but showing a smaller magnitude for intubation and escalation to NIV in the immunocompromised subgroup. There is no evidence of increased harm in the use of HFNC VS. COT. Given this residual uncertainty, the panel decided there is insufficient data to make a separate recommendation.

There is little high-quality data to guide effectiveness of HFNC in COVID-19, however, given the heterogeneity of patients which may include other viral pneumonias and ARDS, it is reasonable to make the same conditional recommendation. Use of HFNC requires separate consideration of resources, including protective personal equipment (PPE) and ventilation, given the currently unknown risks of transmissibility from patients using HFNC versus COT.(50-53) The panel does not make a recommendation regarding the use of awake prone position in HFNC, recognizing there is little evidence and RCTs to address the question.(54-57)

PICO Question 2: *Should HFNC or NIV be used in patients with acute hypoxemic respiratory failure?*

Recommendation 2: *We suggest the use of HFNC over NIV in patients with acute hypoxemic respiratory failure (conditional recommendation, very low certainty of evidence).*

Background

HFNC and NIV are used more frequently in patients with progressive or moderate to severe AHRF (PaO_2/FiO_2 ≤200 mmHg), when the risks of intubation and death are higher.(23, 24). In more severe AHRF (PaO_2/FiO_2 <100), clinicians aim to balancing the benefits of maintaining spontaneous breathing and averting intubation together with its complications (*i.e.*, VAP and ventilator-induced lung injury [VILI]) versus. the harms of delayed intubation, including high inspiratory effort, increased lung stress, and risk of lung injury during non-invasive respiratory support.(58) HFNC is an attractive alternative to NIV for treating patients with AHRF and high respiratory demand.

While NIV provides higher mean airway pressures than HFNC and assists ventilation by effectively unloading respiratory muscles, treatment failure is frequent. NIV failure occurs more likely in patients with more severe ARF: PaO_2/FiO_2 <200 mmHg before treatment and higher SAPSII (>35) are associated with a two-fold risk of intubation.(59) Improvement in gas exchange provided by NIV may help identify patients at greatest risk of treatment failure,

as PaO_2/FiO_2 <175 mmHg after one hour of NIV is associated with need for intubation.(23) Finally, expired tidal volume exceeding 9-9.5 ml/Kg of predicted body weight while undergoing NIV delivered in pressure support mode (PSV) with a low level of assistance can predict treatment failure with good specificity and sensitivity.(60, 61)

There are practical differences between HFNC and NIV which may impact patient comfort and tolerance. While HFNC devices use a similar interface, NIV can be delivered using either a facemask or helmet interface. To date, the most frequently used interface in RCTs has been face mask NIV, although helmet NIV may be more comfortable and allow the application of a more "protective" ventilation with higher PEEP (*i.e.*, 8-12 cmH2O) and lower pressure support values with fewer air leaks and interruptions.(62, 63) Clinicians now have the option of HFNC and NIV with a variety of interfaces for use in AHRF; however, the recent ERS/ATS TF did not offer a recommendation on the use of NIV for de novo AHRF, noting that the majority of the studies used COT as a comparator.(23)

Evidence summary

We identified 5 parallel-group RCTs (33, 64-67) and 2 crossover RCTs (68, 69) comparing HFNC to NIV in AHRF. Three RCTs reported short-term mortality (hospital, ICU, or 28-day), finding that HFNC may reduce mortality (RR 0.77, 95%CI 0.52 to 1.14; RD -4.5%, 95%CI -9.4 to 2.7; very low certainty); however, this is limited by imprecise and inconsistent effects between the studies. One trial reported a possible large reduction in mortality with use of HFNC (RR 0.43, 95%CI 0.25 to 0.78; RD -16.1%, 95%CI -21.4 to -6.2; low certainty). In both, the panel raises concerns that the NIV used does not reflect current real-world practice (lower intensity and duration - only 8 hours/day) and thus the evidence is rated down for indirectness. 5 RCTs evaluated effect of HFNC on intubation, demonstrating that HFNC may reduce intubation (RR 0.84, 95% CI 0.61 to 1.16; RD -4.1%, -10.1 to 4.1; low certainty), but this result is limited by indirectness and imprecision. (33, 64-67)

HFNC may have a small impact on length of stay, potentially decreasing ICU stay by 0.55 days (95% CI -2.0 to 0.89, low certainty) and increasing overall hospital stay by 0.8 days (95% CI -0.59 to 2.19, very low certainty). Pooled analysis of 4 RCTs shows that HFNC may improve patient comfort (SMD -0.23, 95% CI -0.55 to 0.09, moderate certainty) but results in greater degree of perceived dyspnea than NIV (SMD 0.19, 95% CI -0.01 to 0.40, very low certainty).(33, 44, 65,69)

Looking at the physiologic effects of HFNC, pooled analysis of 4 (33,44,67,69) and 3 RCTs (33,67,69) respectively shows that HFNC slightly increases PaO_2 values (MD 19.98 mmHg, 95% CI 11.97 to 28.0, moderate certainty) and PaO_2/FiO_2 ratio (MD 43.26, 95% CI 29.48 to 57.04, moderate certainty), with little difference in $PaCO_2$ values (MD 0.45 mmHg (95% CI 1.94 lower to 1.05 higher, low certainty) or respiratory rate (MD 0.83 RPM, 95% CI -1.04 to 2.7, low certainty).

Justification

The panel judged that the existing evidence generally supports the use of HFNC over NIV as first-line treatment for AHRF, but this evidence is limited by imprecision, and there is still uncertainty as to the true effect of NIV, given concerns about the indirectness of the comparison NIV as used in the studies. In particular, the trial by Frat *et al.* demonstrated the largest benefit of HFNC, but NIV had short therapeutic time (8 hours per day), and lower levels of PEEP than those commonly prescribed (especially with helmet interface) and possibly no humidification used in the NIV arm.(33) Additionally, the included studies generally used facemask which may not be as well tolerated.(70) Therefore, the TF rates down all outcomes for indirectness, resulting in very low certainty for critical outcomes. Reassuringly, for almost every outcome (other than dyspnea) HFNC appeared to be beneficial or at least neutral compared to NIV.

The TF acknowledges uncertainty regarding which patients are most likely to benefit from each device. Individual patient factors and clinical decision-making play an important role in

choosing which respiratory support should be adopted. While NIV may be relatively contraindicated in some patients (e.g., excessive secretions, facial hair/structure resulting in air leaks, poor compliance), and HFNC the clearly superior option, there may be a subset of patients for whom NIV may be preferable. These may be patients with increased work of breathing, respiratory muscle fatigue, and congestive heart failure, in which the positive pressure of NIV may positively impact hemodynamics. A trial of NIV might be considered for select patients with AHRF, pneumonia, or early ARDS if there are no contraindications and close monitoring by an experienced clinical team who can intubate patients promptly if they deteriorate.(23) In such cases individual clinician judgment is key to choose NIV, interface, and settings.

The TF does not identify any major tradeoffs where patient values may play a role in deciding between HFNC and NIV; almost all outcomes favored HFNC. Overall, the TF's considerations for resource use are similar to those in Recommendation 1, though noted that the actual device and setup for NIV require more resources than COT, making the difference between the two alternatives less pronounced. Resource considerations and cost-effectiveness of HFNC versus NIV may vary between regions.

Subgroup Considerations

Benefits of HNFC may be greater in immunocompromised patients. However, these results are entirely derived from one study and remain imprecise, and judged insufficient for a strong recommendation. The TF choose to make only a single recommendation.

No RCTs comparing HFNC to NIV in COVID-19 were available, and the panel choose to not make a separate recommendation. Subsequent to the TF voting, an RCT comparing HFNC to helmet NIV in COVID was published: it found no differences in respiratory support-free days or mortality at 30 or 60 days, but a reduction in intubation at 28 days (OR 0.37; 95%CI 0.17 to 0.82; RD -23%, 95%CI -39 to -5).(71) While suggesting helmet NIV may reduce intubation compared to HFNC in COVID-19, it is interesting that mortality between the

groups is unchanged. While this study demonstrates the viability of both devices in COVID-19, further research is needed before a definitive recommendation can be issued, especially as helmet NIV is not available in all centers and such a recommendation would require substantial change in practice for many hospitals.

PICO *Question* ***3****: Should HFNC or COT be used during breaks from NIV in patients with acute hypoxemic respiratory failure?*

Recommendation 3: *We suggest use of HFNC over COT during breaks from NIV in patients with acute hypoxemic respiratory failure (conditional recommendation, low certainty of evidence)*

Background

While NIV is frequently used to treat ARF, breaks from NIV are necessary for practical reasons (feeding, speaking), patient's tolerance (relief from mask pressure), and to ascertain readiness for weaning from NIV. COT is used during these breaks; however, HFNC may be a more effective alternative. Sequential alternating protocols (e.g., sessions of 2h HFNC followed by 1h NIV) may limit the need for prolonged NIV by maintaining adequate oxygenation. In a small (n= 28) prospective single-centre observational study, it was shown that HFNC was better tolerated than NIV and allowed for significant improvement in oxygenation and tachypnea compared with COT.(72) Thus, for patients treated with NIV, it remains open the question of whether COT or HFNC should be prescribed during breaks.

Evidence Summary

One RCT evaluated 47 patients receiving humidified facemask NIV for ≥24 hours.(73). Half had AHRF, the majority of whom showing a PaO_2/FiO_2 ratio <300. The study was prematurely terminated for slow recruitment rate. Although underpowered to determine differences in intubation rate (2/28 VS. 0/26, p-value: 0.49, very low certainty) the total time spent on NIV between the HFNC and COT groups was similar (1315 (225) minutes VS. 1441

(220) minutes, p-value: 0.07). However, HFNC resulted in better comfort measured with mean±SD visual analogue scores (8.3±2.7 VS. 6.9±2.3), and, during breaks, mean±SD respiratory rate (20.1±4.1 VS. 21.8±5.2) and mean±SD perceived dyspnea (2.1±2.8 VS. 2.4±2.2) were reduced. The frequency of adverse events (e.g., eye irritation, 8% VS. 21.6%) and of difficulty in eating (13.3% VS. 36.2%) were lower with HFNC during breaks compared to COT.

Justification

Given that the direct evidence consisted of a single study, the TF considered indirect evidence from Recommendation 1. Both direct and indirect evidence suggest a small benefit from HFNC over COT during breaks off NIV, with few undesirable effects. The impact upon critical outcomes (e.g., mortality, intubation) is unclear, but likely to be small. Thus, the TF suggests that in the subset of patients with AHRF for whom clinicians and patients choose NIV HFNC may be preferred over COT during breaks. As the potential benefits are small and there is a likely wide variation in resources, these should be the primary factor in deciding whether to prescribe HFNC over COT during breaks from NIV. As the major benefits appear to be linked to patient comfort, rather than to reduction in intubation requirement, the cost-effectiveness is likely to be low.

2. HFNC IN POST-OPERATIVE PATIENTS

Background

Post-operative pulmonary complications (PPC) play a significant role in determining patient morbidity, mortality, and length of hospital stay.(74-76) Most frequent during the first 7 days after an operation, PPC range from atelectasis to ARDS. The risk of ARF, likely the most important PPC, is dependent upon many factors including the surgery (e.g., duration of surgery or type of surgical procedure leading to increased post-operative pain or respiratory muscle dysfunction), anesthesia (e.g., general anesthesia), mechanical ventilation (e.g., intra-

operative high tidal volume ventilation), and patient (e.g., age, co-morbidities, and life-style factors). The choice of post-operative respiratory supportive strategies may affect the risk of PPC. COT is the first-line post-operative respiratory therapy, but it does not provide a reliable FiO_2 or a real support for work of breathing. NIV and continous positive airway pressure (CPAP) are second-line respiratory support when COT fails, leading to airway splinting and reduced work of breathing through better respiratory compliance and inspiratory effort.(23) Both NIV and CPAP appear effective in patients with post-operative ARF, especially after abdominal and thoracic surgery. NIV was shown to reduce intubation rate, incidence of nosocomial infections, length of stay, and mortality rates; therefore, official ERS/ATS clinical practice guidelines suggest NIV for patients with post-operative ARF.(23) Other pre-operative guidelines suggest that NIV should be performed by physicians with skill in airway management and ventilation of patients with lung injury.(77) HFNC should be prescribed in hypoxemic patients with poor tolerance of non-invasive respiratory support. Drawbacks of post-operative NIV/CPAP are related to a monitored setting and to the risk of failure due to poor patient tolerance of the positive pressure or interface, or skin breakdown. HFNC may overcome these limitations.(78, 79) These findings are particularly relevant in surgical hypoxemic patients, given the potential for anastomotic leakage and delayed wound healing when positive pressure NIV or mechanical ventilation are applied.(80, 81) COT shows several drawbacks, including insufficient warming and humidification. Because of increased muco-ciliary clearance,(1) augmented dead space washout, and improved pulmonary mechanics, HFNC may be an effective alternative alongside COT and NIV/CPAP in post-operative patients whose hypoxemia is often highly dependent on alveolar collapse.(82)

According to the PPO risk profile (low versus high), two recommendations have been produced comparing HFNC to COT and NIV in posteoperative patients.

PICO Question 4: *Should HFNC or COT be used in post-operative patients after extubation?*

Recommendation 4: *We suggest the use of either COT or HFNC in postoperative patients at low risk of respiratory complications (conditional recommendation, low certainty of evidence).*

Evidence summary

The TF identified 14 RTCs evaluating HFNC in comparison with COT in post-operative patients.(80, 83-95) HFNC likely has little to no effect upon mortality (RR 0.64, 95%CI 0.19 to 2.14; RD -0.5%, 95%CI -1.1 to 1.5; moderate certainty). It may result in small reduction in risk of reintubation (RR 0.66 95%CI 0.23 to 1.91; RD -1.2, 95%CI -2.8 to 3.3; low certainty) and uncertain reduction in risk of escalation to NIV (RR 0.77, 95%CI 0.42 to 1.40; RD -2.6, -6.8 to 4.7; very low certainty). Length of stay in hospital and ICU is reported in 10 and 11 RCTs, respectively, demonstrating that HFNC has little effect on ICU length of stay (MD 0.02 days, 95% CI -0.09 to 0.13; high certainty), and on hospital stay (MD -0.47 days, 95%CI -0.83 to -0.11; high certainty).

HFNC has little effect on discomfort (SMD 0.54 lower, 95% CI -1.12 to 0.05, low certainty), but may result in higher PaO_2/FiO_2 ratio (MD 34.89 mmHg, 95%CI -15.19 to 84.96; moderate certainty) and PaO_2 values (MD 6.2 mmHg, 95%CI 3.58 to 8.28; high certainty); with no significant effect on $PaCO_2$ values (MD -1.9 mmHg, 95% CI -4.81 to 0.38; high certainty) or respiratory rate (MD -0.14 RPM, 95%CI -0.83 to 0.54; moderate certainty).

Justification

As the evidence was unclear regarding whether the balance of effects favors the routine use of HFNC VS. COT post-operatively, the TF decided on a conditional recommendation for either HFNC or COT in post-operative patients. While point estimates for mortality, reintubation, hospital length of stay, and physiologic variables potentially favor HFNC, the certainty of evidence for critical outcomes (mortality, reintubation, escalation to NIV) is low, limited by imprecision.

The following limitations were found: heterogeneity and low event rates, higher prevalence of patients undergoing cardiac and thoracic surgery, different ways of COT application (e.g., low versus high flow face-mask delivery system). As the panel does not identify any significant undesirable clinical effects with HFNC, either would be reasonable; however, in most centers, it is likely that HFNC will cost more and COT would be the preferred respiratory support. The TF did not identify any major tradeoffs where variability of patient values and preferences would impact the use of HFNC.

Even though costs and cost-effectiveness of HFNC and COT will vary between centers, COT may be favored over HFNC in low income countries in terms of limited resource utilization.

The panel did not identify any significant elements regarding the acceptability of HFNC. HFNC is likely to be a feasible supportive option in patients after surgery, especially those already planned for admission to a monitored setting.

Clinicians and patients may choose to use HFNC over COT in specific circumstances, based upon patient comfort, perceived risk of pulmonary complications, and resources/availability of devices. Key issues to consider if HFNC is to be chosen over COT are related to patient characteristics (e.g., co-morbidities), surgical variables (*i.e.*, risk of complications), resource considerations (e.g., availability of devices, monitoring, staffing, oxygen), and patient preferences (e.g., comfort, dyspnea, etc.).

PICO Question 5*: Should HFNC or NIV be used in post-operative patients after extubation?*

Recommendation 5: *We suggest either HFNC or NIV in post-operative patients at high risk of respiratory complications (conditional recommendation, low certainty of evidence).*

Evidence summary

One trial compared HFNC to NIV in 830 patients with or at high risk of ARF after cardio-thoracic surgery.(78) When compared to NIV (≥4hrs/day, PS level at 8 cmH2O, PEEP level at 4 cmH2O, FiO_2 50%), HFNC (continuous, flow, 50L/min, FiO_2 50%) may result in a small increase in mortality (RR 1.22, 95%CI 0.72 to 2.09; RD 1.2%, 95%CI -1.5 to 6.0; low

certainty), with likely little to no difference in reintubation (RR 1.02, 95%CI 0.73 to 1.44; RD 0.3%, 95%CI -3.7 to 6.0; moderate certainty). HFNC results in little to no difference in length of stay in ICU (MD 0 days, 95% CI -0.6 to 0.6; moderate certainty), or hospital (MD -1 day, 95%CI -2.21 to 0.21, moderate certainty). HFNC has little to no effect upon $PaCO_2$ values and respiratory rate, but results in a slightly lower PaO_2/FiO_2 ratio (MD -63, 95%CI -80 to -46; high certainty). Skin breakdown is significantly more prevalent with NIV than HFNC after 24 hours.

Justification

The evidence comes from a single trial of patients with or at risk for respiratory failure after cardiothoracic surgery, and patients with other types of surgery are described. While HFNC appears to be similar to NIV, data is limited by imprecision. Point estimate for mortality favors NIV over HFNC, but this is limited by very serious imprecision, which does not exclude neither clinically meaningful benefit nor harm from the use of HFNC. As the desirable and undesirable effects appear to be closely balanced between HFNC and NIV, the TF choose to make a conditional recommendation suggesting that either HFNC or NIV could reasonably be used, based upon individual patient, surgical, and resource considerations. A subgroup analysis of this trial demonstrated similar effects in obese subjects (BMI>30 kg/m2) (n=231).(96)

The TF does not identify any major instances where variation in patient values, acceptability, or feasibility would be likely to impact the use of HFNC VS. NIV for patients planned for admission to a monitored setting. Resources and cost-effectiveness are expected to vary.

3. HFNC TO PREVENT EXTUBATION FAILURE IN NON-SURGICAL PATIENTS

***PICO Question 6**: Should HFNC or COT be used in non-surgical patients after extubation?*

Recommendation 6: *We suggest HFNC over COT in non-surgical patients after extubation at low or moderate risk of extubation failure (conditional recommendation, low certainty of evidence).*

Background

Extubation remains a challenge in some patients (e.g. presence of weak cough, poor neurologic status, older patients with severe cardiac or respiratory disease) and between 10-20% of attempts at extubation will fail. (97, 98) Re-intubation may lead to prolonged mechanical ventilation and longer ICU stay, increased hospital morbidity and mortality. Sufficient oxygen delivery after extubation is critical to maintain adequate oxygenation. Extubated patients often require elevated inspiratory flow and adequate oxygen administration. HFNC may prevent hypoxemic episodes after extubation, decrease respiratory rate, facilitate removal of secretions, reduce atelectasis, and lead to a higher probability of extubation success when compared to COT. The question is based on the assessment of HFNC as a first-line therapy for ICU patients after extubation.

Evidence summary

Pooled analysis of RCTs (99-110) shows HFNC when compared to COT likely reduces the rate of reintubation (RR 0.62 95% CI 0.38 to 1.01; RD -5.1% 95% CI -8.2 to 0.1%; moderate certainty) and the need for escalation to NIV (RR 0.38 95% CI 0.17 to 0.85; RD -9.4% 95% CI -12.5 to -2.3%; moderate certainty) for ICU patients at risk of respiratory failure after extubation. There is likely no effect on mortality (RR 1.01 95% CI 0.68 to 1.52, RD -0.1 % 95% CI -3.7 to 4.3%, moderate certainty). Lengths of ICU (MD 0.29 days, 95% CI -0.27 to 0.85 days, high certainty) and hospital stay (MD -1.08 days, 95% CI -4.83 days to 2.66, low certainty) are similar for HFNC and COT. HFNC is associated with small improvement in comfort (SMD 0.77 SD, 95% CI 0.03 to 1.5 SD, high certainty) and reduction of respiratory rate (MD -1.98 RPM 95% CI -3.9 to -0.06; high certainty). Gas exchange is not significantly

different exposed to HFNC or COT, (PaO2 MD 7.57 mmHg, 95%CI 2.68 to 12.46, high certainty; $PaCO_2$ MD 0.15mmHg, 95%CI -1.89 to 1.58 mmHg, high certainty).

Justification

HFNC after extubation in non-surgical patients may reduce reintubation rate and escalation to NIV with no major undesirable side effects. There is no effect on mortality with moderate certainty, limited by imprecision. The TF does not identify any tradeoffs where patient values and preferences would be likely to vary; almost all patients would prefer to avoid re-intubation. The major limitation for widespread use of HFNC is accessibility of HFNC and available resources. A UK cost-effectiveness analysis suggested that HFNC is likely cost-effective even in patients at low-risk of reintubation.(111) Cost-effectiveness regionally varies, and is probably less for patients at low risk of complications.

PICO Question 7: *Should HFNC or NIV be used in non-surgical patients after extubation?*

Recommendation 7: *We suggest the use of NIV over HFNC after extubation for patients at high risk of extubation failure unless there are relative or absolute contraindications to NIV (conditional recommendation, moderate certainty of evidence).*

Background

NIV has been proposed as a method to prevent post-extubation respiratory failure and need for reintubation, especially in patients at high risk of extubation failure. Patients at high risk are those who can develop hypercapnia during the spontaneous breathing trial, those with chronic cardiac and respiratory disorders, with advanced age, and with airway patency problems.(112) Official ERS/ATS clinical practice guidelines for NIV in ARF suggested NIV to prevent post-extubation respiratory failure in patients at high-risk of extubation failure (Conditional recommendation, low certainty of evidence).(23) Indeed early NIV administration after planned extubation decreases both rate of reintubation and mortality.

Compared to NIV, HFNC improves patient comfort and limits the risk of NIV-related adverse events and may be better tolerated alternative to NIV.

Evidence summary

Seven RCTs (16-22) which compared HFNC to NIV in patients at high risk of reintubation were found.(79, 113-118) Two studies reported few outcomes of interest,(114, 117) and one study compared HFNC with CPAP (5 cmH2O through a mechanical valve) and was not included in the comparison.(113) Of the remaining 4 studies two enrolled only patients with Chronic Obstructive Pulmonary Disease (COPD) (115, 118) and one compared NIV interspaced with HFNC between NIV sessions VS. HFNC alone.(116)

Compared to NIV, HFNC increases the rate of reintubation (RR 1.31, 95% CI 1.04 to 1.64; RD 4.4%, 95%CI 0.6 to 9.2; high certainty), with little effect on mortality (RR 1.07 95% CI 0.84 to 1.36; RD 1.0%, 95%CI -2.3 to 5.1; moderate certainty). HFNC results in slightly lower length of stay in ICU (MD 1.0 day lower, 95% CI 1.52 to 0.47 days lower; high certainty) and hospital (MD 1.44 days lower, 95% CI 2.63 to 0.25 days lower; high certainty). Compared to NIV, HFNC provides a small increase in patient comfort (SMD 0.73 SD lower, 95% CI 0.98 to 0.49 SD lower, high certainty). There is no difference with respect to respiratory rate (MD 0.59 RPM lower, 95% CI -2.48 to 1.29; high certainty) and gas exchange (PaO_2/FiO_2 MD 3.86, 95%CI 0.39 to 7.34; high certainty; $PaCO_2$ MD 1.01 mmHg lower; 95%CI -1.47 to -0.55 mmHg, high certainty).

Justification

HFNC appears to result in small but likely clinically important increased risk of reintubation (~4%) compared to NIV in non-surgical patients at high risk of extubation failure. On the other hand, compared to NIV, HFNC slightly improves patient comfort. Therefore, in patients who are intolerant or have contraindications to NIV, HFNC may be an alternative to NIV for preventing post-extubation respiratory failure. NIV interspaced with HFNC breaks

between NIV sessions is a strategy which may be effective to further improve oxygenation and reduce post-extubation respiratory failure by gaining the benefits of NIV, with increased comfort from HFNC. (116) The TF judges the large majority of the patients would likely value avoiding reintubation over the increased comfort of HFNC, and, thus, in patients without any contraindications, NIV would generally be preferred. There is limited evidence related to costs for both NIV and HFNC, and these will likely vary between centers.

4.HFNC IN HYPERCAPNIC RESPIRATORY FAILURE

PICO Question 8*: Should HFNC or NIV be used in patients with acute hypercapnic respiratory failure?*

Recommendation 8: *We suggest a trial of NIV prior to use of HFNC in patients with COPD and acute hypercapnic respiratory failure (conditional recommendation, low certainty of evidence).*

Background

COPD is the fourth leading cause of chronic morbidity in the world.(119) COPD can result in acute exacerbations, characterized by worsening of respiratory symptoms and hypercapnic acute-on-chronic respiratory failure.(120) While other conditions, such as neuromuscular disease, may be characterized by acute episodes of acute respiratory failure, the mechanism for the increase in carbon dioxide is distinct from COPD.(121) Official ERS/ATS guidelines recommend NIV for patients with COPD and acute hypercapnic acidotic respiratory failure (pH ≤7.35), including those requiring endotracheal intubation and mechanical ventilation, unless the patient is immediately deteriorating.(23) HFNC has physiologic rationale (ie. oxygenation, positive pressure, reduced deadspace) for use in hypercapnic exacerbation of COPD, along with its ease of use and patient comfort , make it an alternative to NIV for acute-on-chronic hypercapnic respiratory failure of mild to moderate severity degree of respiratory acidosis.(3, 28, 122) However, its role in COPD and other diseases presenting with acute hypercapnic respiratory failure is not yet well established.

Evidence summary

Five parallel-group RCTs (123-127) and one crossover RCT (128) comparing HFNC to NIV in hypercapnic respiratory failure, of which most patients had COPD, were found. Mean baseline $PaCO_2$ ranged from 56 to 73.7 mmHg, and pH ranged between 7.26 to 7.4, indicating mild to moderate hypercapnic decompensated respiratory failure.

HFNC may not reduce mortality (RR 0.82, 95% CI 0.46 to 1.47; RD -3.1%, 95%CI -9.2 to 8.0, low certainty) or intubation rate (RR 0.79, 95% CI 0.46 to 1.35; RD -3.6%, 95% CI -9.3 to 6.0; low certainty), both limited by very serious imprecision. Length of stay in ICU (MD 0.1, 95% CI -0.73 to 0.94, moderate certainty) and hospital (MD -0.82, 95% CI -1.83 to 0.20) are similar between HFNC and NIV. HFNC may be more comfortable compared to NIV (MD -0.57, 95% CI -0.98 to -0.16, low certainty), although dyspnea is similar (MD -0.31, 95% CI -0.94 to 0.33, moderate certainty). Gas exchange, including $PaCO_2$, and respiratory rate were similar between HFNC and NIV.

Justification

Overall, the evidence for mortality and intubation is of low certainty, primarily due to imprecision, which does not rule out a clinically significant benefit or harm of HFNC VS. NIV. This is insufficient to make a recommendation in favor of HFNC, given the high-certainty evidence for the use of NIV in COPD, and that more evidence would be required before HFNC could be considered equivalent or superior to NIV.(23) Hence, the panel chose to make a weak/conditional recommendation, suggesting a trial of NIV prior to use of HFNC. While NIV has high evidence for hypercapnic acidotic respiratory failure, it cannot be tolerated by some patients, who may prefer HFNC being more comfortable, and allowing easier communication, feeding, and oral care. A trial of NIV allows clinicians to determine the severity of respiratory failure, the response to treatment, and whether a patient can have a transition to HFNC. HFNC should be preferred over COT during breaks off NIV, but also in

exacerbated COPD patients as HFNC significantly reduces the activation of the diaphragm and improves comfort, without affecting gas exchange. (129)

HFNC settings were heterogeneous. The flow was set in a range between 35 and 60 L/min and titrated as much as tolerated by the patients. The temperature was set at 34 or 37°C according to patient's preference, whereas FiO_2 was adjusted to achieve a arterial oxygen saturation with pulse oximetry (SpO_2) between 88% and 92%.

There is poor evidence on resource requirements. The cost of one HFNC device (e.g., interface, circuit, humidity) may be similar to that of a ventilator for NIV, although other resources (e.g., staffing and monitoring), and some ICU ventilators have integrated both HFNC and NIV software, making the interface the only substantive cost difference. In addition, the prescription of HFNC requires fewer resources than NIV, even in terms of healthcare workload. Acceptability and feasibility of HFNC in COPD is likely high, as clinicians are increasingly comfortable with using HFNC.

Discussion

The TF developed eight evidence-based, actionable recommendations, along with implementation considerations to assist patients, clinicians, policy makers, and other healthcare stakeholders to make rational and evidence-based decisions for using HFNC in the acute care setting. The TF identified key areas where further research is necessary to guide practice. (Table 3)

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Table 1: Interpretation of strong and conditional recommendations

	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 preferences.	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.

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.

Reproduced from The GRADE Handbook (6)

Table 2: PICO questions and recommendations

Question	Recommendation
1. Should HFNC or COT be used in patients with acute hypoxemic respiratory failure?	The ERS task force suggests the use of HFNC over COT in patients with acute hypoxemic respiratory failure (conditional recommendation, moderate certainty of evidence).
2. Should HFNC or NIV be used in patients with acute hypoxemic respiratory failure?	The ERS task force suggests the use of HFNC over NIV in acute hypoxemic respiratory failure. (conditional recommendation, very low certainty of evidence)
3. Should HFNC or COT be used during breaks from NIV in patients with acute hypoxemic respiratory failure?	The ERS task force suggests the use of HFNC over COT during breaks from NIV in patients with acute hypoxemic respiratory failure (conditional recommendation, low certainty of evidence)
4. Should HFNC or COT be used in post-operative patients after extubation?	The ERS task force suggests the use of either COT or HFNC in postoperative patients at low risk of respiratory complications. (conditional recommendation, low certainty of evidence)
5. Should HFNC or NIV be used in post-operative patients after extubation?	The ERS task force suggests the use of either HFNC or NIV in postoperative patients at high risk of respiratory complications. (conditional recommendation, low certainty of evidence).
6. Should HFNC or COT be used in non-surgical patients after extubation?	The ERS task force suggests the use of HFNC over COT in non-surgical patients after extubation (conditional recommendation, low certainty of evidence).

Question	Recommendation
7. Should HFNC or NIV be used in non-surgical patients after extubation?	The ERS task force suggests the use of NIV over HFNC for patients at high risk of extubation failure, unless there are absolute or relative contraindications to NIV (conditional recommendation, moderate certainty of evidence).
8. Should HFNC or NIV be used in patients with acute hypercapnic respiratory failure?	The ERS task force suggests a trial of NIV prior to use of HFNC in patients with COPD and acute hypercapnic respiratory failure (conditional recommendation, low certainty of evidence).

Table 3: Research recommendations

Question	Key research recommendations
1. Should HFNC or COT be used in patients with acute hypoxemic respiratory failure?	More evidence is needed to identify patients at high risk of deterioration and therefore more likely to benefit from HFNC. Which treatment (HFNC or COT) results in aerosolization of infectious particles in COVID-19, and what are the clinical implications of this?
2. Should HFNC or NIV be used in patients with acute hypoxemic respiratory failure?	More evidence needed to assess the impact of HFNC vs. NIV in COVID-19 and other viral illnesses , as well as in patients at different risk of induced lung injury, different PaO_2/FiO_2 ratio severity. More evidence is needed regarding effectiveness of HFNC vs. NIV in both helmet and facemask forms. Which treatment (HFNC or COT) results in aerosolization of infectious particles in COVID-19, and what are the clinical implications of this?
3. Should HFNC or COT be used during breaks from NIV in patients with acute hypoxemic respiratory failure?	More evidence is needed to identify patients who are likely to benefit from HFNC during breaks from NIV (hypoxic and hypercapnic populations).
4. Should HFNC or COT be used in post-operative patients after extubation?	More evidence is needed to identify which patients (type of surgery, comorbidities, PaO_2/FiO_2 level) are most likely to benefit from HFNC over COT when used post-operatively according to different settings (high vs

Question	Key research recommendations
	low intensity monitoring); however it is likely that any such effects in low-risk groups will be small.
5. Should HFNC or NIV be used in post-operative patients after extubation?	Further large RTCs are needed to compare NIV and HFNC in different subgroups of surgical patients according to different settings (high vs low intensity monitoring). Additional research is needed to identify the subgroups of post-operative patients at high risk of respiratory failure most likely to benefit from use of combination treatment (NIV plus HFNC) vs. NIV alone.
6. Should HFNC or COT be used in non-surgical patients after extubation?	More evidence is needed to identify which patients (underlying disease, comorbidities, PaO_2/FiO_2 level) according to different settings (high vs low intensity monitoring) are most likely to benefit from post extubation HFNC over COT.
7. Should HFNC or NIV be used in non-surgical patients after extubation?	More evidence is needed to identify which patients (underlying disease, comorbidities, PaO_2/FiO_2 level) according to different settings (high vs low intensity monitoring) are most likely to benefit from postextubation HFNC over COT are most likely to benefit from NIV over HFNC

Question	Key research recommendations
8. Should HFNC or NIV be used in patients with acute hypercapnic respiratory failure?	More randomized data are required to determine populations where HFNC can be a first-line alternative to NIV (eg. severity of COPD; patients with hypercapnic failure from causes other than COPD; hypesecretion, poor mask tolerance, agitation). More evidence needed to predict which patients are likely to successfully transition to HFNC from NIV.

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Supplement: Evidence profiles

ERS Guidelines: High flow nasal cannula in acute respiratory failure

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Recommendation 1: High flow nasal cannula (HFNC) vs conventional oxygen therapy (COT) in hypoxemic respiratory failure

Certainty assessment						№ of patients		Effect		Certainty	Importance
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HFNC	COT	Relative (95% CI)	Absolute (95% CI)		
Mortality (90 day)											
4 RCTs	not serious	not serious	not serious	serious [a]	none	208/659 (31.6%)	208/620 (33.5%)	**RR 0.97** (0.83 to 1.13)	**10 fewer per 1,000** (from 57 fewer to 44 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Mortality (ICU, hospital, or 28 day)											
6 RCTs	not serious	not serious	not serious	serious [a]	none	189/773 (24.5%)	187/734 (25.5%)	**RR 0.99** (0.84 to 1.17)	**3 fewer per 1,000** (from 41 fewer to 43 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Intubation											
11 RCTs	not serious	not serious	not serious	serious [a]	none	231/943 (24.5%)	253/907 (27.9%)	**RR 0.89** (0.77 to 1.02)	**31 fewer per 1,000** (from 64 fewer to 6 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Escalation to NIV											
6 RCTs	not serious	not serious	not serious	serious [a]	none	38/409 (9.3%)	47/388 (12.1%)	**RR 0.76** (0.43 to 1.34)	**29 fewer per 1,000** (from 69 fewer to 41 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Hospital length of stay											
5 RCTs	not serious	not serious	not serious	serious [a]	none	683	660	-	MD **0.72 days lower** (1.54 lower to 0.1 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
ICU length of stay											
2 RCTs	not serious	not serious	not serious	serious [b]	none	494	482	-	MD **1.97 days higher** (1.02 higher to 2.93 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Patient comfort											
6 RCTs	not serious	not serious	not serious	not serious	none	303	293	-	SMD **0.54 lower** (0.86 lower to 0.23 lower)	⨁⨁⨁⨁ HIGH	IMPORTANT
Dyspnea											

Recommendation 1: High flow nasal cannula (HFNC) vs conventional oxygen therapy (COT) in hypoxemic respiratory failure

6 RCTs	not serious	not serious	not serious [c]	serious [a]	none	173	189	-	SMD **0.32 lower** (0.66 lower to 0.03 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
PaO2/FiO2											
4 RCTs	not serious	serious [d]	not serious	serious [a]	none	526	514	-	MD **25.01 higher** (14.21 lower to 64.24 higher)	⨁⨁◯◯ LOW	IMPORTANT
PaO2											
6 RCTs	not serious	not serious	not serious	not serious	none	202	193	-	MD **16.72 higher** (5.74 higher to 27.71 higher)	⨁⨁⨁⨁ HIGH	IMPORTANT
PCO2											
6 RCTs	not serious	not serious	not serious	not serious	none	202	193	-	MD **0.01 higher** (1.17 lower to 1.2 higher)	⨁⨁⨁⨁ HIGH	IMPORTANT
Respiratory rate											
10 RCTs	not serious	not serious	not serious	not serious	none	713	716	-	MD **2.25 lower** (3.24 lower to 1.25 lower)	⨁⨁⨁⨁ HIGH	IMPORTANT

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

Explanations

a. Significant imprecision which does not rule out clinically significant benefit nor harm.

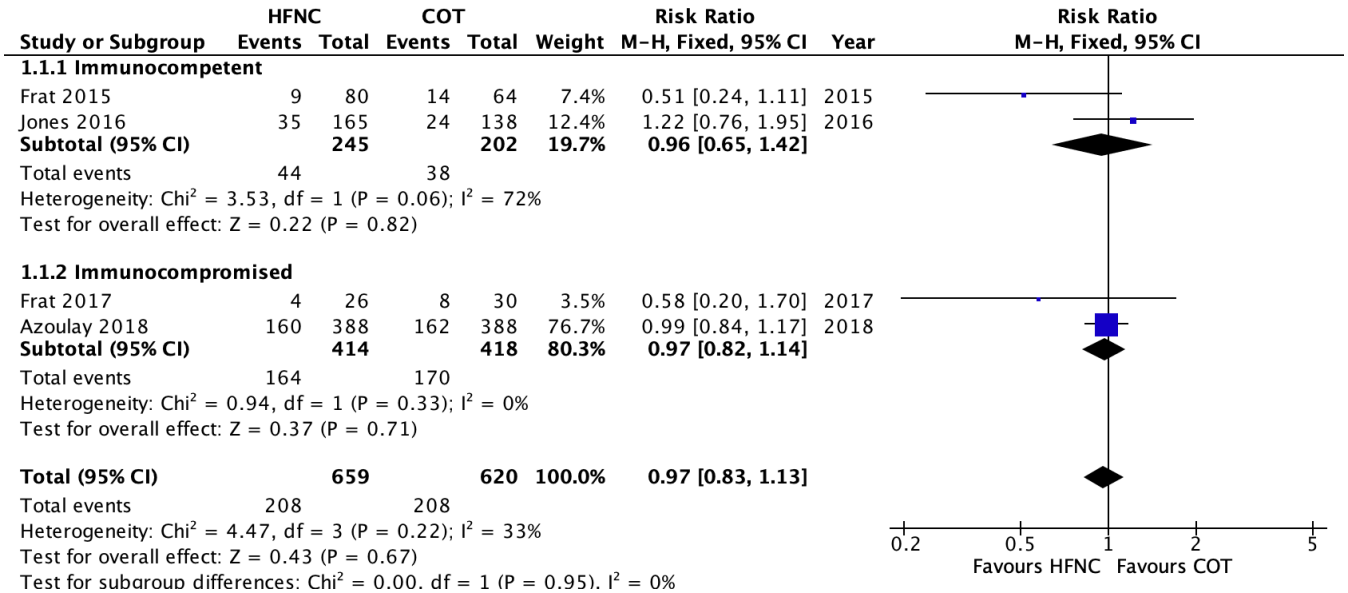
b. Though Azoulay 2018 demonstrates statistically significant increase in ICU length of stay, when estimated means and SD are used, they are not statistically significant when median (IQR) are compared.

c. Most studies used the validated Borg dyspnea scale.

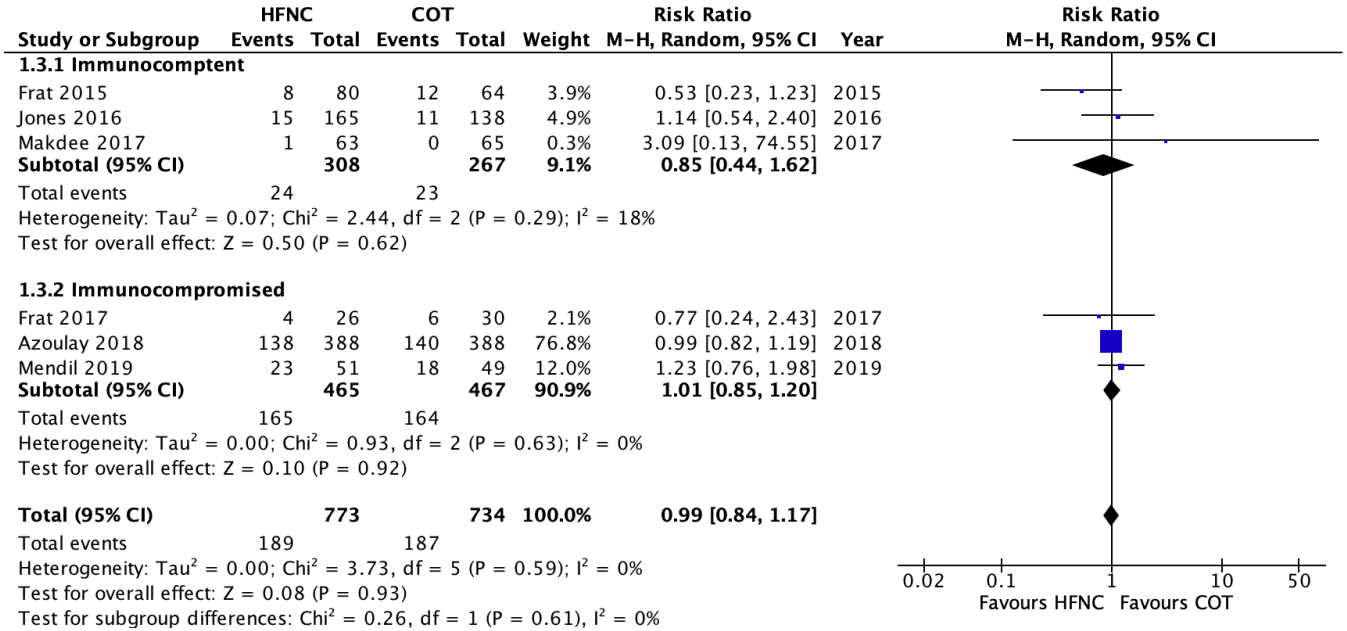
d. Very significant heterogeneity between the Frat 2015 RCT and the other trials (I2= 93%) of likely clinical significance.

Recommendation 1: High flow nasal cannula (HFNC) vs conventional oxygen therapy (COT) in hypoxemic respiratory failure

1. Mortality (90 day)

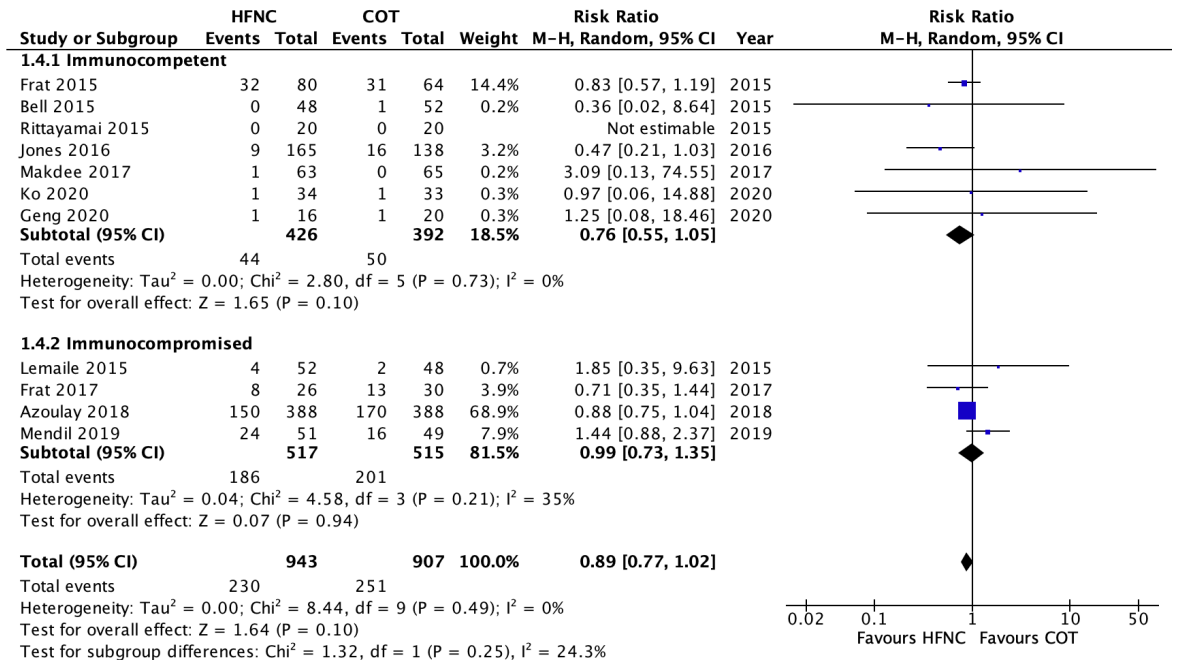


2. Mortality (early - ICU, hospital, or 28 day)

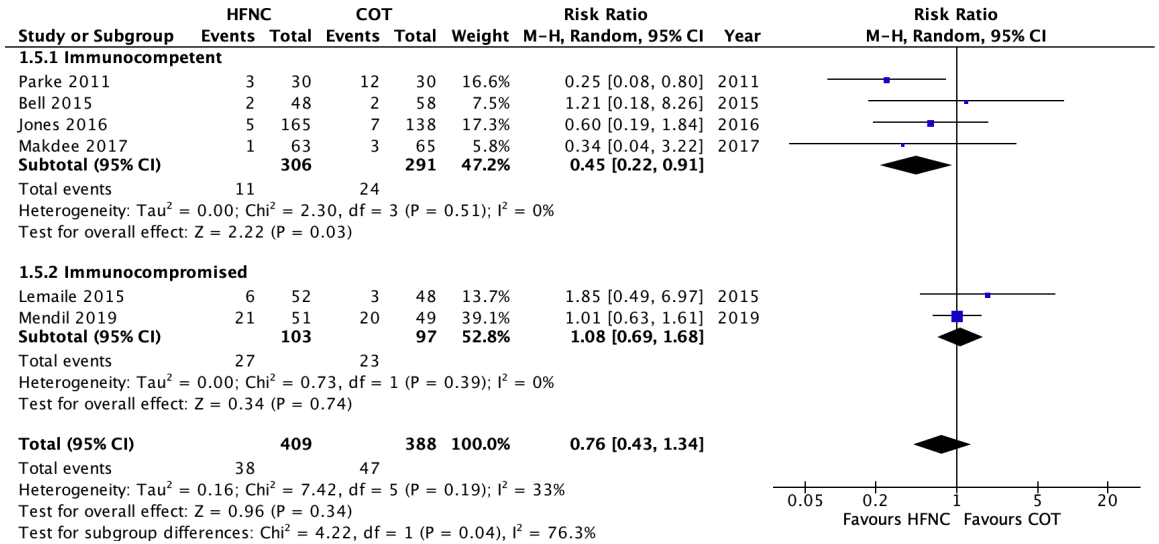


Recommendation 1: High flow nasal cannula (HFNC) vs conventional oxygen therapy (COT) in hypoxemic respiratory failure

3. Intubation



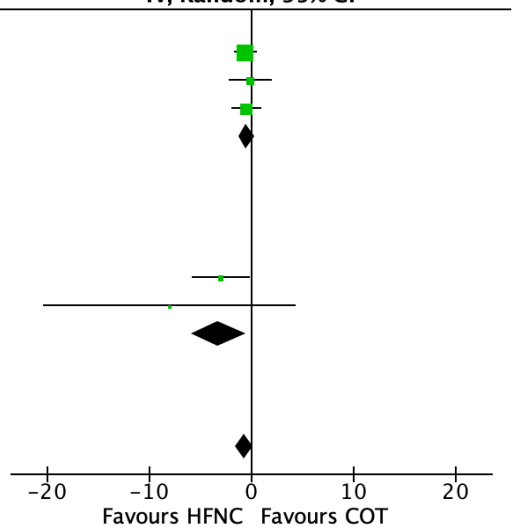
4. Escalation to NIV



Recommendation 1: High flow nasal cannula (HFNC) vs conventional oxygen therapy (COT) in hypoxemic respiratory failure

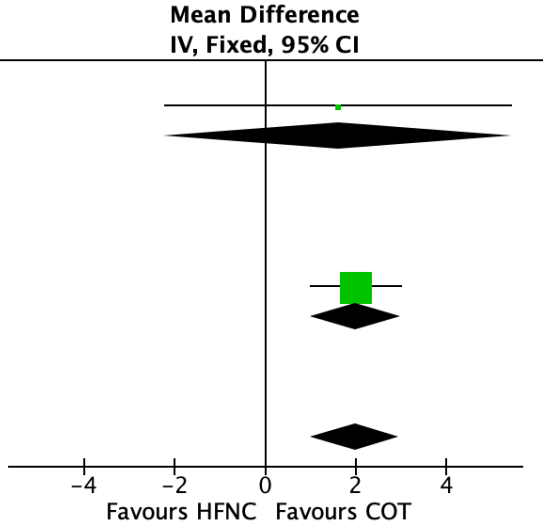
5. Hospital length of stay

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	COT Mean	COT SD	COT Total	Weight	Mean Difference IV, Random, 95% CI	Year
1.7.1 Immunocompetent									
Jones 2016	5	4.1	165	5.6	4.8	138	46.3%	−0.60 [−1.62, 0.42]	2016
Makdee 2017	1.1	6.9	63	1.2	4.32	65	15.2%	−0.10 [−2.10, 1.90]	2017
Geng 2020	6.54	1.85	16	7.02	2.32	20	29.6%	−0.48 [−1.84, 0.88]	2020
Subtotal (95% CI)			**244**			**223**	**91.2%**	**−0.49 [−1.25, 0.26]**	
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.19$, df = 2 (P = 0.91); $I^2 = 0\%$									
Test for overall effect: Z = 1.28 (P = 0.20)									
1.7.2 Immunocompromised									
Azoulay 2018	24	19.2	388	27	20	388	8.4%	−3.00 [−5.76, −0.24]	2018
Mendil 2019	28	30.8	51	36	31.8	49	0.4%	−8.00 [−20.28, 4.28]	2019
Subtotal (95% CI)			**439**			**437**	**8.8%**	**−3.24 [−5.93, −0.55]**	
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.61$, df = 1 (P = 0.44); $I^2 = 0\%$									
Test for overall effect: Z = 2.36 (P = 0.02)									
Total (95% CI)			**683**			**660**	**100.0%**	**−0.72 [−1.54, 0.10]**	
Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 4.51$, df = 4 (P = 0.34); $I^2 = 11\%$									
Test for overall effect: Z = 1.72 (P = 0.08)									
Test for subgroup differences: $Chi^2 = 3.71$, df = 1 (P = 0.05), $I^2 = 73.1\%$									



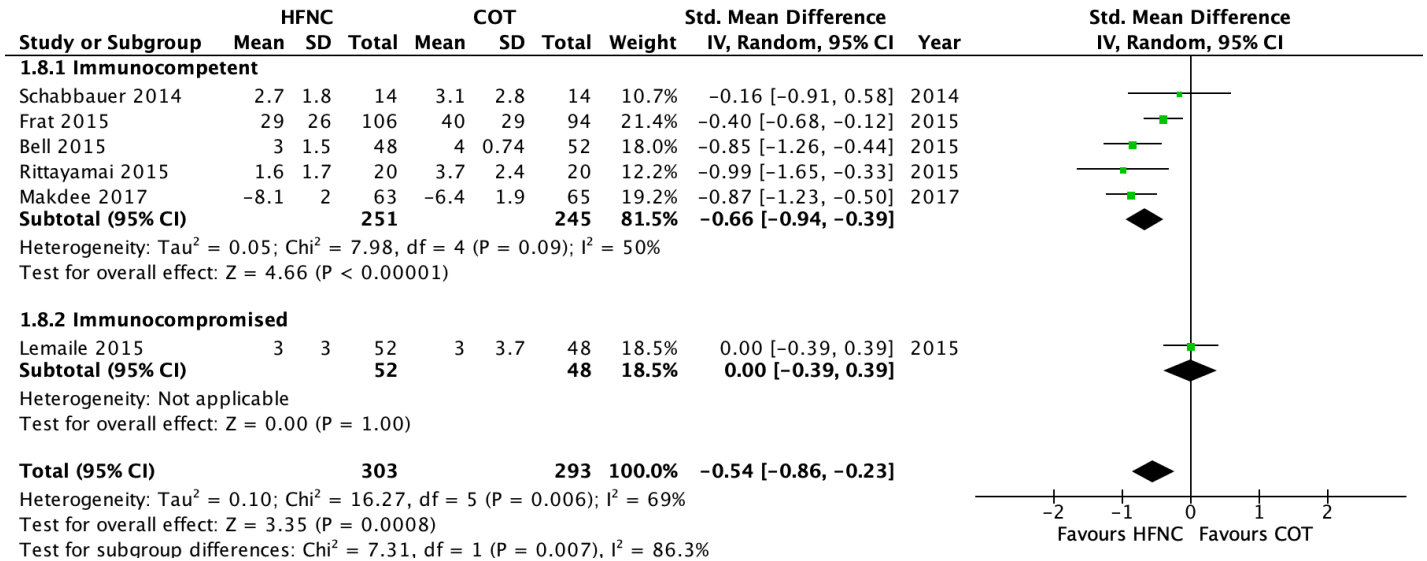
6. ICU length of stay

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	COT Mean	COT SD	COT Total	Weight	Mean Difference IV, Fixed, 95% CI
1.6.1 Immunocomptent								
Frat 2015	10.7	15.8	106	9.1	11.7	94	6.3%	1.60 [−2.23, 5.43]
Subtotal (95% CI)			**106**			**94**	**6.3%**	**1.60 [−2.23, 5.43]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.82 (P = 0.41)								
1.6.2 Immunocompromised								
Azoulay 2018	8	7.4	388	6	6.67	388	93.7%	2.00 [1.01, 2.99]
Subtotal (95% CI)			**388**			**388**	**93.7%**	**2.00 [1.01, 2.99]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.95 (P < 0.0001)								
Total (95% CI)			**494**			**482**	**100.0%**	**1.97 [1.02, 2.93]**
Heterogeneity: $Chi^2 = 0.04$, df = 1 (P = 0.84); $I^2 = 0\%$								
Test for overall effect: Z = 4.03 (P < 0.0001)								
Test for subgroup differences: $Chi^2 = 0.04$, df = 1 (P = 0.84), $I^2 = 0\%$								

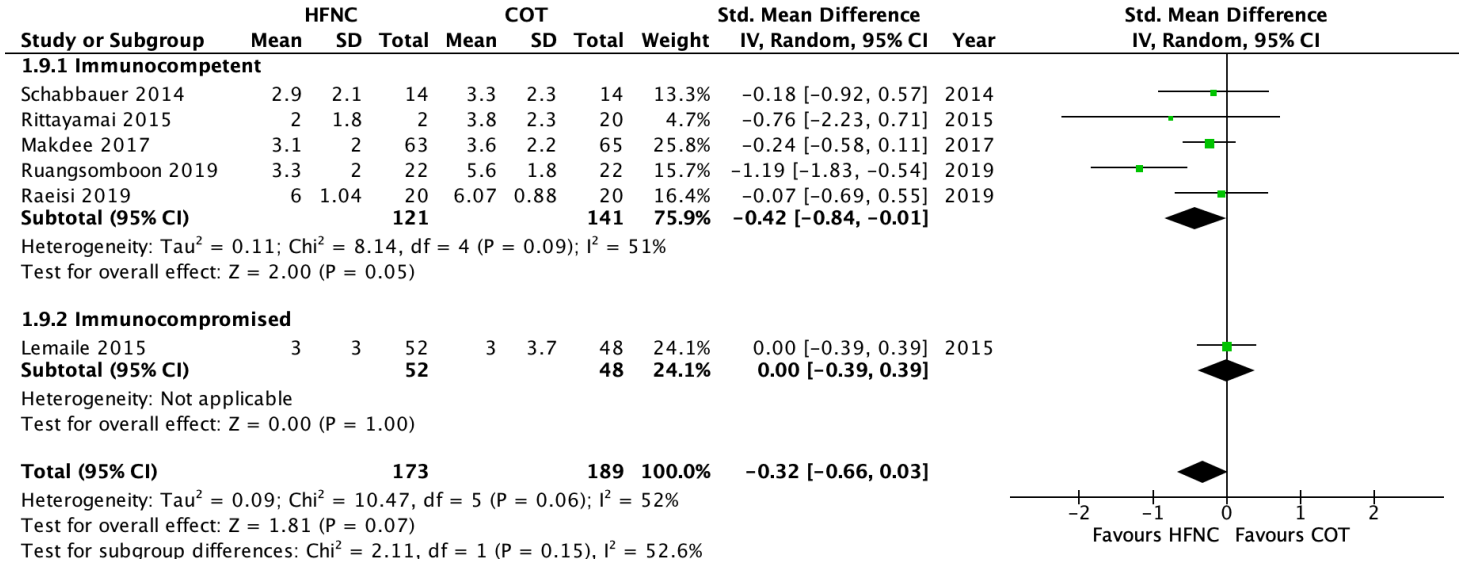


Recommendation 1: High flow nasal cannula (HFNC) vs conventional oxygen therapy (COT) in hypoxemic respiratory failure

7. Patient comfort (various rating systems)



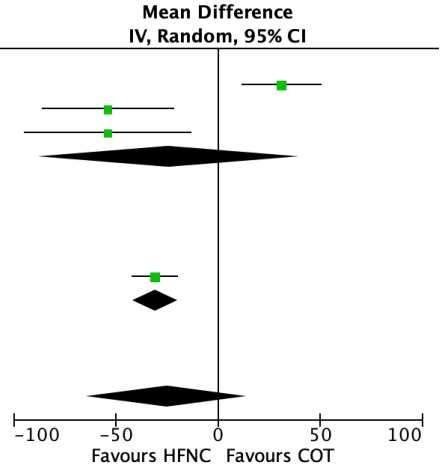
8. Dyspnea (various measures, Borg Dyspnea Scale or visual analog scale)



Recommendation 1: High flow nasal cannula (HFNC) vs conventional oxygen therapy (COT) in hypoxemic respiratory failure

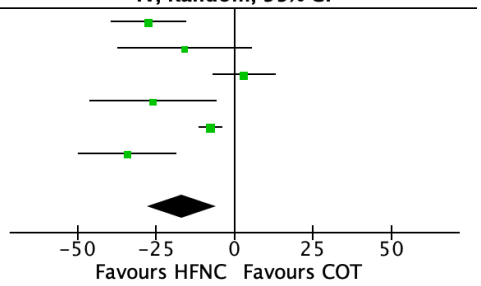
9. PaO2:FiO2

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	COT Mean	COT SD	COT Total	Weight	Mean Difference IV, Random, 95% CI
1.10.1 Immunocompetent								
Frat 2015	−130	60	106	−161	77	94	26.6%	31.00 [11.69, 50.31]
Mauri 2016	−184	53	15	−130	35	15	23.9%	−54.00 [−86.14, −21.86]
Mauri 2017	−205	61	17	−151	60	17	21.8%	−54.00 [−94.67, −13.33]
Subtotal (95% CI)			**138**			**126**	**72.2%**	**−24.15 [−88.18, 39.88]**
Heterogeneity: $Tau^2 = 2941.86$; $Chi^2 = 27.51$, df = 2 ($P < 0.00001$); $I^2 = 93\%$								
Test for overall effect: Z = 0.74 (P = 0.46)								
1.10.2 Immunocompromised								
Azoulay 2018	−150	93.3	388	−119	58.5	388	27.8%	−31.00 [−41.96, −20.04]
Subtotal (95% CI)			**388**			**388**	**27.8%**	**−31.00 [−41.96, −20.04]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.54 (P < 0.00001)								
Total (95% CI)			**526**			**514**	**100.0%**	**−25.01 [−64.24, 14.21]**
Heterogeneity: $Tau^2 = 1409.75$; $Chi^2 = 37.64$, df = 3 ($P < 0.00001$); $I^2 = 92\%$								
Test for overall effect: Z = 1.25 (P = 0.21)								
Test for subgroup differences: $Chi^2 = 0.04$, df = 1 (P = 0.84), $I^2 = 0\%$								



10. PaO2

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	COT Mean	COT SD	COT Total	Weight	Mean Difference IV, Random, 95% CI	Year
Mauri 2017	−97.4	23	17	−70	9.6	17	17.9%	−27.40 [−39.25, −15.55]	
Schabbauer 2014	−101	34	14	−85	22	14	12.3%	−16.00 [−37.21, 5.21]	2014
Frat 2015	−90	35	106	−93	36	94	19.1%	3.00 [−6.87, 12.87]	2015
Mauri 2016	−98	39	15	−72	5.2	15	13.0%	−26.00 [−45.91, −6.09]	2016
Geng 2020	−94.73	4.43	16	−86.98	6.42	20	22.1%	−7.75 [−11.30, −4.20]	2020
Ko 2020	−107.47	44.15	34	−73.25	13.02	33	15.6%	−34.22 [−49.71, −18.73]	2020
Total (95% CI)			**202**			**193**	**100.0%**	**−16.72 [−27.71, −5.74]**	
Heterogeneity: $Tau^2 = 138.87$; $Chi^2 = 28.63$, df = 5 ($P < 0.0001$); $I^2 = 83\%$									
Test for overall effect: Z = 2.98 (P = 0.003)									

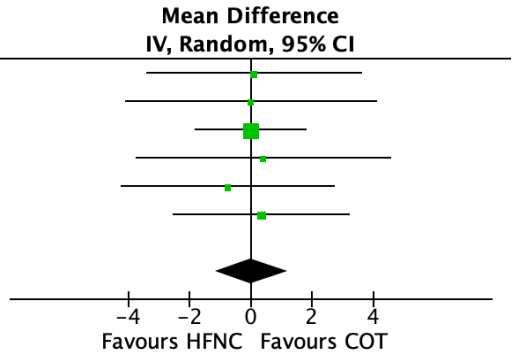


Recommendation 1: High flow nasal cannula (HFNC) vs conventional oxygen therapy (COT) in hypoxemic respiratory failure

11. PCO2 (most commonly PaCO2)

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	COT Mean	COT SD	COT Total	Weight	Mean Difference IV, Random, 95% CI	Year
Mauri 2017	38.3	5.4	17	38.2	5	17	11.5%	0.10 [-3.40, 3.60]	
Schabbauer 2014	37	5	14	37	6	14	8.4%	0.00 [-4.09, 4.09]	2014
Frat 2015	35	7	106	35	6	94	43.2%	0.00 [-1.80, 1.80]	2015
Mauri 2016	41.1	5.9	15	40.7	5.7	15	8.1%	0.40 [-3.75, 4.55]	2016
Ko 2020	31.54	8.14	34	32.3	6.22	33	11.7%	-0.76 [-4.22, 2.70]	2020
Geng 2020	40.22	4.37	16	39.87	4.35	20	17.1%	0.35 [-2.52, 3.22]	2020
Total (95% CI)			**202**			**193**	**100.0%**	**0.01 [-1.17, 1.20]**	

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.28$, df = 5 (P = 1.00); $I^2 = 0\%$
Test for overall effect: Z = 0.02 (P = 0.98)



12. Respiratory rate

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	COT Mean	COT SD	COT Total	Weight	Mean Difference IV, Random, 95% CI	Year
1.13.1 Immunocompetent									
Mauri 2017	18	7	17	24	8	17	3.4%	-6.00 [-11.05, -0.95]	
Schabbauer 2014	26	7	14	28	8	14	2.9%	-2.00 [-7.57, 3.57]	2014
Frat 2015	27	7	106	29	8	94	12.9%	-2.00 [-4.10, 0.10]	2015
Rittayamai 2015	26	6.2	2	27.5	4.9	20	1.2%	-1.50 [-10.36, 7.36]	2015
Mauri 2016	22	5.2	15	24	5.2	15	5.8%	-2.00 [-5.72, 1.72]	2016
Makdee 2017	23.5	3.6	63	26.5	3.9	65	19.8%	-3.00 [-4.30, -1.70]	2017
Ruangsomboon 2019	26	3.7	22	31.9	9.3	22	4.8%	-5.90 [-10.08, -1.72]	2019
Ko 2020	21.32	3.32	34	24.3	3.55	33	16.5%	-2.98 [-4.63, -1.33]	2020
Subtotal (95% CI)			**273**			**280**	**67.2%**	**-2.95 [-3.79, -2.10]**	

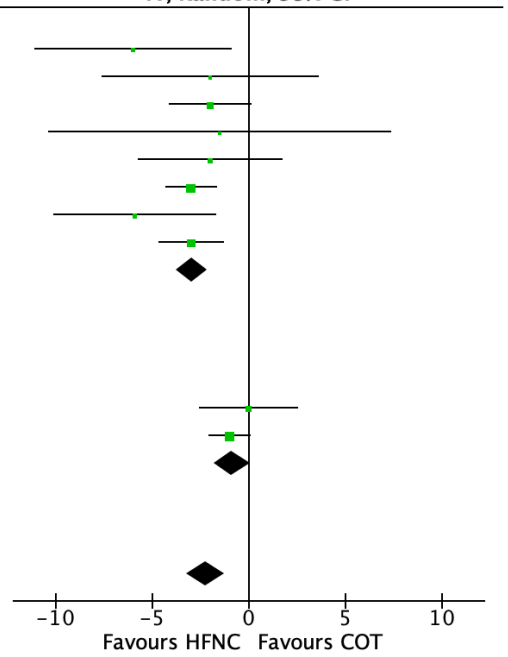
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.57$, df = 7 (P = 0.71); $I^2 = 0\%$
Test for overall effect: Z = 6.84 (P < 0.00001)

1.13.2 Immunocompromised									
Lemaile 2015	25	5.2	52	25	7.4	48	10.2%	0.00 [-2.53, 2.53]	2015
Azoulay 2018	25	7.4	388	26	7.4	388	22.5%	-1.00 [-2.04, 0.04]	2018
Subtotal (95% CI)			**440**			**436**	**32.8%**	**-0.85 [-1.82, 0.11]**	

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.51$, df = 1 (P = 0.47); $I^2 = 0\%$
Test for overall effect: Z = 1.74 (P = 0.08)

Total (95% CI)			**713**			**716**	**100.0%**	**-2.25 [-3.24, -1.25]**	

Heterogeneity: $Tau^2 = 0.86$; $Chi^2 = 15.33$, df = 9 (P = 0.08); $I^2 = 41\%$
Test for overall effect: Z = 4.42 (P < 0.00001)
Test for subgroup differences: $Chi^2 = 10.25$, df = 1 (P = 0.001), $I^2 = 90.2\%$



Recommendation 2: High flow nasal cannula (HFNC) vs non-invasive ventilation (NIV) in hypoxemic respiratory failure

Certainty assessment						№ of patients		Effect		Certainty	Importance
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HFNC	NIV	Relative (95% CI)	Absolute (95% CI)		
Mortality (90 day)											
1 RCT	not serious	not serious	serious [a]	serious [b]	none	13/106 (12.3%)	31/110 (28.2%)	**RR 0.43** (0.24 to 0.78)	**161 fewer per 1,000** (from 214 fewer to 62 fewer)	⨁⨁◯◯ LOW	CRITICAL
Mortality (ICU, hospital or 28 day)											
3 RCTs	not serious	serious [c]	serious [a]	serious [d]	none	35/234 (15.0%)	47/240 (19.6%)	**RR 0.77** (0.52 to 1.14)	**45 fewer per 1,000** (from 94 fewer to 27 more)	⨁◯◯◯ VERY LOW	CRITICAL
Intubation											
5 RCTs	not serious	not serious	serious [a]	serious [d]	none	74/352 (21.0%)	92/356 (25.8%)	**RR 0.84** (0.61 to 1.16)	**41 fewer per 1,000** (from 101 fewer to 41 more)	⨁⨁◯◯ LOW	CRITICAL
Hospital length of stay											
1 RCTs	not serious	not serious	serious [a]	very serious [e]	none	104	100	-	MD **0.8 days higher** (0.59 lower to 2.19 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
ICU length of stay											
2 RCTs	not serious	not serious	serious [a]	serious [d]	none	154	157	-	MD **0.55 days lower** (2 lower to 0.89 higher)	⨁⨁◯◯ LOW	IMPORTANT
Patient comfort											
4 RCTs	not serious	not serious	serious [a]	not serious	none	207	208	-	SMD **0.23 lower** (0.55 lower to 0.09 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Dyspnea											
4 RCTs	not serious	very serious [f]	serious [a]	serious [g]	none	193	194	-	SMD **0.19 higher** (0.01 lower to 0.40 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

Recommendation 2: High flow nasal cannula (HFNC) vs non-invasive ventilation (NIV) in hypoxemic respiratory failure

PaO2/FiO2											
3 RCTs	not serious	not serious	serious [a]	not serious	none	215	219	-	MD **43.26 higher** (29.48 higher to 57.04 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
PaO2											
4 RCTs	not serious	not serious	serious [a]	not serious	none	229	233	-	MD **19.98 mmHg higher** (11.97 higher to 28 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
PCO2											
4 RCTs	not serious	serious [c]	serious [a]	not serious	none	209	211	-	MD **0.45 mmHg lower** (1.94 lower to 1.05 higher)	⨁⨁◯◯ LOW	IMPORTANT
Respiratory rate											
5 RCTs	not serious	serious [c]	serious [a]	not serious	none	302	309	-	MD **0.83 breaths per minute higher** (1.04 lower to 2.7 higher)	⨁⨁◯◯ LOW	IMPORTANT

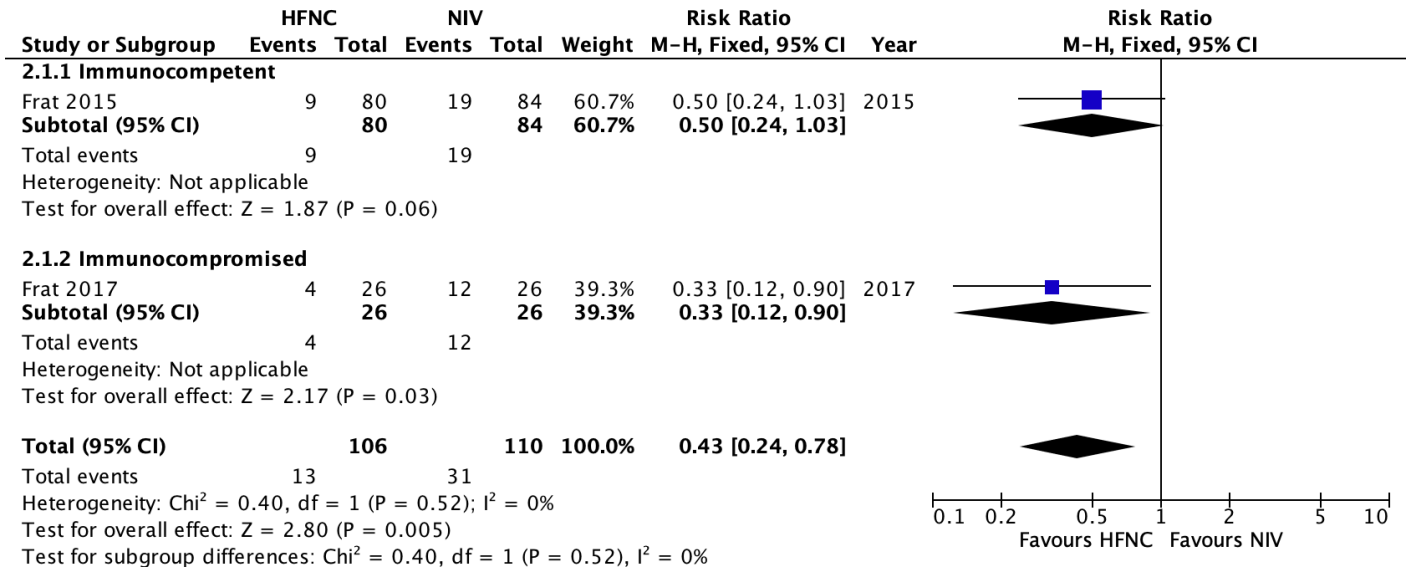
CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; **SMD:** Standardised mean difference

Explanations

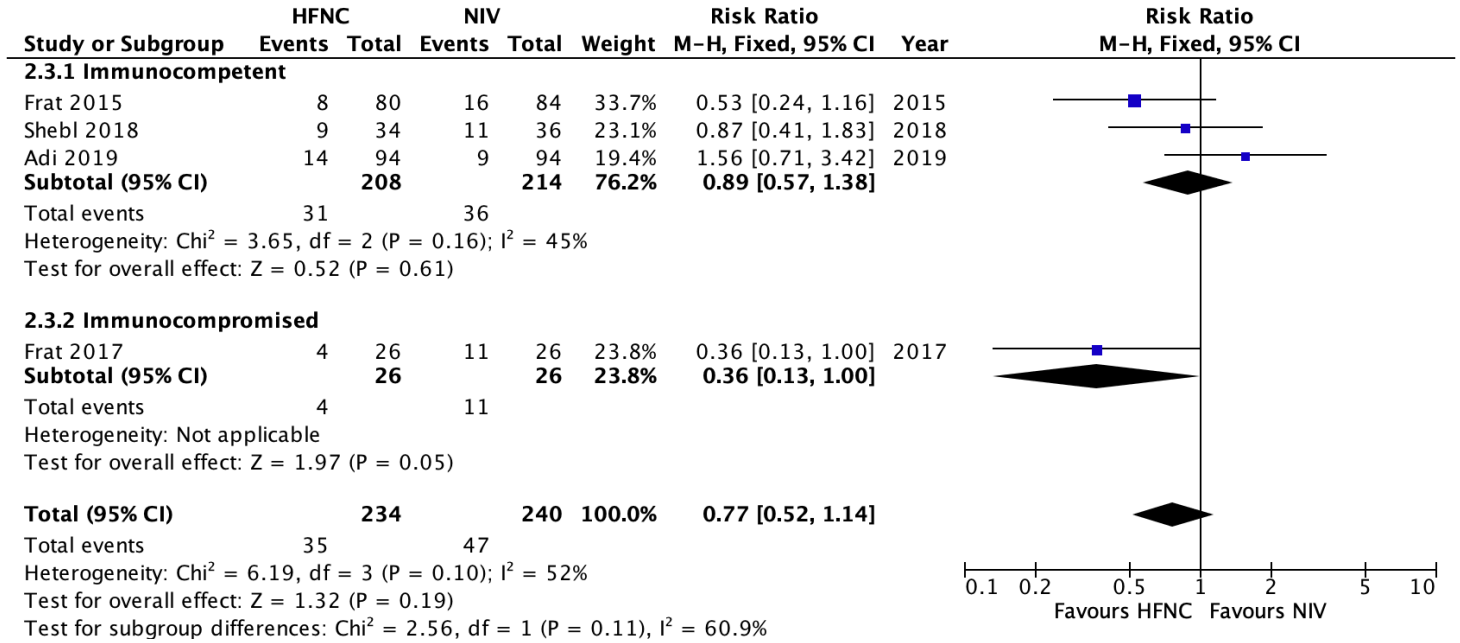
a. Concerns were raised about the short duration of NIV in the study with the largest effects (Frat et al); as well NIV interfaces used (face mask vs. helmet) and use of humidification for secretion clearance during NIV varied between studies. As a result, we rated down for indirectness of the comparator.
b. Optimal information size not met, assuming even a conservative relative risk reduction of 30%; thus we chose to rate down for imprecision, despite a statistically significant reduction in mortality.
c. Substantial heterogeneity (I2>40%) not easily explained by study characteristics.
d. Wide 95% confidence intervals which do not exclude clinically meaningful benefit or harm.
e. Very wide 95% confidence intervals which do not exclude clinically meaningful benefit or harm.
f. Very substantial heterogeneity (I2>80%) with two studies demonstrating opposite effects.
g. We chose not to rate down for imprecision as this was accounted for in considering the very significant inconsistency between the included studies.

Recommendation 2: High flow nasal cannula (HFNC) vs non-invasive ventilation (NIV) in hypoxemic respiratory failure

1. Mortality (90 day)

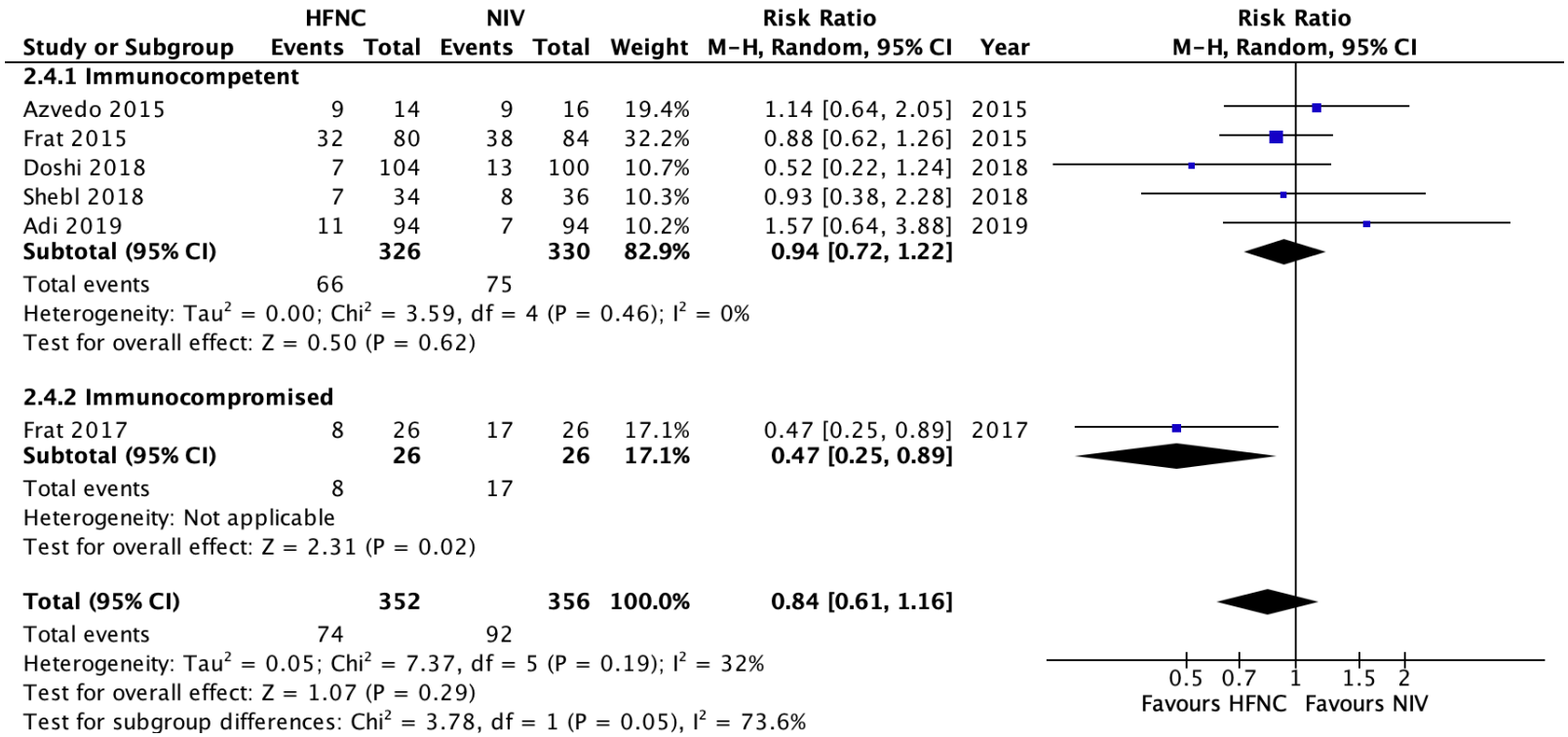


2. Mortality (early - ICU, hospital, or 28 day)

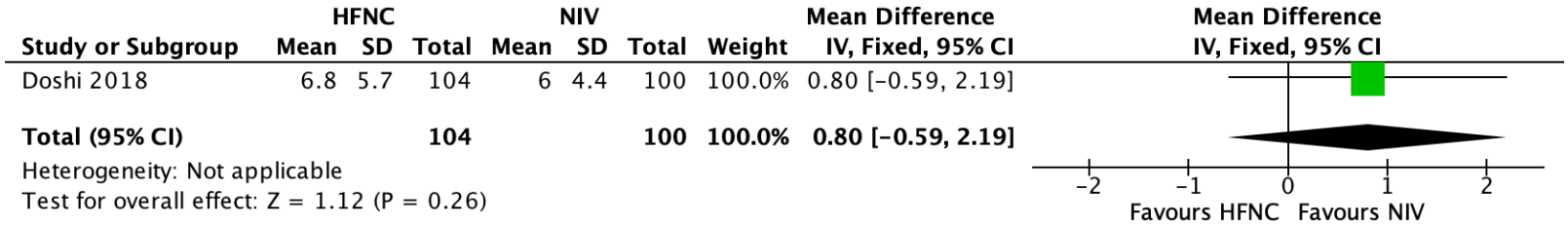


Recommendation 2: High flow nasal cannula (HFNC) vs non-invasive ventilation (NIV) in hypoxemic respiratory failure

3. Intubation



4. Hospital length of stay

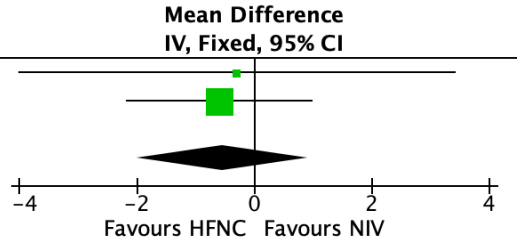


Recommendation 2: High flow nasal cannula (HFNC) vs non-invasive ventilation (NIV) in hypoxemic respiratory failure

5. ICU length of stay

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	NIV Mean	NIV SD	NIV Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Frat 2015	10.7	15.8	106	11	11.6	110	15.2%	-0.30 [-4.01, 3.41]	2015
Doshi 2018	3.3	3.7	48	3.9	4.1	47	84.8%	-0.60 [-2.17, 0.97]	2018
Total (95% CI)			**154**			**157**	**100.0%**	**-0.55 [-2.00, 0.89]**	

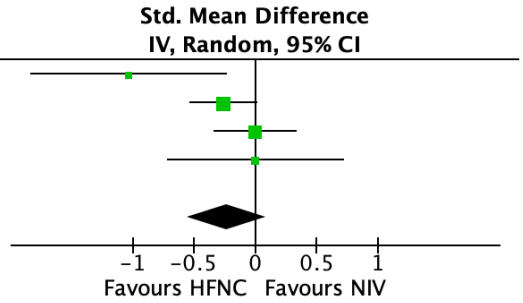
Heterogeneity: $Chi^2 = 0.02$, df = 1 (P = 0.88); $I^2 = 0\%$
Test for overall effect: Z = 0.75 (P = 0.45)



6. Patient comfort (various rating systems)

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	NIV Mean	NIV SD	NIV Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Schabbauer 2014	2.7	1.8	14	5.4	3.1	14	12.5%	-1.03 [-1.83, -0.24]	2014
Frat 2015	38	31	106	46	30	110	38.8%	-0.26 [-0.53, 0.01]	2015
Doshi 2018	2	3	72	2	3.7	69	34.0%	0.00 [-0.33, 0.33]	2018
Grieco 2020	5	3	15	5	3	15	14.7%	0.00 [-0.72, 0.72]	2020
Total (95% CI)			**207**			**208**	**100.0%**	**-0.23 [-0.55, 0.09]**	

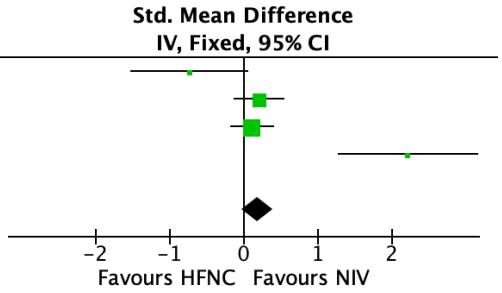
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 6.13$, df = 3 (P = 0.11); $I^2 = 51\%$
Test for overall effect: Z = 1.40 (P = 0.16)



7. Dyspnea (various measures, Borg Dyspnea Scale or visual analog scale)

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	NIV Mean	NIV SD	NIV Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Year
Schabbauer 2014	2.9	2.1	13	5	3.3	14	6.7%	-0.73 [-1.51, 0.05]	2014
Doshi 2018	2.6	2	71	2.2	1.8	71	38.0%	0.21 [-0.12, 0.54]	2018
Adi 2019	21.7	10.64	94	20.43	11.91	94	50.5%	0.11 [-0.17, 0.40]	2019
Grieco 2020	8	2.2	15	3	2.2	15	4.7%	2.21 [1.28, 3.15]	2020
Total (95% CI)			**193**			**194**	**100.0%**	**0.19 [-0.01, 0.40]**	

Heterogeneity: $Chi^2 = 23.58$, df = 3 (P < 0.0001); $I^2 = 87\%$
Test for overall effect: Z = 1.85 (P = 0.06)

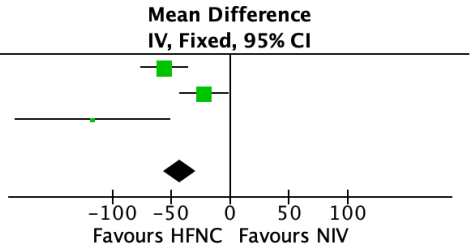


Recommendation 2: High flow nasal cannula (HFNC) vs non-invasive ventilation (NIV) in hypoxemic respiratory failure

8. PaO2:FiO2

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	NIV Mean	NIV SD	NIV Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Frat 2015	130	60	106	186	85	110	49.6%	-56.00 [-75.56, -36.44]	2015
Adi 2019	271.83	73.63	94	294.19	68.52	94	45.9%	-22.36 [-42.69, -2.03]	2019
Grieco 2020	138	52.6	15	255	118	15	4.4%	-117.00 [-182.38, -51.62]	2020
Total (95% CI)			**215**			**219**	**100.0%**	**-43.26 [-57.04, -29.48]**	

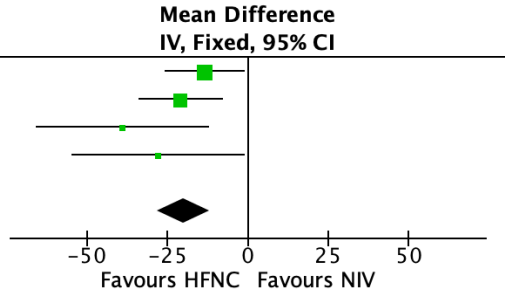
Heterogeneity: Chi² = 10.57, df = 2 (P = 0.005); I² = 81%
Test for overall effect: Z = 6.15 (P < 0.00001)



9. PaO2

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	NIV Mean	NIV SD	NIV Total	Weight	Mean Difference IV, Fixed, 95% CI
Adi 2019	163.1	44.18	94	176.52	41.11	94	43.2%	-13.42 [-25.62, -1.22]
Frat 2015	90	35	106	111	59	110	38.7%	-21.00 [-33.88, -8.12]
Grieco 2020	69	21.5	15	108	48.1	15	9.0%	-39.00 [-65.66, -12.34]
Schabbauer 2014	101	34	14	129	38	14	9.0%	-28.00 [-54.71, -1.29]
Total (95% CI)			**229**			**233**	**100.0%**	**-19.98 [-28.00, -11.97]**

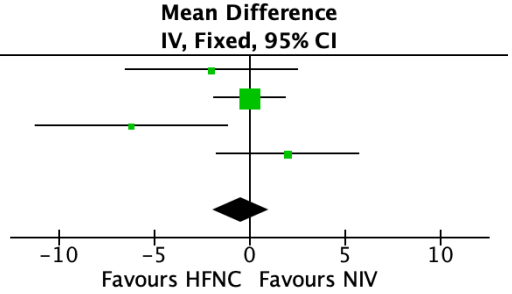
Heterogeneity: Chi² = 3.44, df = 3 (P = 0.33); I² = 13%
Test for overall effect: Z = 4.88 (P < 0.00001)



10. PCO2 (most commonly PaCO2)

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	NIV Mean	NIV SD	NIV Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Schabbauer 2014	37	5	14	39	7	14	11.0%	-2.00 [-6.51, 2.51]	2014
Frat 2015	35	7	106	35	7	110	64.1%	0.00 [-1.87, 1.87]	2015
Doshi 2018	46.3	12.7	74	52.5	17.8	72	8.8%	-6.20 [-11.23, -1.17]	2018
Grieco 2020	33	4.4	15	31	5.9	15	16.1%	2.00 [-1.72, 5.72]	2020
Total (95% CI)			**209**			**211**	**100.0%**	**-0.45 [-1.94, 1.05]**	

Heterogeneity: Chi² = 7.36, df = 3 (P = 0.06); I² = 59%
Test for overall effect: Z = 0.58 (P = 0.56)



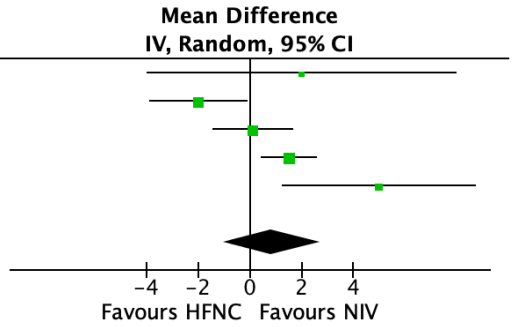
Recommendation 2: High flow nasal cannula (HFNC) vs non-invasive ventilation (NIV) in hypoxemic respiratory failure

11. Respiratory rate

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	NIV Mean	NIV SD	NIV Total	Weight	Mean Difference IV, Random, 95% CI	Year
Schabbauer 2014	26	7	14	24	9	14	7.5%	2.00 [-3.97, 7.97]	2014
Frat 2015	27	7	106	29	7	110	23.9%	-2.00 [-3.87, -0.13]	2015
Doshi 2018	22.2	4.7	73	22.1	4.8	76	26.0%	0.10 [-1.43, 1.63]	2018
Adi 2019	24.51	3.69	94	23	3.61	94	28.6%	1.51 [0.47, 2.55]	2019
Grieco 2020	29	4.4	15	24	5.9	15	14.0%	5.00 [1.28, 8.72]	2020
Total (95% CI)			**302**			**309**	**100.0%**	**0.83 [-1.04, 2.70]**	

Heterogeneity: $Tau^2 = 2.92$; $Chi^2 = 16.23$, df = 4 (P = 0.003); $I^2 = 75\%$

Test for overall effect: Z = 0.87 (P = 0.39)



Recommendation 4: High-flow nasal cannula (HFNC) vs. conventional oxygen therapy (COT) in post-operative patients

Certainty assessment						№ of patients		Effect		Certainty	Importance
№ of studies	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**HFNC**	**COT**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality - Post-operative											
7 RCTs	not serious	not serious	not serious	serious [a]	none	4/526 (0.8%)	7/523 (1.3%)	**RR 0.64** (0.19 to 2.14)	**5 fewer per 1,000** (from 11 fewer to 15 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Re-intubation - Post-operative											
8 RCTs	serious [b]	not serious	not serious	serious [a]	none	14/609 (2.3%)	22/601 (3.7%)	**RR 0.66** (0.23 to 1.91)	**12 fewer per 1,000** (from 28 fewer to 33 more)	⨁⨁◯◯ LOW	CRITICAL
Escalate to NIV - Post-op											
7 RCTs	serious [b]	serious [c]	not serious	serious [a]	none	52/558 (9.3%)	65/552 (11.8%)	**RR 0.77** (0.42 to 1.40)	**27 fewer per 1,000** (from 68 fewer to 47 more)	⨁◯◯◯ VERY LOW	CRITICAL
ICU Length of Stay - Post-op											
10 RCTs	not serious	not serious	not serious	not serious	none	707	709	-	MD **0.02 higher** (0.09 lower to 0.13 higher)	⨁⨁⨁⨁ HIGH	CRITICAL
Hospital Length of Stay - Post-op											
11 RCTs	not serious	not serious	not serious	not serious	none	639	655	-	MD **0.47 lower** (0.83 lower to 0.11 lower)	⨁⨁⨁⨁ HIGH	IMPORTANT
Comfort - Post-op											
6 RCTs	not serious	very serious [d]	not serious	not serious [e]	none	413	415	-	SMD **0.54 lower** (1.12 lower to 0.05 higher)	⨁⨁◯◯ LOW	IMPORTANT
PaO2 - Post-op											
2 RCTs	not serious	not serious	not serious	not serious	none	158	162	-	MD **6.2 lower** (8.82 lower to 3.58 lower)	⨁⨁⨁⨁ HIGH	IMPORTANT
PCO2 - Post-Op											

Recommendation 4: High-flow nasal cannula (HFNC) vs. conventional oxygen therapy (COT) in post-operative patients

5 RCTs	not serious	not serious [f]	not serious	not serious	none	284	285	-	MD **1.9 lower** (4.18 lower to 0.38 higher)	⨁⨁⨁⨁ HIGH	IMPORTANT
PaO2:FiO2 - Post-op											
4 RCTs	not serious	not serious [f]	not serious	not serious	none	159	142	-	MD **34.89 lower** (84.96 lower to 15.19 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Respiratory Rate - Post-op											
3 RCTs	not serious	serious [c]	not serious	not serious	none	178	167	-	MD **0.14 lower** (0.83 lower to 0.54 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT

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

Explanations

a. Wide 95% confidence intervals which do not exclude clinically important benefit or harm.
b. Lack of blinding may have resulted in bias from co-intervention as many trials did not have protocols for escalation of respiratory support.
c. Significant heterogeneity (I2 >50%) with point estimates on both sides of the line of no effect and limited overlap of 95% confidence intervals.
d. Very significant heterogeneity (I2 >90%) with point estimates on both sides of the line of no effect and limited overlap of 95% confidence intervals.
e. We did not rate down for imprecision as this is accounted for in rating down twice for inconsistency.
f. Although there is significant heterogeneity (I2 >90%) the discrepancies in absolute effect sizes are of questionable significance

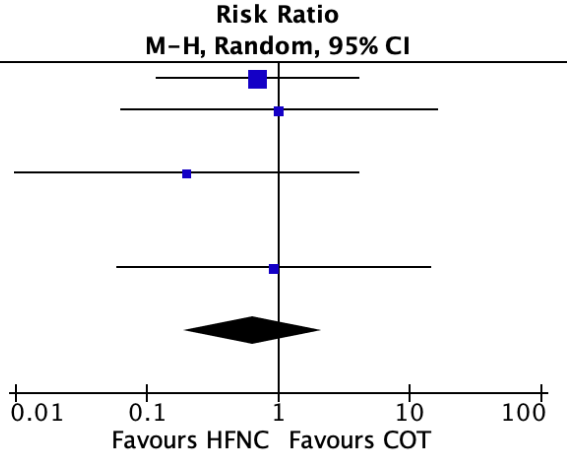
Recommendation 4: High-flow nasal cannula (HFNC) vs. conventional oxygen therapy (COT) in post-operative patients

1. Mortality

Study or Subgroup	HFNC Events	HFNC Total	COT Events	COT Total	Weight	Risk Ratio M-H, Random, 95% CI
Futier 2016	2	108	3	112	46.0%	0.69 [0.12, 4.06]
Parke 2013	1	169	1	171	18.9%	1.01 [0.06, 16.05]
Pennisi 2019	0	47	0	48		Not estimable
Sahin 2018	0	50	2	50	15.9%	0.20 [0.01, 4.06]
Vourc'h 2020	0	47	0	43		Not estimable
Yu 2017	0	56	0	54		Not estimable
Zochios 2018	1	49	1	45	19.2%	0.92 [0.06, 14.25]
Total (95% CI)		**526**		**523**	**100.0%**	**0.64 [0.19, 2.14]**
Total events	4		7			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.76$, df = 3 (P = 0.86); $I^2 = 0\%$

Test for overall effect: Z = 0.72 (P = 0.47)

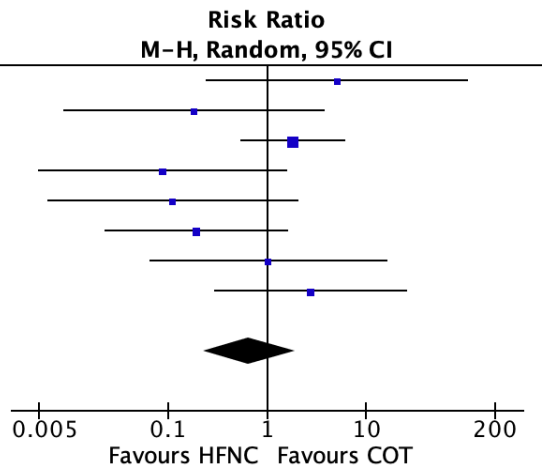


2. Re-intubation

Study or Subgroup	HFNC Events	HFNC Total	COT Events	COT Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Parke 2013	2	169	0	171	9.1%	5.06 [0.24, 104.59]	2013
Corley 2015	0	81	2	74	9.1%	0.18 [0.01, 3.75]	2015
Futier 2016	7	108	4	112	23.7%	1.81 [0.55, 6.02]	2016
Yu 2017	0	56	5	54	9.8%	0.09 [0.00, 1.55]	2017
Sahin 2018	0	50	4	50	9.7%	0.11 [0.01, 2.01]	2018
Zochios 2018	1	51	5	49	14.5%	0.19 [0.02, 1.59]	2018
Pennisi 2019	1	47	1	48	10.5%	1.02 [0.07, 15.86]	2019
Vourc'h 2020	3	47	1	43	13.7%	2.74 [0.30, 25.40]	2020
Total (95% CI)		**609**		**601**	**100.0%**	**0.66 [0.23, 1.91]**	
Total events	14		22				

Heterogeneity: $Tau^2 = 0.88$; $Chi^2 = 11.51$, df = 7 (P = 0.12); $I^2 = 39\%$

Test for overall effect: Z = 0.77 (P = 0.44)



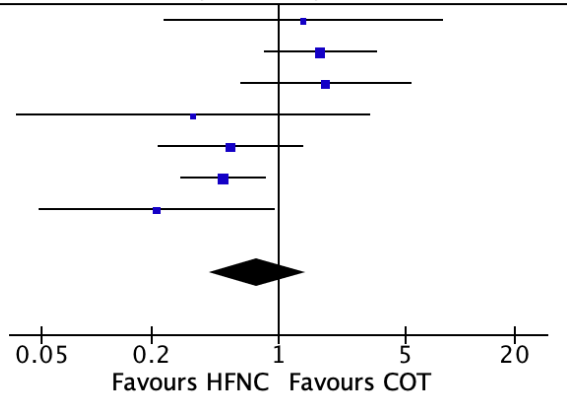
Recommendation 4: High-flow nasal cannula (HFNC) vs. conventional oxygen therapy (COT) in post-operative patients

3. Escalation to NIV

Study or Subgroup	HFNC Events	HFNC Total	COT Events	COT Total	Weight	Risk Ratio M-H, Random, 95% CI
Corley 2015	3	81	2	74	8.3%	1.37 [0.24, 7.97]
Futier 2016	18	108	11	112	20.4%	1.70 [0.84, 3.42]
Parke 2013	9	169	5	171	14.9%	1.82 [0.62, 5.32]
Pennisi 2019	1	47	3	48	5.8%	0.34 [0.04, 3.16]
Sahin 2018	6	50	11	50	17.1%	0.55 [0.22, 1.36]
Vourc'h 2020	13	47	24	43	23.0%	0.50 [0.29, 0.84]
Yu 2017	2	56	9	54	10.4%	0.21 [0.05, 0.95]
Total (95% CI)		**558**		**552**	**100.0%**	**0.77 [0.42, 1.40]**
Total events	52		65			

Heterogeneity: $Tau^2 = 0.34$; $Chi^2 = 14.31$, df = 6 (P = 0.03); $I^2 = 58\%$

Test for overall effect: Z = 0.86 (P = 0.39)

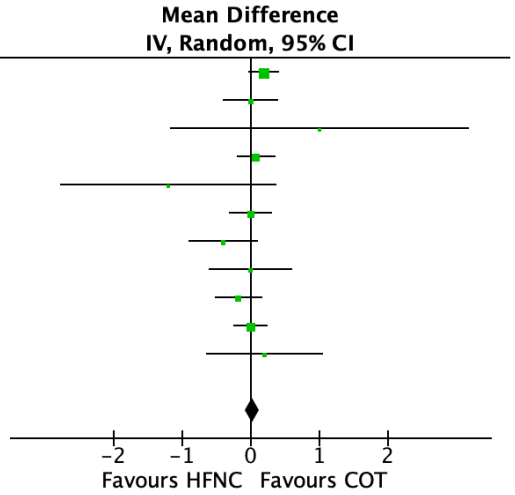


4. ICU length of stay

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	COT Mean	COT SD	COT Total	Weight	Mean Difference IV, Random, 95% CI	Year
Parke 2013	1.39	0.95	169	1.2	1	171	24.8%	0.19 [-0.02, 0.40]	2013
Corley 2015	1.61	1.47	81	1.61	0.995	74	7.4%	0.00 [-0.39, 0.39]	2015
Futier 2016	6	8.9	108	5	7.4	112	0.2%	1.00 [-1.17, 3.17]	2016
Yu 2017	3.72	0.56	56	3.64	0.83	54	15.7%	0.08 [-0.19, 0.35]	2017
Brainard 2017	2	1.2	18	3.2	3.8	26	0.5%	-1.20 [-2.76, 0.36]	2017
Zochios 2018	1	0.74	49	1	0.74	45	12.5%	0.00 [-0.30, 0.30]	2018
Sahin 2018	2.4	0.5	50	2.8	1.7	50	4.8%	-0.40 [-0.89, 0.09]	2018
Pennisi 2019	1	1.48	47	1	1.48	48	3.3%	0.00 [-0.60, 0.60]	2019
Twose 2019	1.04	0.34	10	1.22	0.42	10	10.1%	-0.18 [-0.51, 0.15]	2019
Tatsuishi 2020	1	0.74	72	1	0.74	76	19.2%	0.00 [-0.24, 0.24]	2020
Vourc'h 2020	3.3	2.4	47	3.1	1.6	43	1.7%	0.20 [-0.64, 1.04]	2020
Total (95% CI)			**707**			**709**	**100.0%**	**0.02 [-0.09, 0.13]**	

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 10.31$, df = 10 (P = 0.41); $I^2 = 3\%$

Test for overall effect: Z = 0.41 (P = 0.68)

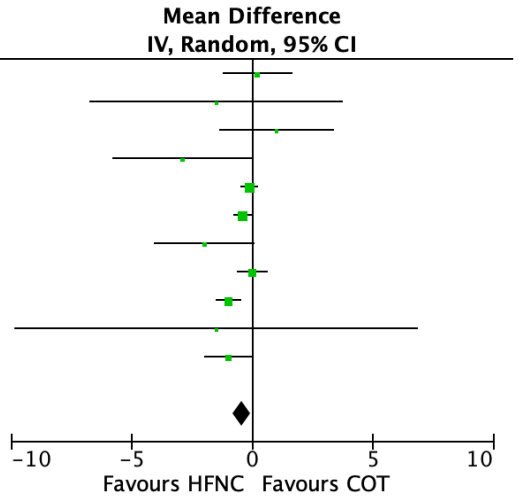


Recommendation 4: High-flow nasal cannula (HFNC) vs. conventional oxygen therapy (COT) in post-operative patients

5. Hospital length of stay

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	COT Mean	COT SD	COT Total	Weight	Mean Difference IV, Random, 95% CI	Year
Parke 2013	11.6	6.6	169	11.4	6.7	171	5.3%	0.20 [-1.21, 1.61]	2013
Ansari 2016	2.5	7.4	28	4	12.6	31	0.5%	-1.50 [-6.71, 3.71]	2016
Futier 2016	12	9.6	108	11	8.1	112	2.2%	1.00 [-1.35, 3.35]	2016
Brainard 2017	6.6	2.1	18	9.5	7	26	1.5%	-2.90 [-5.76, -0.04]	2017
Yu 2017	7.41	0.82	56	7.54	0.91	54	22.7%	-0.13 [-0.45, 0.19]	2017
Sahin 2018	6.5	0.7	50	6.9	1.1	50	21.7%	-0.40 [-0.76, -0.04]	2018
Zochios 2018	7	2.2	49	9	6.7	45	2.8%	-2.00 [-4.05, 0.05]	2018
Pennisi 2019	6	1.48	47	6	1.48	48	15.8%	0.00 [-0.60, 0.60]	2019
Ferrando 2019	3	1	32	4	1	32	18.3%	-1.00 [-1.49, -0.51]	2019
Twose 2019	14.5	12.4	10	16	5.2	10	0.2%	-1.50 [-9.83, 6.83]	2019
Tatsuishi 2020	8	2.2	72	9	3.7	76	9.1%	-1.00 [-1.97, -0.03]	2020
Total (95% CI)			**639**			**655**	**100.0%**	**-0.47 [-0.83, -0.11]**	

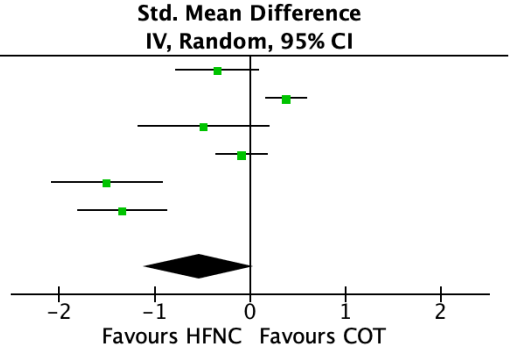
Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 19.16$, df = 10 (P = 0.04); $I^2 = 48\%$
Test for overall effect: Z = 2.55 (P = 0.01)



6. Comfort

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	COT Mean	COT SD	COT Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Tiruvoipati 2010	0.53	1.04	42	0.96	1.42	42	16.9%	-0.34 [-0.77, 0.09]	2010
Parke 2013	-6.94	2.5	169	-7.78	1.9	171	18.1%	0.38 [0.16, 0.59]	2013
Rittayamai 2014	1.4	0.9	17	1.9	1.1	17	14.8%	-0.49 [-1.17, 0.20]	2014
Futier 2016	7.9	2.1	108	8.1	2.4	112	17.9%	-0.09 [-0.35, 0.18]	2016
Song 2017	3	1.1	30	5	1.5	30	15.7%	-1.50 [-2.08, -0.92]	2017
Vourc'h 2020	-4	0.74	47	-3	0.74	43	16.6%	-1.34 [-1.80, -0.88]	2020
Total (95% CI)			**413**			**415**	**100.0%**	**-0.54 [-1.12, 0.05]**	

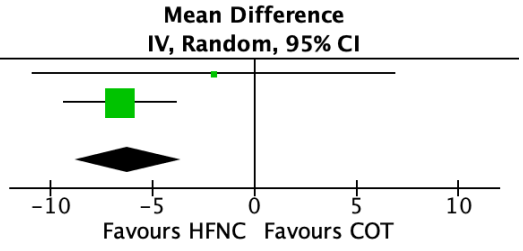
Heterogeneity: $Tau^2 = 0.47$; $Chi^2 = 71.88$, df = 5 (P < 0.00001); $I^2 = 93\%$
Test for overall effect: Z = 1.81 (P = 0.07)



7. PaO2

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	COT Mean	COT SD	COT Total	Weight	Mean Difference IV, Random, 95% CI	Year
Futier 2016	-89	35	108	-87	32	112	8.7%	-2.00 [-10.87, 6.87]	2016
Sahin 2018	-106	6.9	50	-99.4	7.1	50	91.3%	-6.60 [-9.34, -3.86]	2018
Total (95% CI)			**158**			**162**	**100.0%**	**-6.20 [-8.82, -3.58]**	

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.94$, df = 1 (P = 0.33); $I^2 = 0\%$
Test for overall effect: Z = 4.63 (P < 0.00001)

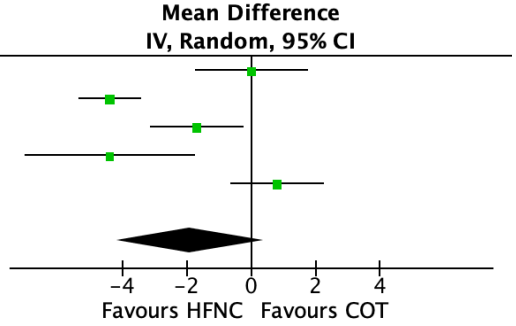


Recommendation 4: High-flow nasal cannula (HFNC) vs. conventional oxygen therapy (COT) in post-operative patients

8. PCO2

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	COT Mean	COT SD	COT Total	Weight	Mean Difference IV, Random, 95% CI	Year
Futier 2016	41	7	108	41	6	112	19.9%	0.00 [-1.73, 1.73]	2016
Sahin 2018	37.9	2.6	50	42.3	2.2	50	21.6%	-4.40 [-5.34, -3.46]	2018
Pennisi 2019	38.9	3.15	47	40.6	3.89	48	20.6%	-1.70 [-3.12, -0.28]	2019
Ferrando 2019	37.9	5.6	32	42.3	5.1	32	17.3%	-4.40 [-7.02, -1.78]	2019
Vourc'h 2020	39.8	3	47	39	3.8	43	20.6%	0.80 [-0.62, 2.22]	2020
Total (95% CI)			**284**			**285**	**100.0%**	**-1.90 [-4.18, 0.38]**	

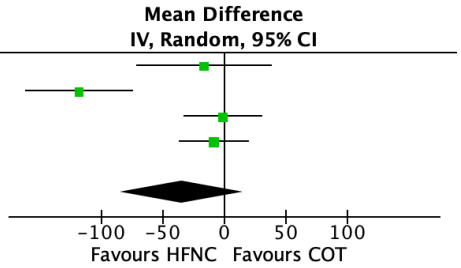
Heterogeneity: $Tau^2 = 6.03$; $Chi^2 = 47.20$, df = 4 ($P < 0.00001$); $I^2 = 92\%$
Test for overall effect: Z = 1.63 (P = 0.10)



9. PaO2/FiO2

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	COT Mean	COT SD	COT Total	Weight	Mean Difference IV, Random, 95% CI	Year
Corley 2015	-175.8	96.3791	33	-159.3	96.3791	19	22.0%	-16.50 [-70.90, 37.90]	2015
Ferrando 2019	-344	104.8	32	-226	66.3	32	24.3%	-118.00 [-160.97, -75.03]	2019
Pennisi 2019	-300	75.2	47	-299	81.3	48	26.5%	-1.00 [-32.48, 30.48]	2019
Vourc'h 2020	-136.5	47	47	-128.1	81.3	43	27.2%	-8.40 [-36.17, 19.37]	2020
Total (95% CI)			**159**			**142**	**100.0%**	**-34.89 [-84.96, 15.19]**	

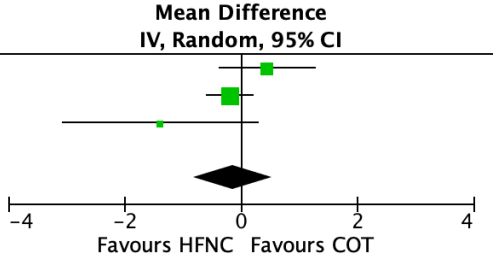
Heterogeneity: $Tau^2 = 2201.88$; $Chi^2 = 21.69$, df = 3 ($P < 0.0001$); $I^2 = 86\%$
Test for overall effect: Z = 1.37 (P = 0.17)



10. Respiratory rate

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	COT Mean	COT SD	COT Total	Weight	Mean Difference IV, Random, 95% CI	Year
Corley 2015	18.29	2.6017	81	17.85	2.6017	74	33.5%	0.44 [-0.38, 1.26]	2015
Sahin 2018	19.3	0.9	50	19.5	1.1	50	53.2%	-0.20 [-0.59, 0.19]	2018
Vourc'h 2020	19.2	4	47	20.6	4.1	43	13.3%	-1.40 [-3.08, 0.28]	2020
Total (95% CI)			**178**			**167**	**100.0%**	**-0.14 [-0.83, 0.54]**	

Heterogeneity: $Tau^2 = 0.19$; $Chi^2 = 4.18$, df = 2 ($P = 0.12$); $I^2 = 52\%$
Test for overall effect: Z = 0.41 (P = 0.68)



Recommendation 5: High flow nasal cannula (HFNC) vs. Non-invasive ventilation (NIV) in post-operative patients

Certainty assessment						№ of patients		Effect		Certainty	Importance
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	HFNC	NIV	Relative (95% CI)	Absolute (95% CI)		
Mortality - Post-op											
1 RCT	not serious	not serious	not serious [a]	very serious [b]	none	28/414 (6.8%)	23/416 (5.5%)	**RR 1.22** (0.72 to 2.09)	**12 more per 1,000** (from 15 fewer to 60 more)	⨁⨁◯◯ LOW	CRITICAL
Re-intubation - Post-op											
1 RCT	not serious [c]	not serious	not serious [a]	serious [d]	none	58/414 (14.0%)	57/416 (13.7%)	**RR 1.02** (0.73 to 1.44)	**3 more per 1,000** (from 37 fewer to 60 more)	⨁⨁⨁◯ MODERATE	CRITICAL
ICU length of stay - Post-op											
1 RCT	not serious	not serious	not serious [a]	not serious [e]	none	414	416	-	MD **0 days** (0.6 lower to 0.6 higher)	⨁⨁⨁⨁ HIGH	IMPORTANT
Hospital length of stay - Post-op											
1 RCT	not serious	not serious	not serious [a]	serious [d]	none	414	416	-	MD **1 lower** (2.21 lower to 0.21 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
PCO2 - Post-op											
1 RCT	not serious	not serious	not serious [a]	not serious	none	414	416	-	MD **1.1 mmHg lower** (2.02 lower to 0.18 lower)	⨁⨁⨁⨁ HIGH	IMPORTANT
PaO2:FIO2 - Post-op											
1 RCT	not serious	not serious	not serious [a]	not serious	none	414	416	-	MD **63 lower** (80 lower to 46 lower)	⨁⨁⨁⨁ HIGH	IMPORTANT
Respiratory Rate - Post-op											
1 RCT	not serious	not serious	not serious [a]	not serious	none	414	416	-	MD **0.9 RPM lower** (1.81 lower to 0.01 higher)	⨁⨁⨁⨁ HIGH	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Recommendation 5: High flow nasal cannula (HFNC) vs. Non-invasive ventilation (NIV) in post-operative patients

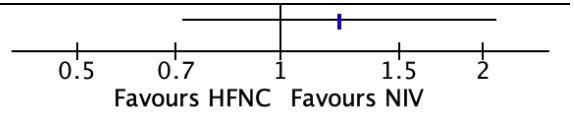
Explanations

a. Single trial recruited patients after cardiothoracic surgery only; patients with other types of surgery are not represented in this evidence.
b. Very wide 95% confidence interval does not exclude moderate harm or small benefit of HFNC.
c. Single included trial used pre-specified criteria for escalation of respiratory support, including intubation.
d. Wide 95% confidence interval does not exclude clinically meaningful benefit or harm.
e. Though not statistically significant, the 95% confidence intervals likely exclude a meaningful benefit (less than 1 day difference).

Recommendation 5: High flow nasal cannula (HFNC) vs. Non-invasive ventilation (NIV) in post-operative patients

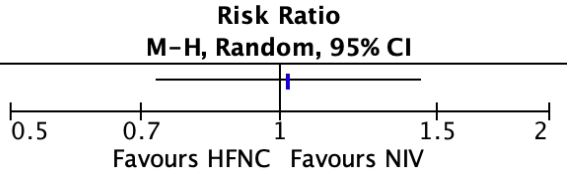
1. Mortality

Study or Subgroup	HFNC Events	HFNC Total	NIV Events	NIV Total	Weight	Risk Ratio M-H, Random, 95% CI
Stephan 2015	28	414	23	416		1.22 [0.72, 2.09]



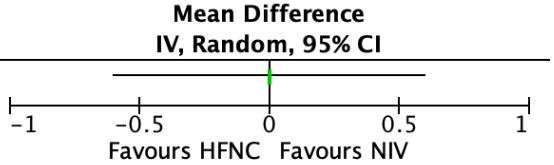
2. Re-intubation

Study or Subgroup	HFNC Events	HFNC Total	NIV Events	NIV Total	Weight	Risk Ratio M-H, Random, 95% CI
Stephan 2015	58	414	57	416		1.02 [0.73, 1.44]



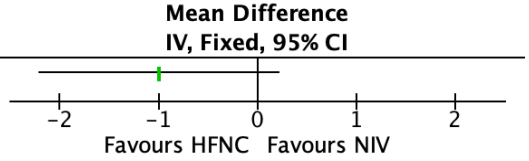
3. ICU length of stay

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	NIV Mean	NIV SD	NIV Total	Weight	Mean Difference IV, Random, 95% CI
Stephan 2015	6	4.4	414	6	4.4	416		0.00 [-0.60, 0.60]



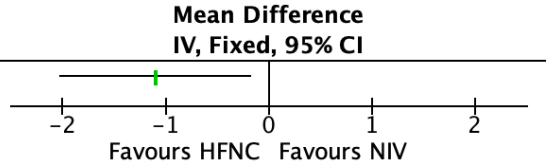
4. Hospital length of stay

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	NIV Mean	NIV SD	NIV Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Stephan 2015	13	9.6	414	14	8.1	416		-1.00 [-2.21, 0.21]	2015



5. PCO2

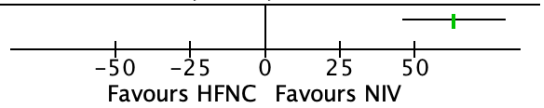
Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	NIV Mean	NIV SD	NIV Total	Weight	Mean Difference IV, Fixed, 95% CI
Stephan 2015	38.2	6.2	414	39.3	7.3	416		-1.10 [-2.02, -0.18]



Recommendation 5: High flow nasal cannula (HFNC) vs. Non-invasive ventilation (NIV) in post-operative patients

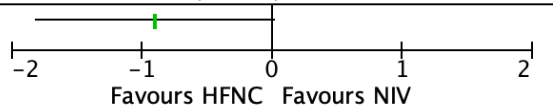
6. PaO2/FiO2

	HFNC			NIV				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Stephan 2015	-198	114	414	-261	135	416		63.00 [46.00, 80.00]	



7. Respiratory rate

	HFNC			NIV				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Stephan 2015	21.6	7.2	414	22.5	6.2	416		-0.90 [-1.81, 0.01]	



Recommendation 6: High-flow nasal cannula (HFNC) vs. conventional oxygen therapy (COT) to prevent extubation failure in non-surgical patients

Certainty assessment						№ of patients		Effect		Certainty	Importance
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	HFNC	COT	Relative (95% CI)	Absolute (95% CI)		
Mortality											
9 RCTs	not serious	not serious	not serious	serious [a]	none	42/503 (8.3%)	41/495 (8.3%)	**RR 1.01** (0.68 to 1.52)	**1 more per 1,000** (from 27 fewer to 43 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Re-intubation											
10 RCTs	serious [b]	not serious	not serious	not serious [c]	none	42/563 (7.5%)	75/564 (13.3%)	**RR 0.62** (0.38 to 1.01)	**51 fewer per 1,000** (from 82 fewer to 1 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Escalate to NIV											
6 RCTs	serious [b]	not serious	not serious	not serious	none	15/260 (5.8%)	40/265 (15.1%)	**RR 0.38** (0.17 to 0.85)	**94 fewer per 1,000** (from 125 fewer to 23 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
ICU Length of Stay											
6 RCTs	not serious	not serious	not serious	not serious [c]	none	485	487	-	MD **0.29 higher** (0.27 lower to 0.85 higher)	⨁⨁⨁⨁ HIGH	IMPORTANT
Hospital Length of Stay											
4 RCTs	not serious	serious [d]	not serious	serious [a]	none	424	417	-	MD **1.08 lower** (4.83 lower to 2.66 higher)	⨁⨁◯◯ LOW	IMPORTANT
Comfort											
3 RCTs	not serious	not serious [e]	not serious	not serious	none	89	89	-	SMD **0.77 lower** (1.5 lower to 0.03 lower)	⨁⨁⨁⨁ HIGH	IMPORTANT
PaO2											
5 RCTs	not serious	not serious	not serious	not serious	none	165	154	-	MD **7.57 higher** (2.68 higher to 12.46 higher)	⨁⨁⨁⨁ HIGH	IMPORTANT
PCO2											

Recommendation 6: High-flow nasal cannula (HFNC) vs. conventional oxygen therapy (COT) to prevent extubation failure in non-surgical patients

7 RCTs	not serious	not serious	not serious	not serious	none	460	446	-	MD **0.15 lower** (1.89 lower to 1.58 higher)	⨁⨁⨁⨁ HIGH	IMPORTANT
PaO2:FiO2											
4 RCTs	not serious	serious [d]	not serious	serious [a]	none	378	383	-	MD **14.13 higher** (20.48 lower to 48.75 higher)	⨁⨁◯◯ LOW	IMPORTANT
Respiratory Rate											
7 RCTs	not serious	not serious [f]	not serious	not serious	none	213	200	-	MD **1.98 lower** (3.9 lower to 0.06 lower)	⨁⨁⨁⨁ HIGH	IMPORTANT

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

Explanations

a. Wide 95% confidence intervals do not exclude clinically significant benefit nor harm.
b. Lack of blinding may have resulted in bias from co-intervention, though several trials did have specific criteria for escalation of respiratory support.
c. Though not statistically significant, 95% confidence interval likely excludes a significant differences.
d. Large values of I2 (>70%) with point estimates on both sides of the line of no effect.
e. Significant statistical heterogeneity, however all estimates of effect favour HFNC.
f. Although significant statistical heterogeneity, the absolute differences are of questionable clinical significance.

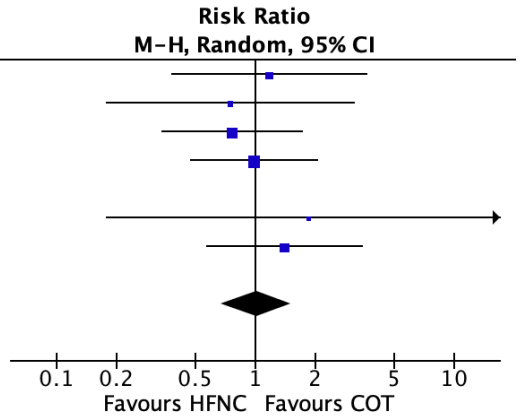
Recommendation 6: High-flow nasal cannula (HFNC) vs. conventional oxygen therapy (COT) to prevent extubation failure in non-surgical patients

1. Mortality

Study or Subgroup	HFNC Events	HFNC Total	COT Events	COT Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Maggiore 2014	6	53	5	52	13.0%	1.18 [0.38, 3.62]	2014
Perbet 2014	3	40	4	40	8.0%	0.75 [0.18, 3.14]	2014
Hernandez (low risk) 2016	10	264	13	263	25.3%	0.77 [0.34, 1.72]	2016
Fernandez 2017	12	78	12	77	30.4%	0.99 [0.47, 2.06]	2017
Arman 2017	0	8	0	7		Not estimable	2017
Hu 2020	2	29	1	27	3.0%	1.86 [0.18, 19.38]	2020
Cho 2020	9	31	6	29	20.3%	1.40 [0.57, 3.45]	2020
Total (95% CI)		**503**		**495**	**100.0%**	**1.01 [0.68, 1.52]**	
Total events	42		41				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.47$, df = 5 (P = 0.92); $I^2 = 0\%$

Test for overall effect: Z = 0.07 (P = 0.94)

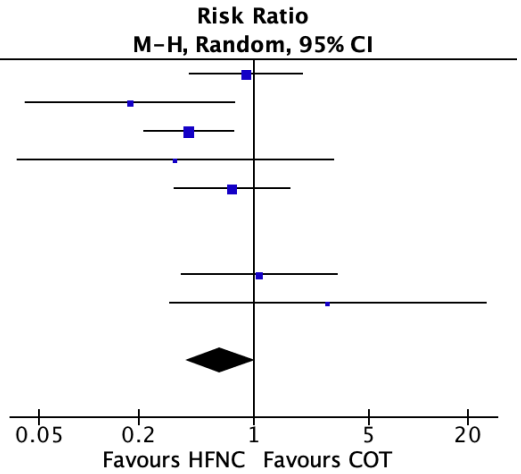


2. Re-intubation

Study or Subgroup	HFNC Events	HFNC Total	COT Events	COT Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Perbet 2014	9	40	10	40	21.1%	0.90 [0.41, 1.98]	2014
Maggiore 2014	2	53	11	52	9.0%	0.18 [0.04, 0.77]	2014
Hernandez (low risk) 2016	13	264	32	263	26.6%	0.40 [0.22, 0.75]	2016
Song 2017	1	30	3	30	4.4%	0.33 [0.04, 3.03]	2017
Fernandez 2017	9	78	12	77	20.5%	0.74 [0.33, 1.66]	2017
Arman 2017	0	8	0	7		Not estimable	2017
Hu 2020	0	29	0	27		Not estimable	2020
Matsuda 2020	5	30	6	39	14.0%	1.08 [0.37, 3.21]	2020
Cho 2020	3	31	1	29	4.4%	2.81 [0.31, 25.48]	2020
Total (95% CI)		**563**		**564**	**100.0%**	**0.62 [0.38, 1.01]**	
Total events	42		75				

Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 8.88$, df = 6 (P = 0.18); $I^2 = 32\%$

Test for overall effect: Z = 1.90 (P = 0.06)



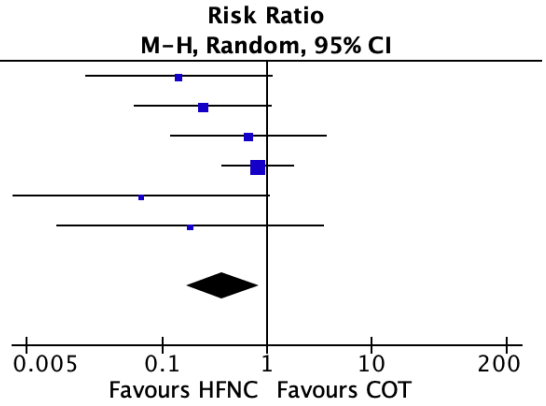
Recommendation 6: High-flow nasal cannula (HFNC) vs. conventional oxygen therapy (COT) to prevent extubation failure in non-surgical patients

3. Escalation to NIV

Study or Subgroup	HFNC Events	HFNC Total	COT Events	COT Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Perbet 2014	1	40	7	40	12.4%	0.14 [0.02, 1.11]	2014
Maggiore 2014	2	53	8	52	19.5%	0.25 [0.05, 1.10]	2014
Song 2017	2	30	3	30	16.2%	0.67 [0.12, 3.71]	2017
Fernandez 2017	10	78	12	77	37.9%	0.82 [0.38, 1.79]	2017
Hu 2020	0	29	7	27	7.3%	0.06 [0.00, 1.04]	2020
Matsuda 2020	0	30	3	39	6.8%	0.18 [0.01, 3.44]	2020
Total (95% CI)		**260**		**265**	**100.0%**	**0.38 [0.17, 0.85]**	
Total events	15		40				

Heterogeneity: $Tau^2 = 0.29$; $Chi^2 = 7.09$, df = 5 (P = 0.21); $I^2 = 29\%$

Test for overall effect: Z = 2.34 (P = 0.02)

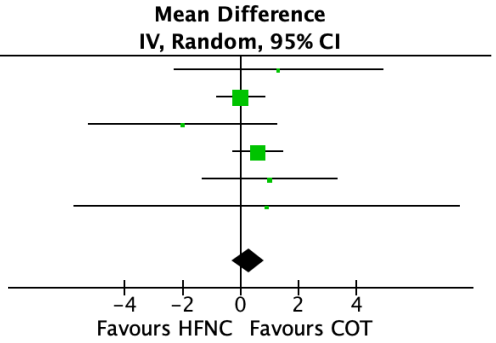


4. ICU length of stay

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	COT Mean	COT SD	COT Total	Weight	Mean Difference IV, Random, 95% CI	Year
Maggiore 2014	11.7	10.2	53	10.4	8.5	52	2.4%	1.30 [-2.29, 4.89]	2014
Hernandez (low risk) 2016	6	4.4	264	6	5.2	263	45.8%	0.00 [-0.82, 0.82]	2016
Fernandez 2017	12	13.3	78	14	5.9	77	3.0%	-2.00 [-5.23, 1.23]	2017
Matsuda 2020	4.4	1.8	30	3.8	1.8	39	42.3%	0.60 [-0.26, 1.46]	2020
Hu 2020	10	4.4	29	9	4.4	27	5.8%	1.00 [-1.31, 3.31]	2020
Cho 2020	14.7	9.6	31	13.8	15.7	29	0.7%	0.90 [-5.74, 7.54]	2020
Total (95% CI)			**485**			**487**	**100.0%**	**0.29 [-0.27, 0.85]**	

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.61$, df = 5 (P = 0.61); $I^2 = 0\%$

Test for overall effect: Z = 1.02 (P = 0.31)

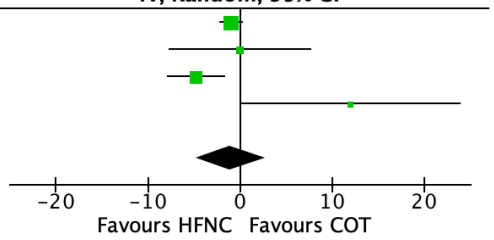


Recommendation 6: High-flow nasal cannula (HFNC) vs. conventional oxygen therapy (COT) to prevent extubation failure in non-surgical patients

5. Hospital length of stay

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	COT Mean	COT SD	COT Total	Weight	Mean Difference IV, Random, 95% CI	Year
Hernandez (low risk) 2016	11	6.7	264	12	7.4	263	42.2%	−1.00 [−2.21, 0.21]	2016
Fernandez 2017	27	26.7	78	27	21.5	77	15.6%	0.00 [−7.63, 7.63]	2017
Blaudszun 2017	8.6	4.3	51	13.4	9.9	48	34.1%	−4.80 [−7.84, −1.76]	2017
Cho 2020	37.7	25.8	31	25.7	20.9	29	8.1%	12.00 [0.15, 23.85]	2020
Total (95% CI)			**424**			**417**	**100.0%**	**−1.08 [−4.83, 2.66]**	

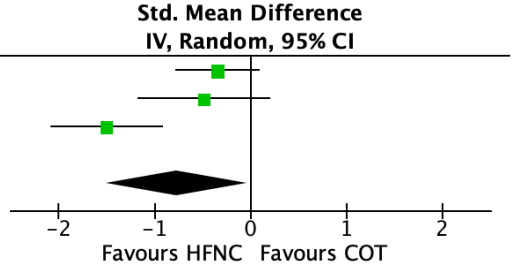
Heterogeneity: $Tau^2 = 8.26$; $Chi^2 = 10.27$, df = 3 (P = 0.02); $I^2 = 71\%$
Test for overall effect: Z = 0.57 (P = 0.57)



6. Comfort

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	COT Mean	COT SD	COT Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Tiruvoipati 2010	0.53	1.04	42	0.96	1.42	42	36.4%	−0.34 [−0.77, 0.09]	2010
Rittayamai 2014	1.4	0.9	17	1.9	1.1	17	30.6%	−0.49 [−1.17, 0.20]	2014
Song 2017	3	1.1	30	5	1.5	30	33.1%	−1.50 [−2.08, −0.92]	2017
Total (95% CI)			**89**			**89**	**100.0%**	**−0.77 [−1.50, −0.03]**	

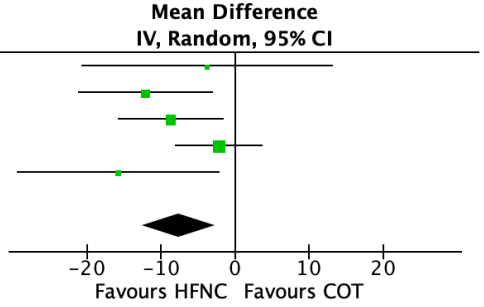
Heterogeneity: $Tau^2 = 0.34$; $Chi^2 = 10.42$, df = 2 (P = 0.005); $I^2 = 81\%$
Test for overall effect: Z = 2.05 (P = 0.04)



7. PaO2

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	COT Mean	COT SD	COT Total	Weight	Mean Difference IV, Random, 95% CI	Year
Tiruvoipati 2010	−102.14	40.25	42	−98.35	38.54	42	7.5%	−3.79 [−20.64, 13.06]	2010
Maggiore 2014	−97.5	29.2	53	−85.4	16.3	52	20.2%	−12.10 [−21.12, −3.08]	2014
Song 2017	−83.2	10.5	27	−74.5	13.1	19	27.4%	−8.70 [−15.80, −1.60]	2017
DiMussi 2018	−75.1	6.9	14	−72.9	8.6	14	34.1%	−2.20 [−7.98, 3.58]	2018
Hu 2020	−102.4	25.4	29	−86.6	26.4	27	10.8%	−15.80 [−29.39, −2.21]	2020
Total (95% CI)			**165**			**154**	**100.0%**	**−7.57 [−12.46, −2.68]**	

Heterogeneity: $Tau^2 = 9.58$; $Chi^2 = 5.84$, df = 4 (P = 0.21); $I^2 = 32\%$
Test for overall effect: Z = 3.04 (P = 0.002)

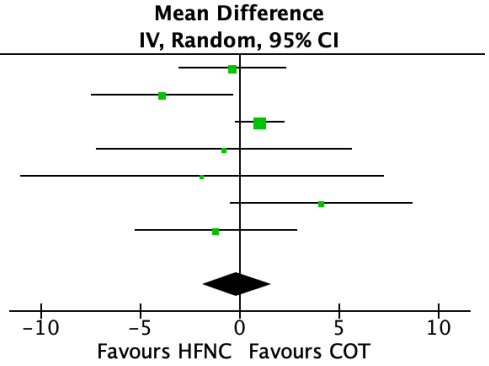


Recommendation 6: High-flow nasal cannula (HFNC) vs. conventional oxygen therapy (COT) to prevent extubation failure in non-surgical patients

8. PCO2

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	COT Mean	COT SD	COT Total	Weight	Mean Difference IV, Random, 95% CI	Year
Tiruvoipati 2010	37.53	6.23	42	37.91	6.22	42	20.2%	-0.38 [-3.04, 2.28]	2010
Maggiore 2014	32.3	7.1	53	36.2	11	52	14.7%	-3.90 [-7.45, -0.35]	2014
Hernandez (low risk) 2016	37	8	264	36	6	263	32.5%	1.00 [-0.21, 2.21]	2016
Song 2017	41.4	6.5	27	42.2	13.1	19	6.2%	-0.80 [-7.18, 5.58]	2017
DiMussi 2018	49.9	11.9	14	51.8	12.7	14	3.3%	-1.90 [-11.02, 7.22]	2018
Hu 2020	41.3	7.5	29	37.2	9.6	27	10.6%	4.10 [-0.43, 8.63]	2020
Cho 2020	35.9	7	31	37.1	8.8	29	12.4%	-1.20 [-5.24, 2.84]	2020
Total (95% CI)			**460**			**446**	**100.0%**	**-0.15 [-1.89, 1.58]**	

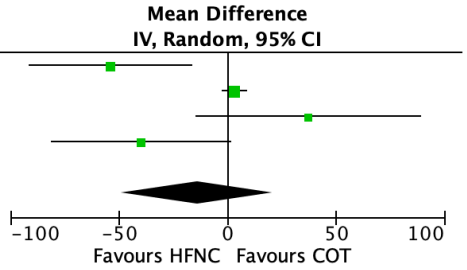
Heterogeneity: $Tau^2 = 2.02$; $Chi^2 = 10.46$, df = 6 (P = 0.11); $I^2 = 43\%$
Test for overall effect: Z = 0.17 (P = 0.86)



9. PaO2/FiO2

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	COT Mean	COT SD	COT Total	Weight	Mean Difference IV, Random, 95% CI	Year
Maggiore 2014	-313.3	83.8	53	-259.2	110.1	52	24.2%	-54.10 [-91.58, -16.62]	2014
Hernandez (low risk) 2016	-105	32	264	-108	34	263	33.6%	3.00 [-2.64, 8.64]	2016
Cho 2020	-277.1	102.5	31	-314.2	102.1	29	19.3%	37.10 [-14.70, 88.90]	2020
Matsuda 2020	-264	105	30	-224	53	39	22.9%	-40.00 [-81.09, 1.09]	2020
Total (95% CI)			**378**			**383**	**100.0%**	**-14.13 [-48.75, 20.48]**	

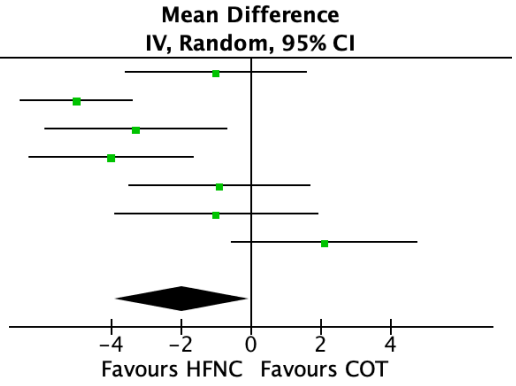
Heterogeneity: $Tau^2 = 920.91$; $Chi^2 = 14.46$, df = 3 (P = 0.002); $I^2 = 79\%$
Test for overall effect: Z = 0.80 (P = 0.42)



10. Respiratory rate

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	COT Mean	COT SD	COT Total	Weight	Mean Difference IV, Random, 95% CI	Year
Tiruvoipati 2010	18.68	5.51	42	19.68	6.5	42	14.0%	-1.00 [-3.58, 1.58]	2010
Maggiore 2014	21	4	53	26	4.3	52	16.6%	-5.00 [-6.59, -3.41]	2014
Rittayamai 2014	19.8	3.2	17	23.1	4.4	17	14.0%	-3.30 [-5.89, -0.71]	2014
Song 2017	22	4	27	26	4	19	14.6%	-4.00 [-6.35, -1.65]	2017
DiMussi 2018	20.5	2.9	14	21.4	4	14	14.0%	-0.90 [-3.49, 1.69]	2018
Hu 2020	21	5	29	22	6	27	13.1%	-1.00 [-3.90, 1.90]	2020
Cho 2020	22.8	5.9	31	20.7	4.5	29	13.8%	2.10 [-0.54, 4.74]	2020
Total (95% CI)			**213**			**200**	**100.0%**	**-1.98 [-3.90, -0.06]**	

Heterogeneity: $Tau^2 = 5.11$; $Chi^2 = 26.84$, df = 6 (P = 0.0002); $I^2 = 78\%$
Test for overall effect: Z = 2.03 (P = 0.04)



Recommendation 7: High flow nasal cannula (HFNC) vs. non-invasive ventilation (NIV) to prevent extubation failure in non-surgical patients

Certainty assessment						№ of patients		Effect		Certainty	Importance
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	HFNC	NIV	Relative (95% CI)	Absolute (95% CI)		
Mortality - General ICU											
5 RCTs	not serious	not serious	not serious	serious [a]	none	111/729 (15.2%)	112/784 (14.3%)	**RR 1.07** (0.84 to 1.36)	**10 more per 1,000** (from 23 fewer to 51 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Re-intubation - General ICU											
5 RCTs	not serious [b]	not serious	not serious	serious	none	139/746 (18.6%)	115/803 (14.3%)	**RR 1.31** (1.04 to 1.64)	**44 more per 1,000** (from 6 more to 92 more)	⨁⨁⨁⨁ HIGH	CRITICAL
ICU length of stay - General ICU											
4 RCTs	not serious	not serious	not serious	not serious	none	658	705	-	MD **1.0 days lower** (1.52 lower to 0.47 lower)	⨁⨁⨁⨁ HIGH	IMPORTANT
Hospital length of stay - General ICU											
3 RCTs	not serious	not serious	not serious	not serious	none	636	695	-	MD **1.44 days lower** (2.63 lower to 0.25 lower)	⨁⨁⨁⨁ HIGH	IMPORTANT
Comfort - General ICU											
4 RCTs	not serious	not serious	not serious	not serious	none	85	79	-	SMD **0.73 SD lower** (0.98 lower to 0.49 lower)	⨁⨁⨁⨁ HIGH	IMPORTANT
PCO2 - General ICU											
3 RCTs	not serious	not serious	not serious	not serious	none	356	376	-	MD **1.01 mmHg lower** (1.47 lower to 0.55 lower)	⨁⨁⨁⨁ HIGH	IMPORTANT
PaO2:FIO2 - General ICU											
3 RCTs	not serious	not serious	not serious	not serious [c]	none	356	376	-	MD **3.86 higher** (0.39 higher to 7.34 higher)	⨁⨁⨁⨁ HIGH	IMPORTANT
Respiratory Rate - General ICU											
2 RCTs	not serious	not serious [d]	not serious	not serious [c]	none	66	62	-	MD **0.59 respirations per minute lower** (2.48 lower to 1.29 higher)	⨁⨁⨁⨁ HIGH	IMPORTANT

Recommendation 7: High flow nasal cannula (HFNC) vs. non-invasive ventilation (NIV) to prevent extubation failure in non-surgical patients

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

Explanations

a. Wide 95% confidence intervals do not exclude the possibility of meaningful benefit nor harm.
b. Lack of blinding may have resulted in bias from co-intervention, though most trials did have specific criteria for escalation of respiratory support, including intubation.
c. Though not statistically significant, 95% confidence interval likely excludes a meaningful difference.
d. Statistically significant statistical heterogeneity, but considerable overlap of confidence intervals.

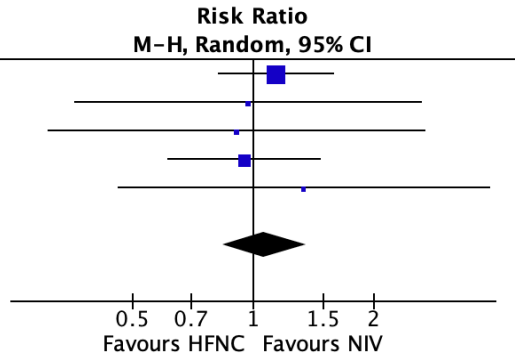
Recommendation 7: High flow nasal cannula (HFNC) vs. non-invasive ventilation (NIV) to prevent extubation failure in non-surgical patients

1. Mortality

Study or Subgroup	HFNC Events	HFNC Total	NIV Events	NIV Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Hernandez (high risk) 2016	59	290	56	314	53.6%	1.14 [0.82, 1.59]	2016
Theerawit 2020	7	71	7	69	5.9%	0.97 [0.36, 2.63]	2017
Jing 2018	5	22	5	20	5.0%	0.91 [0.31, 2.68]	2018
Thille 2019	33	302	39	339	30.4%	0.95 [0.61, 1.47]	2019
Tan 2020	7	44	5	42	5.1%	1.34 [0.46, 3.88]	2020
Total (95% CI)		**729**		**784**	**100.0%**	**1.07 [0.84, 1.36]**	
Total events	111		112				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.72$, df = 4 (P = 0.95); $I^2 = 0\%$

Test for overall effect: Z = 0.52 (P = 0.61)

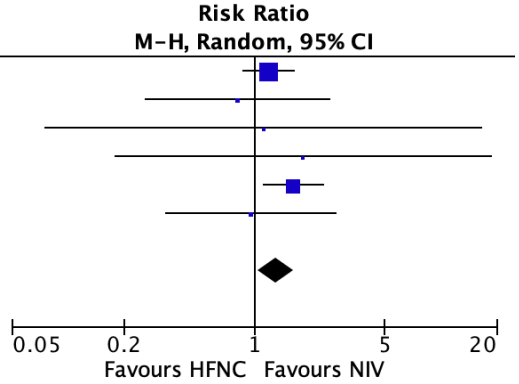


2. Re-intubation

Study or Subgroup	HFNC Events	HFNC Total	NIV Events	NIV Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Hernandez (high risk) 2016	66	290	60	314	52.3%	1.19 [0.87, 1.63]	2016
Theerawit 2020	5	71	6	69	3.9%	0.81 [0.26, 2.53]	2017
Guoqiang 2018	1	17	1	19	0.7%	1.12 [0.08, 16.52]	2018
Jing 2018	2	22	1	20	0.9%	1.82 [0.18, 18.55]	2018
Thille 2019	59	302	41	339	37.6%	1.62 [1.12, 2.33]	2019
Tan 2020	6	44	6	42	4.6%	0.95 [0.33, 2.73]	2020
Total (95% CI)		**746**		**803**	**100.0%**	**1.31 [1.04, 1.64]**	
Total events	139		115				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.73$, df = 5 (P = 0.74); $I^2 = 0\%$

Test for overall effect: Z = 2.33 (P = 0.02)

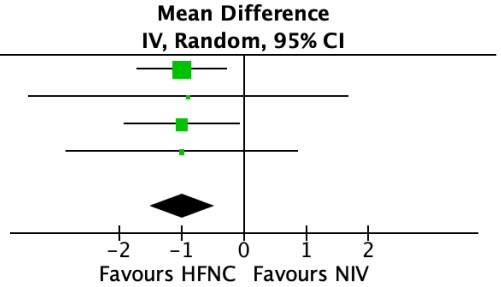


Recommendation 7: High flow nasal cannula (HFNC) vs. non-invasive ventilation (NIV) to prevent extubation failure in non-surgical patients

3. ICU length of stay

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	NIV Mean	NIV SD	NIV Total	Weight	Mean Difference IV, Random, 95% CI	Year
Hernandez (high risk) 2016	3	3.7	290	4	5.2	314	54.4%	-1.00 [-1.72, -0.28]	2016
Jing 2018	8.5	3.5	22	9.4	4.8	20	4.2%	-0.90 [-3.46, 1.66]	2018
Thille 2019	11	5.9	302	12	5.9	339	33.3%	-1.00 [-1.92, -0.08]	2019
Tan 2020	7.5	3	44	8.5	4.7	32	8.1%	-1.00 [-2.85, 0.85]	2020
Total (95% CI)			**658**			**705**	**100.0%**	**-1.00 [-1.52, -0.47]**	

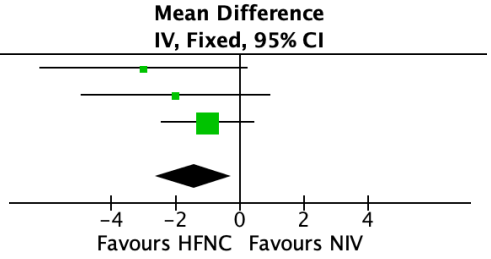
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.01$, df = 3 (P = 1.00); $I^2 = 0\%$
Test for overall effect: Z = 3.70 (P = 0.0002)



4. Hospital length of stay

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	NIV Mean	NIV SD	NIV Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Hernandez (high risk) 2016	23	23.7	290	26	15.6	314	13.6%	-3.00 [-6.23, 0.23]	2016
Thille 2019	23	17.8	302	25	20	339	16.5%	-2.00 [-4.93, 0.93]	2019
Tan 2020	10	2.7	44	11	3.9	42	69.9%	-1.00 [-2.42, 0.42]	2020
Total (95% CI)			**636**			**695**	**100.0%**	**-1.44 [-2.63, -0.25]**	

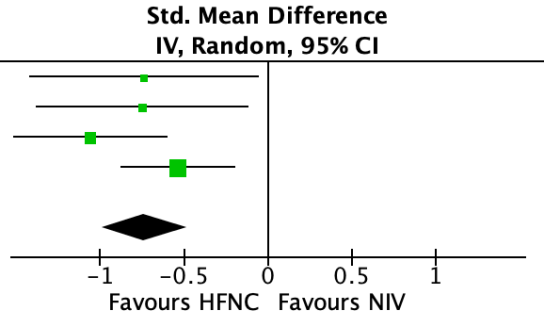
Heterogeneity: $Chi^2 = 1.40$, df = 2 (P = 0.50); $I^2 = 0\%$
Test for overall effect: Z = 2.37 (P = 0.02)



5. Comfort

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	NIV Mean	NIV SD	NIV Total	Weight	Std. Mean Difference IV, Random, 95% CI
Guoqiang 2018	-6	3	19	-4	2.2	17	12.7%	-0.74 [-1.42, -0.06]
Jing 2018	3.6	1.9	22	5.2	2.3	20	14.7%	-0.75 [-1.38, -0.12]
Tan 2020	-7	1.5	44	-5	2.2	42	27.1%	-1.06 [-1.51, -0.60]
Theerawit 2020	2.8	1.8	71	3.8	1.9	69	45.4%	-0.54 [-0.88, -0.20]
Total (95% CI)			**156**			**148**	**100.0%**	**-0.73 [-0.98, -0.49]**

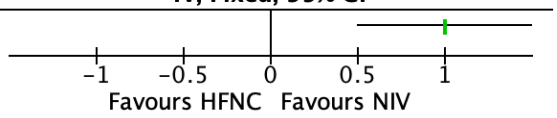
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 3.26$, df = 3 (P = 0.35); $I^2 = 8\%$
Test for overall effect: Z = 5.82 (P < 0.00001)



Recommendation 7: High flow nasal cannula (HFNC) vs. non-invasive ventilation (NIV) to prevent extubation failure in non-surgical patients

6. Dyspnea

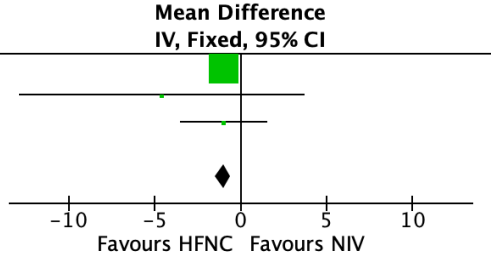
Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	NIV Mean	NIV SD	NIV Total	Weight	Mean Difference IV, Fixed, 95% CI
Tan 2020	3	1.5	44	2	0.74	42		1.00 [0.50, 1.50]



8. PCO2

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	NIV Mean	NIV SD	NIV Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Hernandez (high risk) 2016	46	3.1	290	47	2.8	314	96.2%	−1.00 [−1.47, −0.53]	2016
Jing 2018	56.9	10	22	61.5	16.3	20	0.3%	−4.60 [−12.88, 3.68]	2018
Tan 2020	51	6.5	44	52	5.2	42	3.5%	−1.00 [−3.48, 1.48]	2020
Total (95% CI)			**356**			**376**	**100.0%**	**−1.01 [−1.47, −0.55]**	

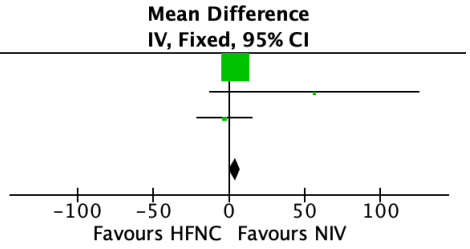
Heterogeneity: $Chi^2 = 0.72$, df = 2 (P = 0.70); $I^2 = 0\%$
Test for overall effect: Z = 4.28 (P < 0.0001)



9. PaO2/FiO2

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	NIV Mean	NIV SD	NIV Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Hernandez (high risk) 2016	−99	2	290	−103	32	314	96.0%	4.00 [0.45, 7.55]	2016
Jing 2018	−201.2	92.4	22	−257.5	130.7	20	0.3%	56.30 [−12.78, 125.38]	2018
Tan 2020	−230.3	44	44	−227.2	40.5	42	3.8%	−3.10 [−20.96, 14.76]	2020
Total (95% CI)			**356**			**376**	**100.0%**	**3.86 [0.39, 7.34]**	

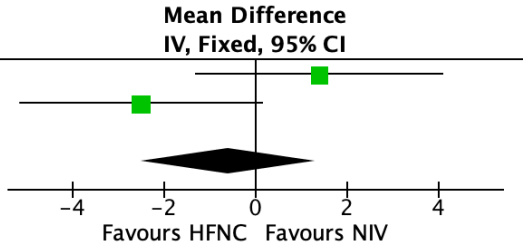
Heterogeneity: $Chi^2 = 2.80$, df = 2 (P = 0.25); $I^2 = 29\%$
Test for overall effect: Z = 2.18 (P = 0.03)



9. Respiratory rate

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	NIV Mean	NIV SD	NIV Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Jing 2018	22.4	4.4	22	21	4.5	20	48.9%	1.40 [−1.30, 4.10]	2018
Tan 2020	19	5.6	44	21.5	6.8	42	51.1%	−2.50 [−5.14, 0.14]	2020
Total (95% CI)			**66**			**62**	**100.0%**	**−0.59 [−2.48, 1.29]**	

Heterogeneity: $Chi^2 = 4.10$, df = 1 (P = 0.04); $I^2 = 76\%$
Test for overall effect: Z = 0.61 (P = 0.54)



Recommendation 8: High-flow nasal cannula (HFNC) vs. non-invasive ventilation (NIV) in hypercapnic respiratory failure

Certainty assessment						№ of patients		Effect		Certainty	Importance
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HFNC	NIV	Relative (95% CI)	Absolute (95% CI)		
Mortality - RCTs											
4 RCTs	not serious	not serious	not serious [a]	very serious [b]	none	18/127 (14.2%)	21/123 (17.1%)	**RR 0.82** (0.46 to 1.47)	**31 fewer per 1,000** (from 92 fewer to 80 more)	⨁⨁◯◯ LOW	CRITICAL
Intubation - RCTs											
4 RCTs	not serious	not serious	not serious [a]	very serious [b]	none	19/141 (13.5%)	23/134 (17.2%)	**RR 0.79** (0.46 to 1.35)	**36 fewer per 1,000** (from 93 fewer to 60 more)	⨁⨁◯◯ LOW	CRITICAL
ICU length of stay - RCTs											
3 RCTs	not serious	not serious	not serious	serious [c]	none	118	117	-	MD **0.1 higher** (0.73 lower to 0.94 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Hospital length of stay - RCTs											
4 RCTs	not serious	not serious	not serious	serious [c]	none	178	174	-	MD **0.82 days lower** (1.83 lower to 0.2 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Comfort (lower is better) (Scale from: 0 to 10)											
2 RCTs	not serious [d]	serious [e]	not serious	serious [f]	none	49	52	-	SMD **0.57 SD lower** (0.98 lower to 0.16 lower)	⨁⨁◯◯ LOW	IMPORTANT
Dyspnea											
3 RCTs	not serious [d]	not serious	not serious	serious [c]	none	77	76	-	MD **0.31 lower** (0.94 lower to 0.33 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
PaO2/FiO2 - RCTs (follow up: mean 6 hours)											

Recommendation 8: High-flow nasal cannula (HFNC) vs. non-invasive ventilation (NIV) in hypercapnic respiratory failure

2 RCTs	not serious	not serious	not serious [a]	not serious	none	44	44	-	MD **0.52 lower** (3.59 lower to 2.56 higher)	⨁⨁⨁⨁ HIGH	IMPORTANT
PO2 - RCTs											
3 RCTs	not serious	not serious	not serious	not serious	none	151	109	-	MD **0.32 higher** (3.83 lower to 4.47 higher)	⨁⨁⨁⨁ HIGH	IMPORTANT
PCO2 - RCTs											
6 RCTs	not serious	serious [e]	not serious	serious [c]	none	230	227	-	MD **0.79 mmHg lower** (5.19 lower to 3.61 higher)	⨁⨁◯◯ LOW	IMPORTANT
Respiratory rate - RCTs											
5 RCTs	not serious	not serious	not serious	not serious	none	148	144	-	MD **0.40 lower** (1.60 lower to 0.8 higher)	⨁⨁⨁⨁ HIGH	IMPORTANT

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

Explanations

a. NIV settings in comparison group appear to have been reasonable and titrated to patient need in most studies.
b. Very wide 95% confidence intervals resulting in very serious imprecision.
c. Wide 95% confidence intervals which do not rule out significant benefit nor harm.
d. High statistical heterogeneity with study point estimates on opposite sides of the line of no effect.
e. Lack of blinding of patients may result in bias, but given the immediacy of the comfort/discomfort using NIV/HFNC we judge patient assessments of comfort and dyspnea to be of lower risk of bias.
f. Statistically significant but optimal information size not met.

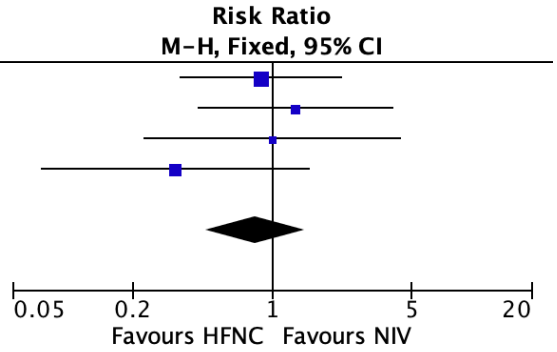
Recommendation 8: High-flow nasal cannula (HFNC) vs. non-invasive ventilation (NIV) in hypercapnic respiratory failure

1. Mortality

Study or Subgroup	HFNC Events	HFNC Total	NIV Events	NIV Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Lee 2016	7	44	8	44	37.5%	0.88 [0.35, 2.21]	2016
Wang 2019	6	23	4	20	20.0%	1.30 [0.43, 3.97]	2019
Papachatzakis 2020	3	20	3	20	14.0%	1.00 [0.23, 4.37]	2020
Cortegiani 2020	2	40	6	39	28.5%	0.33 [0.07, 1.51]	2020
Total (95% CI)		**127**		**123**	**100.0%**	**0.82 [0.46, 1.47]**	
Total events	18		21				

Heterogeneity: $Chi^2 = 2.14$, df = 3 (P = 0.54); $I^2 = 0\%$

Test for overall effect: Z = 0.66 (P = 0.51)

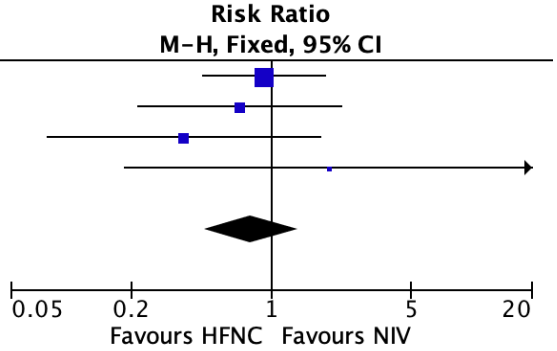


2. Intubation

Study or Subgroup	HFNC Events	HFNC Total	NIV Events	NIV Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Lee 2016	11	44	12	44	50.9%	0.92 [0.45, 1.85]	2016
Wang 2019	4	23	5	20	22.7%	0.70 [0.22, 2.24]	2019
Doshi 2020	2	34	5	31	22.2%	0.36 [0.08, 1.75]	2020
Cortegiani 2020	2	40	1	39	4.3%	1.95 [0.18, 20.64]	2020
Total (95% CI)		**141**		**134**	**100.0%**	**0.79 [0.46, 1.35]**	
Total events	19		23				

Heterogeneity: $Chi^2 = 1.72$, df = 3 (P = 0.63); $I^2 = 0\%$

Test for overall effect: Z = 0.86 (P = 0.39)

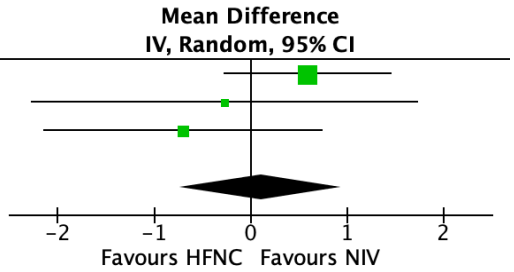


Recommendation 8: High-flow nasal cannula (HFNC) vs. non-invasive ventilation (NIV) in hypercapnic respiratory failure

3. ICU length of stay

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	NIV Mean	NIV SD	NIV Total	Weight	Mean Difference IV, Random, 95% CI	Year
Wang 2019	9.09	1.56	23	8.5	1.32	20	57.1%	0.59 [-0.27, 1.45]	2019
Cong 2019	18.04	6.15	84	18.31	7.01	84	15.6%	-0.27 [-2.26, 1.72]	2019
Doshi 2020	1.8	1.2	11	2.5	2.3	13	27.3%	-0.70 [-2.14, 0.74]	2020
Total (95% CI)			**118**			**117**	**100.0%**	**0.10 [-0.73, 0.94]**	

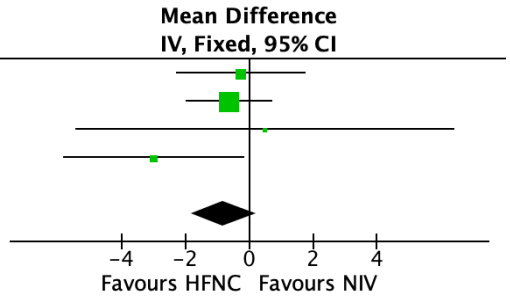
Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 2.51$, df = 2 (P = 0.29); $I^2 = 20\%$
Test for overall effect: Z = 0.24 (P = 0.81)



4. Hospital length of stay

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	NIV Mean	NIV SD	NIV Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Cong 2019	18.04	6.15	84	18.31	7.01	84	26.0%	-0.27 [-2.26, 1.72]	2019
Doshi 2020	4.37	3.08	34	5.01	2.39	31	58.0%	-0.64 [-1.97, 0.69]	2020
Papachatzakis 2020	11.5	8.5	20	11	10.5	20	2.9%	0.50 [-5.42, 6.42]	2020
Cortegiani 2020	10	7.4	40	13	5.2	39	13.0%	-3.00 [-5.81, -0.19]	2020
Total (95% CI)			**178**			**174**	**100.0%**	**-0.82 [-1.83, 0.20]**	

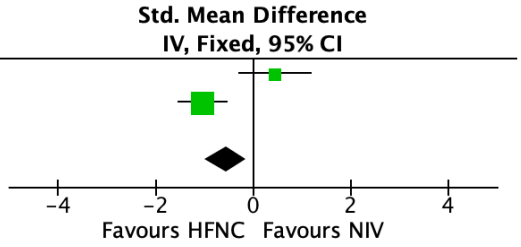
Heterogeneity: $Chi^2 = 2.86$, df = 3 (P = 0.41); $I^2 = 0\%$
Test for overall effect: Z = 1.58 (P = 0.11)



5. Comfort

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	NIV Mean	NIV SD	NIV Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Year
Sklar 2018	-6	2.2	15	-7	2.2	15	32.0%	0.44 [-0.28, 1.17]	2018
Cortegiani 2020	0	1.5	34	2	2.2	37	68.0%	-1.04 [-1.54, -0.54]	2020
Total (95% CI)			**49**			**52**	**100.0%**	**-0.57 [-0.98, -0.16]**	

Heterogeneity: $Chi^2 = 10.93$, df = 1 (P = 0.0009); $I^2 = 91\%$
Test for overall effect: Z = 2.71 (P = 0.007)

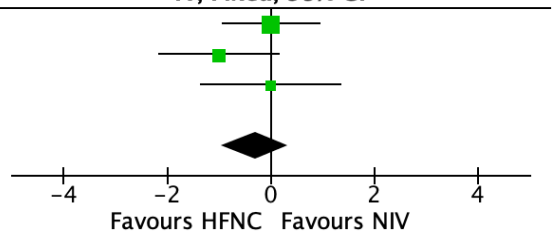


Recommendation 8: High-flow nasal cannula (HFNC) vs. non-invasive ventilation (NIV) in hypercapnic respiratory failure

6. Dyspnea

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	NIV Mean	NIV SD	NIV Total	Weight	Mean Difference IV, Fixed, 95% CI
Cortegiani 2020	5	2	34	5	2	37	46.9%	0.00 [-0.93, 0.93]
Doshi 2020	2	2	28	3	2.2	24	30.7%	-1.00 [-2.15, 0.15]
Sklar 2018	1	2.2	15	1	1.5	15	22.4%	0.00 [-1.35, 1.35]
Total (95% CI)			**77**			**76**	**100.0%**	**-0.31 [-0.94, 0.33]**

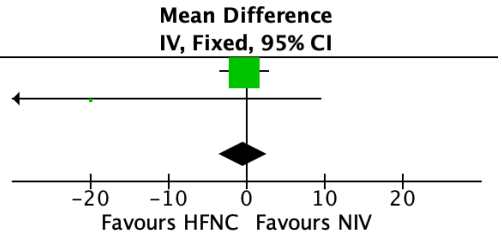
Heterogeneity: $Chi^2 = 2.01$, df = 2 (P = 0.37); $I^2 = 1\%$
Test for overall effect: Z = 0.94 (P = 0.35)



7. PaO2/FiO2

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	NIV Mean	NIV SD	NIV Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Lee 2016	-134.8	7.3	44	-134.5	7.5	44	98.9%	-0.30 [-3.39, 2.79]	2016
Cortegiani 2020	-2.2	62.3	40	17.8	70.8	39	1.1%	-20.00 [-49.44, 9.44]	2020
Total (95% CI)			**84**			**83**	**100.0%**	**-0.52 [-3.59, 2.56]**	

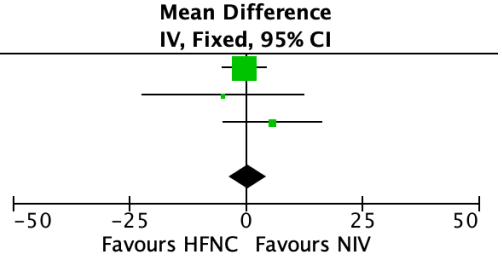
Heterogeneity: $Chi^2 = 1.70$, df = 1 (P = 0.19); $I^2 = 41\%$
Test for overall effect: Z = 0.33 (P = 0.74)



8. PO2

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	NIV Mean	NIV SD	NIV Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Cong 2019	81.87	15.27	84	82.22	15.64	84	78.7%	-0.35 [-5.02, 4.32]	2019
Doshi 2020	83	43	27	88	14.8	25	5.8%	-5.00 [-22.23, 12.23]	2020
Cortegiani 2020	3.1	20.7	40	-2.6	26.6	39	15.5%	5.70 [-4.83, 16.23]	2020
Total (95% CI)			**151**			**148**	**100.0%**	**0.32 [-3.83, 4.47]**	

Heterogeneity: $Chi^2 = 1.45$, df = 2 (P = 0.48); $I^2 = 0\%$
Test for overall effect: Z = 0.15 (P = 0.88)

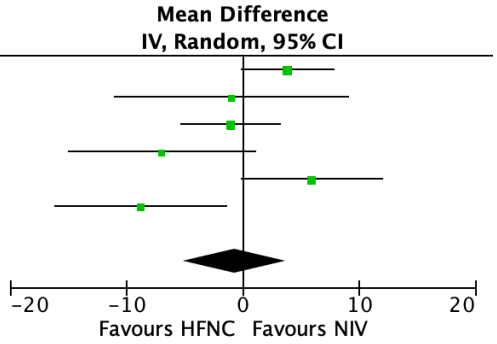


Recommendation 8: High-flow nasal cannula (HFNC) vs. non-invasive ventilation (NIV) in hypercapnic respiratory failure

9. PCO2

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	NIV Mean	NIV SD	NIV Total	Weight	Mean Difference IV, Random, 95% CI	Year
Lee 2016	56.4	10.1	44	52.6	8.8	44	21.5%	3.80 [-0.16, 7.76]	2016
Sklar 2018	53	14	15	54	14	15	11.1%	-1.00 [-11.02, 9.02]	2018
Cong 2019	58.87	14.42	84	59.95	13.56	84	21.0%	-1.08 [-5.31, 3.15]	2019
Doshi 2020	50	11.9	27	57	17	25	13.9%	-7.00 [-15.03, 1.03]	2020
Cortegiani 2020	64	14.9	40	58.1	12.4	39	17.5%	5.90 [-0.14, 11.94]	2020
Papachatzakis 2020	50.8	9.4	20	59.6	13.9	20	15.1%	-8.80 [-16.15, -1.45]	2020
Total (95% CI)			**230**			**227**	**100.0%**	**-0.79 [-5.19, 3.61]**	

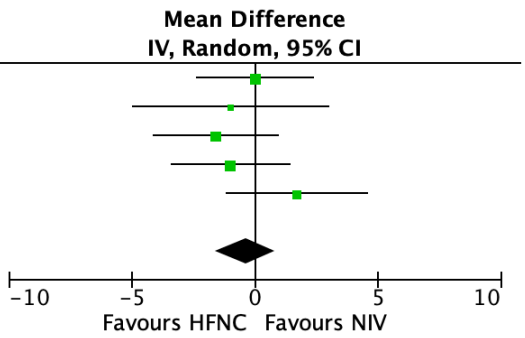
Heterogeneity: $Tau^2 = 19.33$; $Chi^2 = 15.83$, df = 5 (P = 0.007); $I^2 = 68\%$
Test for overall effect: Z = 0.35 (P = 0.72)



10. Respiratory rate

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	NIV Mean	NIV SD	NIV Total	Weight	Mean Difference IV, Random, 95% CI	Year
Lee 2016	24	5.9	44	24	5.4	44	25.8%	0.00 [-2.36, 2.36]	2016
Sklar 2018	18	5.2	15	19	5.9	15	9.1%	-1.00 [-4.98, 2.98]	2018
Papachatzakis 2020	15.7	3.5	20	17.3	4.6	20	22.5%	-1.60 [-4.13, 0.93]	2020
Doshi 2020	21	3.7	29	22	5.2	26	24.8%	-1.00 [-3.41, 1.41]	2020
Cortegiani 2020	-6	6	40	-7.7	6.9	39	17.7%	1.70 [-1.15, 4.55]	2020
Total (95% CI)			**148**			**144**	**100.0%**	**-0.40 [-1.60, 0.80]**	

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.38$, df = 4 (P = 0.50); $I^2 = 0\%$
Test for overall effect: Z = 0.65 (P = 0.52)



Supplement: Evidence to Decision and Voting Results Supplement

ERS Guidelines: High flow nasal cannula in acute respiratory failure

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Question 1: Should HFNC or COT be used for acute hypoxic respiratory failure?

Recommendation:
We suggest the use of HFNC over COT in patients with purely hypoxic respiratory failure. (conditional recommendation, moderate certainty).

Desirable effects	Trivial	Small	Moderate	Large	Varies	Unsure
Undesirable effects	Large	Moderate	Small	Trivial	Varies	Unsure
Certainty of evidence of effects	Very low	Low	Moderate	High	No included studies	
Variability in values	Important uncertainty or variability		Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability	
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour intervention or comparison	Probably favours the intervention / Favours the intervention	Varies	Unsure
Resources required	Large costs	Moderate costs	Negligible costs or savings	Moderate savings / Large savings	Varies	Unsure
Certainty of evidence of required resources	Very low	Low	Moderate	High	No included studies	
Cost effectiveness	Favours the comparison	Probably favours the comparison	Does not favour intervention or comparison	Probably favours the intervention / Favours the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact	Probably increased / Increased	Varies	Unsure
Acceptability	No	Probably no	Probably yes	Yes	Varies	Unsure
Feasibility	No	Probably no	Probably yes	Yes	Varies	Unsure

Recommendation and voting results

Strong recommendation for comparison over intervention	Conditional recommendation for comparison over intervention	Conditional recommendation for either the intervention or the comparison **1 votes (5%)**	Conditional recommendation for intervention over comparison **16 votes (84%)**	Strong recommendation for intervention over comparison **2 votes (11%)**	No recommendation

Panel comments

If there is sufficient monitoring and continuous availability of personel for endotracheal intubation and start mechanical ventilation. The major danger is prolonged HFNO in a patient who's bound to be intubated.
Moderate certainty of evidence for critical outcomes (mortality, intubation, escalation to NIV).In addition the balance between desirable and undesirable effects is probably favors to intervention

Question 2: Should HFNC or NIV be used for acute hypoxic respiratory failure?

Recommendation:
We suggest the use of HFNC over NIV in purely hypoxic respiratory failure. (conditional recommendation, low certainty)

Desirable effects	Trivial	Small	Moderate	Large	Varies	Don't know
Undesirable effects	Large	Moderate	Small	Trivial	Varies	Don't know
Certainty of evidence of effects	Very low	Low	Moderate	High	No included studies	
Variability in values	Important uncertainty or variability		Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability	
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour intervention or comparison	Probably favours the intervention / Favours the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs or 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	Favours the comparison	Probably favours the comparison	Does not favour intervention or comparison	Probably favours the intervention / Favours 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

Recommendation and voting results

Strong recommendation for comparison over intervention	Conditional recommendation for comparison over intervention	Conditional recommendation for either the intervention or the comparison **4 votes (21%)**	Conditional recommendation for intervention over comparison **13 votes (68%)**	Strong recommendation for intervention over comparison **2 votes (11%)**	No recommendation

Panel comments

Depends on local expertise and patient tolerability. Limiting to just one approach may be inferior to having both available and trialing which one works best for the individual patient. If a unit needs to start using either; preference for starting to use HFNO.
HFNC appears more comfortable, easier to set up

Question 3: Should HFNC or COT be used during breaks from NIV in patients with acute hypoxic respiratory failure?

Recommendation:
We suggest the use of HFNC over COT during breaks from NIV in patients with acute hypoxic respiratory failure (conditional recommendation, low certainty)

Desirable effects	Trivial	Small	Moderate	Large	Varies	Don't know
Undesirable effects	Large	Moderate	Small	Trivial	Varies	Don't know
Certainty of evidence of effects	Very low	Low	Moderate	High	No included studies	
Variability in values	Important uncertainty or variability		Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability	
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour intervention or comparison	Probably favours the intervention / Favours the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs or 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	Favours the comparison	Probably favours the comparison	Does not favour intervention or comparison	Probably favours the intervention / Favours 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

Recommendation and voting results

Strong recommendation for comparison over intervention	Conditional recommendation for comparison over intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for intervention over comparison	Strong recommendation for intervention over comparison	No recommendation
	1 vote (5%)	**14 votes (74%)**	**4 votes (21%)**		

Panel comments

It seems reasonable to use HFNC vs COT during breaks of NIV in patients with high inspiratory demand or whose hypoxemia is highly dependent on alveolar collapse, but makes sense given results of Q1
It based on only one study with no strong results.

Question 4: Should HFNC or COT be used in postoperative patients?

Recommendation:
We suggest that either HFNC or COT are appropriate to use in postoperative patients at low risk of respiratory complications. (conditional recommendation, low certainty)

Desirable effects	Trivial	Small	Moderate	Large	Varies	Don't know
Undesirable effects	Large	Moderate	Small	Trivial	Varies	Don't know
Certainty of evidence of effects	Very low	Low	Moderate	High	No included studies	
Variability in values	Important uncertainty or variability		Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability	
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour intervention or comparison	Probably favours the intervention / Favours the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs or 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	Favours the comparison	Probably favours the comparison	Does not favour intervention or comparison	Probably favours the intervention / Favours 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

Recommendation and voting results

Strong recommendation for comparison over intervention	Conditional recommendation for comparison over intervention **1 vote (5%)**	Conditional recommendation for either the intervention or the comparison **14 votes (74%)**	Conditional recommendation for intervention over comparison **4 votes (21%)**	Strong recommendation for intervention over comparison	No recommendation

Panel comments

COT should be used however, if clinical judgement deems that HFT should be used for example to help with secretions then it should be considered in specific patients
Because many of the studies included heterogeneous patients, finally it is unclear whether HFNC is more effective than COT in some groups of patients (obese, high risk and/or patients undergoing cardiac or thoracic surgery)
Reducing escalation is the main argument, even with a low certainty

Question 5: Should HFNC or NIV be used in postoperative patients at high risk of respiratory complications?

Recommendation:
We suggest the use of either HFNC or NIV in postoperative patients at high risk of respiratory complications. (conditional recommendation, low certainty).

Desirable effects	Trivial	Small	Moderate	Large	Varies	Unsure
Undesirable effects	Large	Moderate	Small	Trivial	Varies	Unsure
Certainty of evidence of effects	Very low	Low	Moderate	High	No included studies	
Variability in values	Important uncertainty or variability		Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability	
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour intervention or comparison	Probably favours the intervention / Favours the intervention	Varies	Unsure
Resources required	Large costs	Moderate costs	Negligible costs or savings	Moderate savings / Large savings	Varies	Unsure
Certainty of evidence of required resources	Very low	Low	Moderate	High	No included studies	
Cost effectiveness	Favours the comparison	Probably favours the comparison	Does not favour intervention or comparison	Probably favours the intervention / Favours the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact	Probably increased / Increased	Varies	Unsure
Acceptability	No	Probably no	Probably yes	Yes	Varies	Unsure
Feasibility	No	Probably no	Probably yes	Yes	Varies	Unsure

Recommendation and voting results

Strong recommendation for comparison over intervention	Conditional recommendation for comparison over intervention	Conditional recommendation for either the intervention or the comparison **17 votes (94%)**	Conditional recommendation for intervention over comparison **1 vote (6%)**	Strong recommendation for intervention over comparison	No recommendation

Panel comments

The usage should be clinical led. if a patient has skin breakdown due to NIV, HFT should be considered
NIV may be more effective than HFNC in surgical patients at high risk of respiratory failure. A small number of trials have compared HFNC and NIV in post-operative patients.
HFNC for comfort and possibly cost. simplier to use than NIV

Question 6: Should HFNC or COT be used in nonsurgical patients at low risk of extubation failure?

Recommendation:
We suggest the use of HFNC over COT in non-surgical patients after extubation at low or moderate risk of extubation failure (conditional recommendation, moderate certainty).

Desirable effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of evidence of effects	Very low	Low	Moderate	High		No included studies	
Variability in values	Important uncertainty or variability		Possibly important uncertainty or variability	Probably no important uncertainty or variability		No important uncertainty or variability	
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour intervention or comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs or 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	Favours the comparison	Probably favours the comparison	Does not favour intervention or comparison	Probably favours the intervention	Favours 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

Recommendation and voting results

Strong recommendation for comparison over intervention	Conditional recommendation for comparison over intervention	Conditional recommendation for either the intervention or the comparison **3 votes (16%)**	Conditional recommendation for intervention over comparison **13 votes (68%)**	Strong recommendation for intervention over comparison **3 votes (16%)**	No recommendation

Panel comments

Other studies reported potential benefits of NIV in these patients at high risk of reintubation.
The certainty of evidence for some outcomes is low or moderate, limited mainly by the imprecision and risk of bias of the included studies.
In high risk patients

Question 7: Should HFNC or NIV be used in nonsurgical patients at high risk of extubation failure?

Recommendation:
We suggest the use of NIV over HFNC after extubation for patients at high risk of extubation failure unless there are relative or absolute contraindications to NIV (conditional recommendation, moderate certainty).

Desirable effects	Trivial	Small	Moderate	Large	Varies	Don't know
Undesirable effects	Large	Moderate	Small	Trivial	Varies	Don't know
Certainty of evidence of effects	Very low	Low	Moderate	High	No included studies	
Variability in values	Important uncertainty or variability		Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability	
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour intervention or comparison	Probably favours the intervention / Favours the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs or 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	Favours the comparison	Probably favours the comparison	Does not favour intervention or comparison	Probably favours the intervention / Favours 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

Recommendation and voting results

Strong recommendation for comparison over intervention **3 votes (18%)**	Conditional recommendation for comparison over intervention **13 votes (76%)**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for intervention over comparison	Strong recommendation for intervention over comparison **1 vote (6%)**	No recommendation

Panel comments

Question 8: Should HFNC or NIV be used in patients with hypercapnic respiratory failure due to COPD?

Recommendation:
We suggest a trial of NIV prior to use of HFNC in patients with COPD and acute hypercapnic respiratory failure (conditional recommendation, low certainty).

Desirable effects	Trivial	Small	Moderate	Large	Varies	Don't know
Undesirable effects	Large	Moderate	Small	Trivial	Varies	Don't know
Certainty of evidence of effects	Very low	Low	Moderate	High	No included studies	
Variability in values	Important uncertainty or variability		Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability	
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour intervention or comparison	Probably favours the intervention / Favours the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs or 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	Favours the comparison	Probably favours the comparison	Does not favour intervention or comparison	Probably favours the intervention / Favours 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

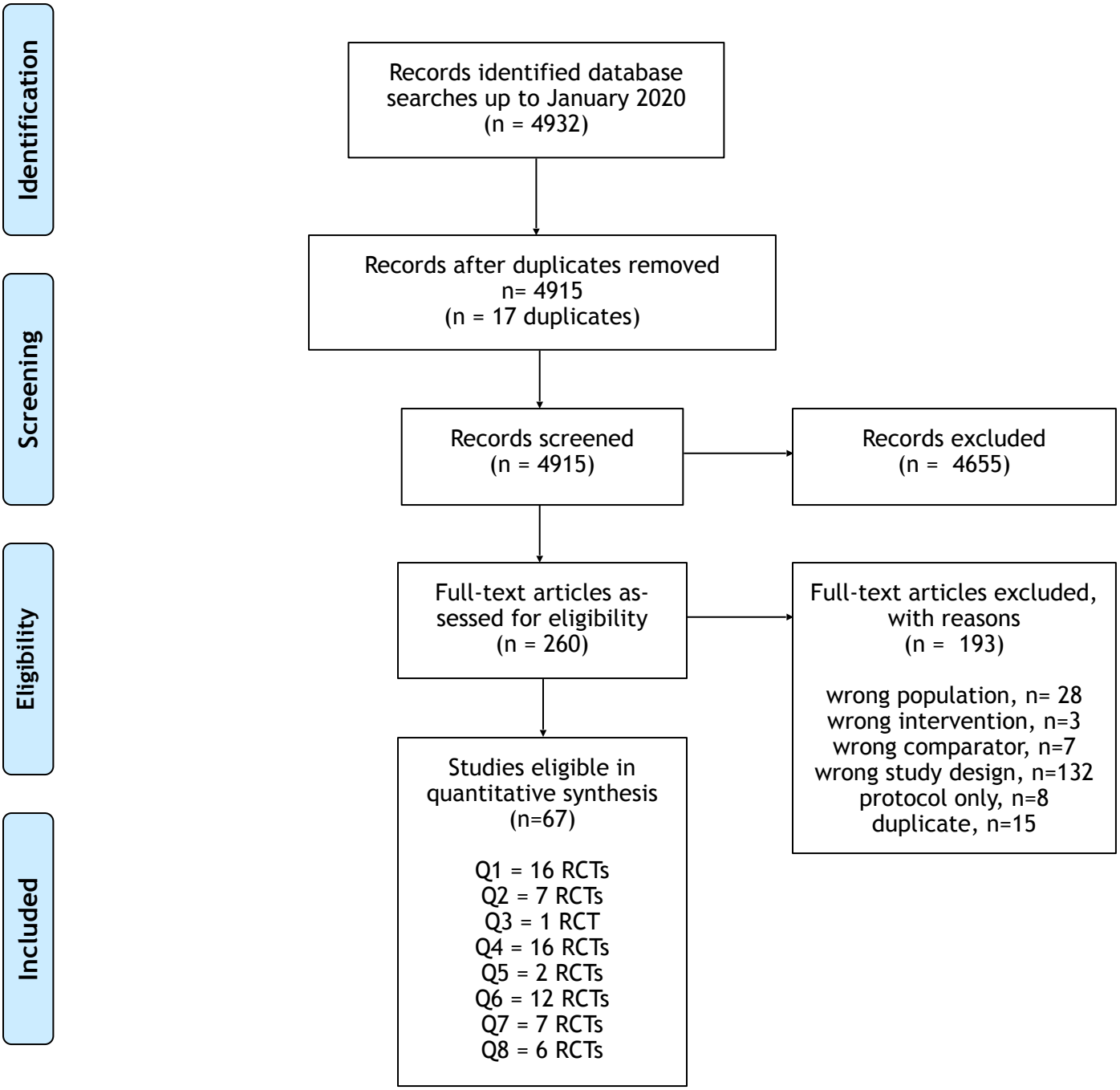
Recommendation and voting results

Strong recommendation for comparison over intervention **3 votes (19%)**	Conditional recommendation for comparison over intervention **13 votes (81%)**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for intervention over comparison	Strong recommendation for intervention over comparison	No recommendation

Panel comments

Studies comparing HFNC and NIV included small samples of patients and reported no actual benefits of HFNC
Definition of which type of Acute Hypercapnic respiratory failure is mandatory , A COPD patients has nothing to do with an hpercapnic Lenovo hypoxemic patiemts or a hypercapnic neuromuscolar patients
The certainty of evidence regarding the effects of HFNC vs. NIV in hypercapnic failure are very limited, but may be useful in less sick patients or those who cannot tolerate NIV
It might be worth modulating the strength of recommendation based on the severity of hypercapnic ARF (eg. severe hypercapnia in COPD, the recommendation should be stronger for NIV)

Supplementary Figure 1: PRISMA Diagram of Included Studies



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097