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High flow nasal cannula in the immediate post-operative period: a systematic review and meta-analysis

Short title: **High flow nasal cannula in the post-operative period.**

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Abbreviation List:

NIV – non-invasive ventilation

IMV – invasive ventilation

HFNC – high flow nasal cannula

RCT – randomized control trial

ROB – risk of bias

GRADE - Grading of Recommendations, Assessment, Development, and Evaluation

MD – mean difference

RR – relative risk

CI – confidence interval

ICU – intensive care unit

Abstract

Background: Recent studies have demonstrated that high flow nasal cannula (HFNC) prevents intubation in acute hypoxic respiratory failure when compared to conventional oxygen therapy (COT). However, the data examining routine HFNC use in the immediate post-operative period is less clear.

Research Question: Is routine HFNC use superior to COT or non-invasive ventilation (NIV) in preventing intubation in post-operative patients?

Study Design and Methods: We comprehensively searched databases (MEDLINE, EMBASE, Web of Science) to identify randomized controlled trials (RCTs) that compared the effect of HFNC use to COT or NIV in the immediate post-operative period on reintubation, escalation of respiratory support, hospital mortality, ICU and hospital length of stay, post-operative hypoxemia and treatment complications. We assessed individual study risk of bias using the revised Cochrane ROB 2 tool and rated certainty in outcomes using GRADE framework.

Results: We included 11 RCTs enrolling 2201 patients. Ten compared HFNC to COT and one to NIV. Compared to COT, HFNC use in the post-operative period was associated with a lower reintubation rate (RR 0.32, 95% CI 0.12 to 0.88, 2.9% absolute risk reduction (ARR), moderate certainty) and decreased escalation of respiratory support (RR 0.54, 95% CI 0.31 to 0.94, ARR 5.8%, very low certainty). Post-hoc subgroup analysis suggested that this effect was driven by obese and/or high risk patients (subgroup differences, p 0.06). We did not find differences in any

of the other stated outcomes between HFNC and COT. HFNC was also no different from NIV in reintubation rate, respiratory therapy failure or ICU LOS.

Interpretation: With moderate certainty evidence, prophylactic HFNC reduces reintubation and escalation of respiratory support compared to COT in the immediate post-operative period following cardiothoracic surgery. This effect is likely driven by high risk and/or obese patients. These findings support post-op prophylactic HFNC use in the high risk/obese cardiothoracic patients.

Acute respiratory failure is one of the most common complications following cardiac or non-cardiac surgery [1–3]. Post-operative respiratory failure, often due to atelectasis or pulmonary edema, is associated with increased mortality (as high as 27%) [1], increased intensive care unit (ICU) length of stay (LOS), longer rehabilitation, and poorer long-term functional outcomes [4]. Hypoxia and hypoxemia are common presentations of post-operative respiratory failure [5]. Depending on patient phenotype and the type of surgery performed, rates of post-operative respiratory failure as high as 10% - 50% have been demonstrated [1]. Oxygen therapy administered with low-flow nasal cannula or Venturi Mask are typically applied to post-operative patients prophylactically following extubation to prevent hypoxia. If respiratory failure develops and low-flow oxygen therapy fails, non-invasive ventilation (NIV) and/or invasive mechanical ventilation (IMV) are instituted as the next step [6–8]. However, both NIV and IMV are resource intensive, associated with patient discomfort and high-risk for complications [9,10].

High flow nasal cannula (HFNC) enables delivery of heated and humidified oxygen at flow rates that more closely approximate the inspiratory needs of dyspneic patients [11]. HFNC also provides a modest amount of positive end-expiratory pressure and decrease both pharyngeal dead space and nasopharyngeal resistance [12,13]. Furthermore, HFNC may be more comfortable and less obtrusive than other forms of oxygen delivery for patients [13]. Recent studies, including a systematic review and meta-analysis performed by our group, have demonstrated that HFNC prevents intubation when compared to conventional oxygen therapy (COT) in acute hypoxic respiratory failure [14]. The data examining HFNC applied in the post-operative period (within 24 hours of surgery) is less clear [15–17] . We sought to conduct a systematic review and meta-analysis comparing HFNC to COT when used routinely in the immediate post-operative period.

Methods

We registered our protocol on PROSPERO (CRD42019147870) and report our findings using a PRISMA checklist (e-Table 1).

Data Sources and Searches

We performed a comprehensive search of relevant databases (MEDLINE, EMBASE, and Web of Science) from January 1, 2007 (as HFNC was not widely used before this time) to April 15, 2019. We used keywords including human" OR "adult" OR "mature" or "grown" AND "high flow nasal cannula" OR "high flow nasal therapy" OR "high flow nasal oxygen" OR "high flow oxygen therapy" OR "high flow therapy" OR "optiflow (respiration)" OR "nasal highflow". We did not exclude studies based on language or trial quality. We updated the literature search on November 6, 2019.

Study Selection

Two independent reviewers (DW, DG) screened all citations in duplicates in two stages by first examining the title and abstracts and then, for selected citations, the full texts. We captured reasons for study exclusion after reviewing the full texts of identified trials. A third reviewer (BR) adjudicated disagreements.

We included all RCTs that compared HFNC to other non-invasive oxygen delivery modalities (traditional nasal cannula, Venturi Mask, NIV, etc.) in the immediate post-operative period. We included trials examining both cardiac and non-cardiac surgery. We excluded case series, case reports and observational studies. Our outcomes of interest included reintubation, escalation of respiratory therapy, hospital mortality, ICU LOS, hospital LOS, post-operative hypoxemia and complications. Escalation of respiratory therapy was defined as escalation to NIV or mechanical ventilation for the HFNC arm, and as escalation to HFNC, NIV or mechanical ventilation for the COT arm. Reintubation was defined as intubation of the trachea within 48 hours after post-operative extubation in the ICU or the post-anesthesia recovery room.

Data Extraction and Quality Assessment

Two independent reviewers (DC, DG, or DW) working in pairs abstracted data in duplicate using a standardized data abstraction form. A third reviewer (BR) adjudicated disagreements. We collected data on trial characteristics, demographic data, interventional and control details, and outcomes. We contacted individual trial authors for missing data.

We assessed risk of bias (ROB) in duplicate using the revised Cochrane risk of bias 2.0 tool for RCTs [18]. We assessed each RCT using the following domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. For each domain, we rated ROB to be “low”, “high”, or “some concerns” based on an algorithm that used signalling questions specific to each domain. The overall ROB for each trial was the highest risk attributed to any domain. Overall certainty of evidence was

assessed for each outcome using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework[19].

Data Analysis

We used the DerSimonnian-Laird random effects model with inverse-variance weighting to generate pooled treatment effects across studies. Heterogeneity between trials was assessed using a combination of the Chi^2 test, the I^2 statistic, and visual inspection of the forest plots [20]. We present results of dichotomous outcomes using relative risk (RR) and continuous outcomes as mean difference (MD) both with 95% confidence intervals (CIs). We also provide absolute differences with 95% CIs. We performed all statistical analysis using RevMan 5.3 (Cochrane Collaboration, Oxford) software.

We planned four *a priori* subgroup analyses: (i) post-operative cardiac surgical patients versus non-cardiac surgical patients, (ii) patients at high risk of respiratory failure (as defined by the investigators in each trial) versus those at low risk of respiratory failure, (iii) obese patients versus non-obese patients and (iv) high ROB studies versus low ROB studies. *A priori*, we hypothesized that cardiac surgery patients at high risk, obese patients and trials at high ROB would show greater benefit with HFNC therapy. We also performed a *post hoc* subgroup analysis, where we combined patients at high risk of respiratory failure and obese patients as an overall *"high risk"* subgroup. We hypothesized that this subgroup would show greater benefit with HFNC therapy.

We conducted trial sequential analysis [21] using the random effects model for trials reporting reintubation. For this analysis, we used a statistical significance level of 5%, a power of 80% and a RR reduction of 15% to represent a clinically important difference. We used a model variance-based heterogeneity correction. We performed trial sequential analysis using Trial Sequential Analysis version 0.9.5.10 beta (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark, www.ctu.dk/tsa).

Results

Search Strategy and Study Characteristics

We reviewed 650 citations and included 11 RCTs (n=2201) after screening. [5,15–17,22–28] (Figure 1). We excluded one RCT that compared HFNC to high flow face mask (using minimum flows of 15 Litre/min) as this comparator was judged to be an alternative delivery system and very similar to HFNC [29].

Table 1 shows the characteristics of the included RCTs which randomized between 51 to 830 patients. Only one RCT compared HFNC to NIV[15]. The remaining trials compared HFNC to COT. NIV was too different as a comparator to pool with COT, and therefore we did not include this trial in the quantitative analysis. Six of the eleven RCTs were conducted in post-cardiac surgery patients [15,17,22,24–26], while of the remaining five, four were conducted in post-thoracic surgery patients [16,23,27,28] and one trial was conducted in patients after major thoracic and abdominal surgery [5].

Four of the included studies examined patients at moderate to high risk of post-operative respiratory complications [5,15,26,28]. In two of the RCTs, this was defined as an ARISCAT risk score of 26 or greater [5,28], with the maximum possible score being 123 and a sigmoid relationship between score and risk. In the third trial, examining post-cardiac surgery patients, high risk was defined as any patient who had at least one risk factor for post-operative pulmonary complications [including history of COPD, asthma, lower respiratory tract infection in preceding four weeks, a BMI ≥ 35 kg.m2, or current (within last six weeks) heavy smokers (>10 pack years)][26]. The fourth trial only included post-cardiac surgery patients who were deemed to be at risk for needing post-operative oxygen therapy based on predefined risk factors including BMI > 30, LVEF < 40%, and a previous failed extubation[15](Table 1). Two trials examined obese patients exclusively [17,25] while two RCTs specifically excluded obese people [5,27]. All trials, except for the RCT that used NIV as a comparator[15], used HFNC prophylactically, rather than as a treatment for respiratory failure.

Nine RCTs utilized the Fisher and Paykel Optiflow™ device while one trial used the MaxVenturi® device [16]. Another trial[22] did not specify the type of HFNC device used. All HFNC devices provided heated and humidified nasal oxygen at high flows titrated between 25 to 60 L/min) with the goal of keeping the patient comfortable and aiming for a SpO2 target > 90%.

e-Table 2 summarizes the ROB for each individual trial. None of the trials blinded patients or clinicians. Given that all our outcomes were hard endpoints, we felt that there was unlikely to be significant risk of bias from lack of blinding. Thus, all trials except one[16] were judged to be at low ROB.

Outcomes

In e-Table 3 we depict the GRADE certainties and pooled estimates for pooled outcomes.

Reintubation/Need for Escalation

Compared to COT, HFNC use in the immediate post-operative period significantly decreased the need for reintubation (900 patients in 6 trials, RR 0.32, 95% CI 0.12 to 0.88, ARR 2.9%, 95% CI 0.5% to 3.7% reduction, moderate certainty, Figure 2). The reintubation rate was 0.9% (4/454) in the HFNC group and 4.3% (19/446) in the COT group. The trial sequential analysis for this outcome showed that the required information size (n=28 364) was not met and, consequently, we rated down the certainty for this outcome based on imprecision. HFNC use was also associated with a significant decrease in the need for escalation of respiratory support (RR 0.54, 95% CI 0.31 to 0.94, ARR 5.8%, 95% CI 2.1% to 9.5% reduction, Figure 3) with very low certainty evidence.

Other Outcomes of Interest

We did not find a difference between HFNC and COT on other outcomes including hospital mortality (RR 0.64, 95% CI 0.19 to 2.14, ARR 0.7%, 95% CI 1.5% reduction to 2.1% increase, low certainty, Figure 4), ICU LOS (MD 0.04 days higher, 95% CI 0.11 days lower to 0.19 days higher, high certainty, e-Figure 1), hospital LOS (MD 0.43 days lower, 95% CI 0.82 days lower to 0.04 days lower, moderate certainty, e-Figure 2) and the incidence of post-operative hypoxemia (RR 0.94, 95% CI 0.79 to 1.13, ARR 2.9%, 95% CI 10% reduction to 6.2% increase,

low certainty, e-Figure 3). Post-operative hypoxia was variable defined among the included trials with two trials defining it as SpO2 < 93% [5,24], while others defined it based on a PaO_2/FiO_2 ratio < 300 [27,28].

Complications were heterogeneously reported across trials and were not amenable to pooling. We summarize complications in e-Table 4.

NIV Comparator

Compared to NIV, HFNC showed no difference in reintubation rate (p = 0.99) or the rate of respiratory therapy failure (absolute difference 0.9%; 95%CI, −4.9%to 6.6%, p = .003). Although, we did not find a difference in ICU LOS, we noted that skin breakdown was more common with NIV after 24 hours (p < 0.001).

Subgroup and Sensitivity Analysis

Subgroup analysis based on the type of surgery, risk of post-operative respiratory complications, and obesity did not show credible subgroup effects for any outcomes of interest (e-Figure 4 - 9). However, the post-hoc “high risk” subgroup consisting of obese patients and patients at high risk of post-operative respiratory complications did show a significant subgroup effect, with the high risk group showing clear benefit in reintubation risk while the average risk group did not (high risk group RR 0.14, 95% CI 0.04 to 0.54; average risk group RR 1.01, 95% CI 0.21 to 4.97; test for subgroup differences p 0.06, I^2 70.9%) (Figure 2). We also performed two post hoc

sensitivity analysis excluding: 1) two trials that excluded obese patients [5,27] and 2) one trial that focused on patients having thoracoabdominal surgery[5]. The former was done to ensure that inclusion of studies with only low risk patients (non-obese) did not underestimate the outcomes. The latter was done to exclude the only study that examined patients with abdominal surgery to ensure that the generalizability of our conclusions was consistent for cardiac and thoracic surgery. Neither sensitivity analysis changed the overall results or conclusions. We performed a final sensitivity analysis using the Paule Mandel/empirical Bayes approach to pool treatment effects for the three most critical outcomes (reintubation rate, escalation of respiratory support and mortality) to ensure the robustness of our results. This analysis did not change the overall results or conclusions of this review (e-Figures 10, 11 and 12).

Discussion

The typical post-operative patient behaves differently from those with critically illness as they are usually previously well, without structural lung disease, and are typically intubated to facilitate anesthesia and surgery. Our findings show that HFNC, when used in the immediate post-operative period, is associated with significant reductions in reintubation and escalation of respiratory support when compared to COT in high risk cardiothoracic patients (Figure 2 and Figure 3). However, there were no significant effects on other important clinical outcomes including mortality, ICU length of stay and hospital length of stay. Only one trial compared HFNC to NIV and demonstrated comparable effects on outcomes.

Unlike critically ill patients, patients having surgery undergo planned extubation immediately after surgery or within a few hours of surgery for cardiac surgical patients[30]. Patient who develop respiratory failure in the post-operative period and require re-intubation have been shown to have significantly higher mortality, ICU LOS, hospital LOS and costs [31,32]. When a post-operative patient fails COT or is deemed to be at high risk for failure, most clinicians consider using NIV in these patients to prevent reintubation[6–8]. However, NIV may be poorly tolerated, can cause skin breakdown, and often requires admission to a monitored setting such as surgical step down unit or ICU [15]. HFNC is often better tolerated and may not require the same level of monitoring as NIV[15]. Stephan et al. [15] showed that in post-operative cardiothoracic patients, HFNC did not increase the rate of escalating respiratory support or re-intubation compared to NIV. As such, prophylactic HFNC application immediately after extubation in post-operative patients may prevent re-intubation without requiring the level of care that is necessitated by NIV use.

Of the trials included in this review, all but one[5] exclusively examined patients undergoing major cardiac or thoracic surgery. Since intrathoracic surgery has the highest risk of post-operative pulmonary complications[33], it stands to reason that this patient population is most likely to benefit from HFNC after extubation. While upper abdominal surgery also carries a high risk of pulmonary complications[33], the trial by Futier et al[5] did not show differences in treatment effect between HFNC and COT treated patients. Therefore, although our pooled analysis demonstrated potential benefit in all surgical types, the utility of HFNC following upper abdominal surgery remains uncertain.

Although previous meta-analyses have examined HFNC use in this population and found inconsistent results, we believe this may partly be explained by clinical heterogeneity. One previous meta-analysis [34] examined cardiac surgery patients only, excluding those following thoracic or abdominal surgery. Conversely another [35] included all patients after extubation (both critically ill and post-operative) – thus combining different patient populations. Two other meta-analysis examined HFNC use in postoperative patents and reported similar reductions in escalation of respiratory therapy and reintubation rates[36,37]. However, since the publication of these meta-analyses, five new RCT's have been published [22,23,25–27]. Moreover, one meta-analysis pooled both observational and randomized control trials together - a practice that has been questioned[36] while the other included only four RCTs[37], and did not include seven additional eligible RCTs[5,15,22,23,25–27] that have been published since. Additionally, neither systematic review pre-registered their protocol. Our meta-analysis includes data from all of published RCTs on this topic and thus represents the most comprehensive analysis of current trial data. Strengths of our study include the comprehensive search, topic pre-registration, and assessment of certainty using the GRADE approach.

Our review also has limitations. First, the included trials studied heterogeneous populations, however, when possible, we performed subgroup analysis by type of surgery (cardiac surgery vs. non-cardiac surgery), level of risk (high risk patients vs average risk patients) and obesity. To this end, statistical heterogeneity was generally low and none of our subgroups demonstrated credible effects suggesting the importance of the clinical heterogeneity may be limited. Second, all included trials were, by necessity, unblinded which may have influenced individual trial

results. Finally, although more than 2000 patients were included in this review, the event rate for most of the outcomes of interest was low resulting in imprecision in the pooled results.

Since the included trials only examined cardio-thoracic and major abdominal surgery, the effect of using HFNC post-operatively in other surgical patients at risk of respiratory failure (neurosurgery, ENT surgery or major vascular surgery) remains unknown[38]. Given that HFNC is likely most beneficial in high-risk surgeries, HFNC use in other patient populations and settings requires investigation. Similarly, further study is also needed examining the role of NIV in post-operative patients compared to HFNC alone or in combination with HFNC.

Interpretation

HFNC likely prevents reintubation and escalation of respiratory therapy, while having no significant effect on mortality or length of stay, compared to conventional oxygen therapy in the immediate post-operative period in cardiothoracic surgery patients with moderate certainty evidence. These findings support prophylactic use of HFNC in the cardiothoracic patient population, particularly in high risk and obese patients.

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Author Contributions and Guarantor Statement

DC had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. DC, BR, KB, DG, DW, SE and YV contributed substantially to study design, data collection and data analysis. All authors helped with study interpretation, writing and editing of the manuscript.

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Dr Mauri received personal fees from Fisher and Paykel, Drager and Mindray unrelated to the present work. Dr. Mancebo received personal fees from Faron, Medtronic and Janssen. Fisher Paykel and A-Lung provided medical equipment for multicenter trials (high flow nasal oxygen therapy and extracorporeal CO2 removal respectively). IMT Medical provided travel and hotel expenses to attend a meeting. Dr. Maggiore is the principal investigator of the RINO trial (clinicaltrials.gov, NCT02107183), which was supported by Fisher and Paykel Healthcare, and received lecture fees from Draeger Medical and General Electric Healthcare. Dr Ricard received travel expenses coverage from Fisher and Paykel Healthcare to attend scientific meetings. Fisher and Paykel Healthcare provided support for the ongoing High Flow ACRF trial ((NCT03406572). Dr. Jaber reports receiving consulting fees from Drager, Fisher & Paykel, Medtronic, Baxter and Fresenius-Xenios. Dr. Frat received personal fess from Fisher and Paykel Healthcare for lectures, reimbursement of travels and accommodations for medical meeting and equipment for centers for clinical studies. Dr. Hernandez received personal fees and travel

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Other Contributions

This manuscript was written as an initiative of the PLUG (Pleural pressure working group, https://www.plugwgroup.org), a working group of the Acute Respiratory Failure section of the European Society of Intensive Care Medicine (ESICM).

References

1. Arozullah AM, Daley J, Henderson WG, Khuri SF. Multifactorial Risk Index for Predicting Postoperative Respiratory Failure in Men After Major Noncardiac Surgery. *Ann Surg* [Internet] 2000 [cited 2019 Aug 28];232(2):242–253. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10903604
2. Xue FS, Li BW, Zhang GS, et al. The Influence of Surgical Sites on Early Postoperative Hypoxemia in Adults Undergoing Elective Surgery. *Anesth Analg* [Internet] 1999 [cited 2019 Aug 29];88(1):213–219. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9895095
3. Ranucci M, Ballotta A, Rovere MT La, Castelvecchio S, Surgical and Clinical Outcome Research (SCORE) Group. Postoperative Hypoxia and Length of Intensive Care Unit Stay after Cardiac Surgery: The Underweight Paradox? *PLoS One* [Internet] 2014 [cited 2019

Aug 29];9(4):e93992. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24709952

4. Neto AS, Hemmes SN, Barbas CS, et al. Incidence of mortality and morbidity related to postoperative lung injury in patients who have undergone abdominal or thoracic surgery: a systematic review and meta-analysis. *Lancet Respir Med* [Internet] 2014 [cited 2019 Aug 29];2(12):1007–1015. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25466352
5. Futier E, Paugam-Burtz C, Godet T, et al. Effect of early postextubation high-flow nasal cannula vs conventional oxygen therapy on hypoxaemia in patients after major abdominal surgery: a French multicentre randomised controlled trial (OPERA). *Intensive Care Med* [Internet] 2016 [cited 2019 Aug 29];42(12):1888–1898. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27771739
6. Zarbock A, Mueller E, Netzer S, Gabriel A, Feindt P, Kindgen-Milles D. Prophylactic Nasal Continuous Positive Airway Pressure Following Cardiac Surgery Protects From Postoperative Pulmonary Complications. *Chest* [Internet] 2009 [cited 2019 Aug 29];135(5):1252–1259. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19017864
7. Kindgen-Milles D, Müller E, Buhl R, et al. Nasal-Continuous Positive Airway Pressure Reduces Pulmonary Morbidity and Length of Hospital Stay Following Thoracoabdominal Aortic Surgery. *Chest* [Internet] 2005 [cited 2019 Aug 29];128(2):821–828. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16100174
8. Squadrone V, Coha M, Cerutti E, et al. Continuous Positive Airway Pressure for Treatment of Postoperative Hypoxemia. *JAMA* [Internet] 2005 [cited 2019 Aug 29];293(5):589. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15687314
9. Torres MF, Porfírio GJ, Carvalho AP, Riera R. Non-invasive positive pressure ventilation for prevention of complications after pulmonary resection in lung cancer patients.

Cochrane Database Syst Rev [Internet] 2019 [cited 2019 Aug 29];Available from: http://doi.wiley.com/10.1002/14651858.CD010355.pub3

10. Nava S, Gregoretti C, Fanfulla F, et al. Noninvasive ventilation to prevent respiratory failure after extubation in high-risk patients*. *Crit Care Med* [Internet] 2005 [cited 2019 Aug 29];33(11):2465–2470. Available from: https://insights.ovid.com/crossref?an=00003246-200511000-00003
11. Lee JH, Rehder KJ, Williford L, Cheifetz IM, Turner DA. Use of high flow nasal cannula in critically ill infants, children, and adults: a critical review of the literature. *Intensive Care Med* [Internet] 2013 [cited 2019 Jan 6];39(2):247–57. Available from: http://link.springer.com/10.1007/s00134-012-2743-5
12. Cortegiani A, Accurso G, Mercadante S, Giarratano A, Gregoretti C. High flow nasal therapy in perioperative medicine: from operating room to general ward. *BMC Anesthesiol* [Internet] 2018 [cited 2019 Jan 6];18(1):166. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30414608
13. Simon M, Wachs C, Braune S, Heer G de, Frings D, Kluge S. High-Flow Nasal Cannula Versus Bag-Valve-Mask for Preoxygenation Before Intubation in Subjects With Hypoxemic Respiratory Failure. *Respir Care* [Internet] 2016;61(9):1160–1167. Available from: http://rc.rcjournal.com/cgi/doi/10.4187/respcare.04413
14. Rochwerg B, Granton D, Wang DX, et al. High flow nasal cannula compared with conventional oxygen therapy for acute hypoxemic respiratory failure: a systematic review and meta-analysis. *Intensive Care Med* [Internet] 2019 [cited 2019 Apr 3];Available from: http://www.ncbi.nlm.nih.gov/pubmed/30888444
15. Stéphan F, Barrucand B, Petit P, et al. High-Flow Nasal Oxygen vs Noninvasive Positive

Airway Pressure in Hypoxemic Patients After Cardiothoracic Surgery. *JAMA* [Internet] 2015 [cited 2019 Aug 29];313(23):2331. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2015.5213

16. Brainard J, Scott BK, Sullivan BL, et al. Heated humidified high-flow nasal cannula oxygen after thoracic surgery — A randomized prospective clinical pilot trial. *J Crit Care* [Internet] 2017 [cited 2019 Aug 29];40:225–228. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28454060
17. Corley A, Bull T, Spooner AJ, Barnett AG, Fraser JF. Direct extubation onto high-flow nasal cannulae post-cardiac surgery versus standard treatment in patients with a BMI ≥30: a randomised controlled trial. *Intensive Care Med* [Internet] 2015 [cited 2019 Aug 29];41(5):887–894. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25851385
18. Sterne JAC, Savović J, Page MJ, et al. RoB 2: A revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366.
19. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* [Internet] 2008 [cited 2017 Jul 8];336(7650). Available from: http://www.bmj.com/content/336/7650/924
20. Deeks, J; Higgins J. Statistical Algorithms in Review Manager 5. Statistical Methods Group of the Cochrane Collaboration - Google Scholar [Internet]. Stat. Methods Groups Cochrane Collab. 2010 [cited 2017 Jul 8];Available from: https://scholar-google-ca.libaccess.lib.mcmaster.ca/scholar?hl=en&q=Statistical+Algorithms+in+Review+Manager+5.+Statistical+Methods+Group+of+the+Cochrane+Collaboration&btnG=&as_sdt=1%2C5&as_sdtp=
21. Wetterslev J, Jakobsen JC, Gluud C. Trial Sequential Analysis in systematic reviews with

meta-analysis. *BMC Med Res Methodol* [Internet] 2017 [cited 2019 Jun 5];17(1):39. Available from: http://bmcmedresmethodol.biomedcentral.com/articles/10.1186/s12874-017-0315-7

22. Tatsuishi W, Sato T, Kataoka G, Sato A, Asano R, Nakano K. High-Flow Nasal Cannula Therapy With Early Extubation for Subjects Undergoing Off-Pump Coronary Artery Bypass Graft Surgery. *Respir Care* 2019;respcare.06382.
23. Ansari BM, Hogan MP, Collier TJ, et al. A Randomized Controlled Trial of High-Flow Nasal Oxygen (Optiflow) as Part of an Enhanced Recovery Program After Lung Resection Surgery. *Ann Thorac Surg* [Internet] 2016 [cited 2019 Aug 29];101(2):459–464. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26409713
24. Parke R, McGuinness S, Dixon R, Jull A. Open-label, phase II study of routine high-flow nasal oxygen therapy in cardiac surgical patients. *Br J Anaesth* [Internet] 2013 [cited 2019 Aug 29];111(6):925–931. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23921199
25. Sahin M, El H, Akkoç I. Comparison of Mask Oxygen Therapy and High-Flow Oxygen Therapy after Cardiopulmonary Bypass in Obese Patients. *Can Respir J* [Internet] 2018 [cited 2019 Aug 29];2018:1–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29623135
26. Zochios V, Collier T, Blaudszun G, et al. The effect of high-flow nasal oxygen on hospital length of stay in cardiac surgical patients at high risk for respiratory complications: a randomised controlled trial. *Anaesthesia* [Internet] 2018 [cited 2019 Aug 29];73(12):1478–1488. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30019747
27. Pennisi MA, Bello G, Congedo MT, et al. Early nasal high-flow versus Venturi mask

oxygen therapy after lung resection: a randomized trial. *Crit Care* [Internet] 2019 [cited 2019 Aug 30];23(1):68. Available from: https://ccforum.biomedcentral.com/articles/10.1186/s13054-019-2361-5

28. Yu Y, Qian X, Liu C, Zhu C. Effect of High-Flow Nasal Cannula versus Conventional Oxygen Therapy for Patients with Thoracoscopic Lobectomy after Extubation. *Can Respir J* [Internet] 2017 [cited 2019 Aug 29];2017:1–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28298878

29. Nicolet J, Poulard F, Baneton D, Rigal J-C, Blanloeil Y. Oxygénation nasale à haut débit pour hypoxémie après chirurgie cardiaque. *Ann Fr Anesth Reanim* [Internet] 2011 [cited 2019 Aug 29];30(4):331–334. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0750765811000499

30. Silbert BS, Santamaria JD, O'Brien JL, Blyth CM, Kelly WJ, Molnar RR. Early Extubation Following Coronary Artery Bypass Surgery: A Prospective Randomized Controlled Trial. *Chest* [Internet] 1998 [cited 2019 Sep 11];113(6):1481–1488. Available from: https://www.sciencedirect.com/science/article/abs/pii/S0012369216314866

31. Rady MY, Ryan T. Perioperative predictors of extubation failure and the effect on clinical outcome after cardiac surgery. *Crit Care Med* [Internet] 1999 [cited 2019 Sep 11];27(2):340–7. Available from: https://insights.ovid.com/crossref?an=00003246-199902000-00041

32. Glossop AJ, Shepherd N, Bryden DC, Mills GH. Non-invasive ventilation for weaning, avoiding reintubation after extubation and in the postoperative period: a meta-analysis. *Br J Anaesth* [Internet] 2012 [cited 2019 Sep 11];109(3):305–314. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0007091217320950

33. Mazo V, Sabaté S, Canet J, et al. Prospective external validation of a predictive score for postoperative pulmonary complications. *Anesthesiology* 2014;121(2):219–231.

34. Zhu Y, Yin H, Zhang R, Wei J. High-flow nasal cannula oxygen therapy vs conventional oxygen therapy in cardiac surgical patients: A meta-analysis. *J Crit Care* [Internet] 2017 [cited 2019 Sep 5];38:123–128. Available from: https://www.sciencedirect.com/science/article/abs/pii/S0883944116302957#aep-article-footnote-id2

35. Huang H-W, Sun X-M, Shi Z-H, et al. Effect of High-Flow Nasal Cannula Oxygen Therapy Versus Conventional Oxygen Therapy and Noninvasive Ventilation on Reintubation Rate in Adult Patients After Extubation: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J Intensive Care Med* [Internet] 2018 [cited 2019 Sep 5];33(11):609–623. Available from: http://journals.sagepub.com/doi/10.1177/0885066617705118

36. Lu Z, Chang W, Meng SS, et al. Effect of high-flow nasal cannula oxygen therapy compared with conventional oxygen therapy in postoperative patients: A systematic review and meta-analysis. BMJ Open. 2019;9(8).

37. Wu X, Cao W, Zhang B, Wang S. Effect of high-flow nasal cannula oxygen therapy vs conventional oxygen therapy on adult postcardiothoracic operation A meta-analysis. Med. (United States). 2018;97(41).

38. Brueckmann B, Villa-Uribe JL, Bateman BT, et al. Development and validation of a score for prediction of postoperative respiratory complications. *Anesthesiology* 2013;118(6):1276–1285.

Take Home Pullout

Study Question: Is routine HFNC use superior to COT or non-invasive ventilation (NIV) in preventing intubation in post-operative patients?

Results: Compared to COT, HFNC use in the post-operative period was associated with a lower reintubation rate (RR 0.32, 95% CI 0.12 to 0.88, 2.9% absolute risk reduction (ARR), moderate certainty) and decreased escalation of respiratory support (RR 0.50, 95% CI 0.28 to 0.92, ARR 7.5%, very low certainty). Post-hoc subgroup analysis suggested that this effect was driven by obese and/or high risk patients (subgroup differences, p 0.06).

Interpretation: Moderate certainty evidence supports post op prophylactic HFNC use in the high risk/obese cardiothoracic patient.

Figure Legend

Figure 1: PRISMA flow diagram – study selection. RCT = randomized control trial.

Figure 2: Effect of HFNC on reintubation rate when compared to conventional oxygen therapy. Studies are grouped by high risk (obese and/or high risk of postoperative respiratory complications) and average risk. df = degrees of freedom, HFNC = high flow nasal cannula

Figure 3: Effect of HFNC on escalation of respiratory support when compared to conventional oxygen therapy. Studies are grouped by high risk (obese and/or high risk of postoperative respiratory complications) and average risk. df = degrees of freedom, HFNC = high flow nasal cannula

Figure 4: Effect on HFNC on mortality when compared to conventional oxygen therapy. df = degrees of freedom, HFNC = high flow nasal cannula

Table 1: Characteristics of included studies

Trial	Country	Number of Patients Randomized	Population	Intervention Details	Comparator Details	Outcomes
Ansari, 2016	Cambridge, UK	59	**Inclusion:** elective lung resection surgery, and age more than 18 years. **Exclusion**: pneumonectomy, contraindication to HFNC, and mobilization limitation leading to inability to perform 6MWT	(OptiFlow, Fisher & Paykel Healthcare) Flow: Started at 50 L/min and titrated to sats and comfort Duration: First 24 hours	Simple facemask or nasal prongs at 2 – 4 L/min Duration: 24 hours and then as needed.	Hospital LOS, 6MWT, difference between pre-op and post FEV1
Brainard, 2017	Aurora, Colorado	51	**Inclusion:** > 18 years of age undergoing thoracic surgery with scheduled admission to the intensive care unit post-operatively. **Exclusion:** pregnant or breastfeeding, obstructive sleep apnea, lung transplantation,	(OptiFlow, Fisher & Paykel Healthcare) Flow: Started at 40 L/min and titrated to sats and comfort Duration: First 48 hours or discharge from ICU	Nasal cannula or face mask oxygen Duration: First 48 hours or discharge from ICU	Post-operative pulmonary complications (composite of severe hypoxemia (SpO2< 90% with FiO2≥ 50%), acute respiratory failure escalation of therapy to

			previous pneumonectomy, home oxygen > 4L/min, or inability to adhere to assigned treatment for the intended duration			non-invasive ventilation, re-intubation, occurrence of hospital-acquired pneumonia, or re-admission to the ICU), ICU LOS, hospital LOS
Corley, 2015	Brisbane, Australia	155	**Inclusion:** > 18 years with a BMI over 30 kg/m2 and scheduled to undergo cardiac surgery on cardiopulmonary bypass. **Exclusion:** Ventilation time > 36 h, extubation onto NIV, requirement for tracheostomy, and extubation as part of end-of-life treatment	(OptiFlow, Fisher & Paykel Healthcare) Flow: Started at 35 L/min and titrated to sats and comfort Duration: 8 hours minimum and longer if needed	Simple facemask or nasal prongs Duration: 8 hours or longer as needed.	ICU LOS, escalation of respiratory therapy, re-intubation, average PF ratio in first 24 hours
Futier, 2016	France	220	**Inclusion:** All adult patients scheduled for abdominal, or abdominal and thoracic surgery with an anticipated duration of 2 h or more and an ARISCAT risk	(OptiFlow, Fisher & Paykel Healthcare)**:** Flow: Started at 50 L/min and titrated to sats and comfort Duration: First 24 hours	Nasal prongs or facemask Duration: First 24 hours	Hospital mortality, hypoxia, ICU LOS, hospital LOS, escalation of respiratory support, reintubation,

			score of 26 points or more, were eligible for recruitment. **Exclusion:** body mass index greater than 35 kg/m2, life-threatening condition requiring emergency surgery, obstructive sleep apnoea syndrome and pregnant patients**.**			complications
Parke, 2013	Auckland, New Zealand	341	**Inclusion:** adult patients with elective cardiac surgery utilizing cardiopulmonary bypass **Exclusion:** contraindication to HFNC. If participants had not met the extubation criteria by 10 a.m. the day after surgery	(OptiFlow, Fisher & Paykel Healthcare) Flow: Started at 45 L/min and titrated to sats and comfort Duration: First 48 hours	Simple facemask or nasal prongs Duration: First 48 hours	28-day mortality, ICU LOS, hospital LOS, escalation of respiratory care, reintubation, post-op FEV1
Pennisi, 2019	Rome, Italy	96	**Inclusion:** All adult patients scheduled for elective thoracotomic pulmonary lobar resection for malignant disease **Exclusion:** pregnancy, body mass	(OptiFlow, Fisher & Paykel Healthcare) Flow: 50 L/min Duration: First 48 hours	Venturi mask (OS/60 K, FIAB, Florence, Italy) Duration: First 48 hours	ICU LOS, hospital LOS, escalation of respiratory therapy, reintubation, average PF ratio in first 48 hours, hypoxia

			index≥35 kg/m2, history of obstructive sleep apnea syndrome, long-term oxygen therapy due to chronic pulmonary disease, tracheostomy, and any nasal/facial defect that could impede HFNC or Venturi mask use.			
Sahin, 2018	Istanbul, Turkey	100	**Inclusion:** All adult patients undergoing CABG with BMI > 30. **Exclusion:** hemodynamic instability, patients with tracheostomy, obstructive sleep apnea, active pulmonary disease, known low cardiac output and emergency surgery	(OptiFlow, Fisher & Paykel Healthcare) Flow: Started at 25 L/min and titrated to oxygen saturation and comfort Duration: First 48 hours	Simple face mask Duration: First 48 hours	Hospital mortality, ICU LOS, hospital LOS, escalation of respiratory therapy, reintubation, post op day 2 FEV1, complications
Stephan, 2015	France	830	**Inclusion:** All adult patients undergoing cardiothoracic surgery and meeting any of the following criteria: 1. Failure of a spontaneous breathing trial, defined as arterial	(OptiFlow, Fisher & Paykel Healthcare) Flow: Started at 50 L/min and titrated to sats and comfort Duration: Until SaO2 > 95% on 6 L/min or PF >300	BiPAP with full face mask Settings: 8/4 and titration to adequate volumes and comfort Duration: Until fewer	ICU mortality, ICU LOS, hospital LOS, escalation of respiratory therapy, reintubation, dyspnea score, comfort score, pneumonia,

oxygen saturation (SaO2) less than 90% with 12 L of oxygen during a T-tube trial or PaO2 less than 75mmHg with a fraction of inspired oxygen (FIO2) of at least 50% during low level pressure support 2. Successful spontaneous breathing trial with any of the following preexisting risk factors: BMI < 30, left ventricular ejection fraction <40% and failure of previous extubation 3. Successful spontaneous breathing trial followed by failed extubation, defined as at least 1 of the following: PaO2:FIO2 ratio less than 300, respiratory rate greater than 25/min for at least 2 hours, and use of accessory respiratory muscles or paradoxical respiration.	than 4 hours per day of BiPAP were needed	pneumothorax, colonic pseudo-obstruction

			Exclusion: obstructive sleep apnea, tracheostomy, do-not-intubate status, delirium, nausea and vomiting, bradypnea, impaired consciousness, and hemodynamic instability.			
Tatsuishi, 2019	Tokyo, Japan	148	**Inclusion:** All adult patients undergoing off-pump CABG **Exclusion:** Concomitant procedures such as valve surgery or aortic surgery; chronic kidney disease; uncomfortable with HFNC	HFNC (company not specified) Flow: 45 – 60 L/min Duration: Till the end of post op day 1	Simple face mask with humidification Duration: Till the end of post op day 1	Loss of lung volume, duration and amount of oxygen therapy, post-operative diuretic use, ICU LOS, hospital LOS
Yu, 2017	Shanghai, China	110	**Inclusion:** Patients who underwent planned thoracoscopic lobectomy because of lung tumor with ARISCAT > 26. **Exclusion:** Immunocompromised; pregnant; converted to an open thoracotomy because of poor	(OptiFlow, Fisher & Paykel Healthcare) Flow: Started at 35 L/min, then titrated to sats and comfort Duration: First 72 hours	Nasal prongs or facemask Duration: First 72 hours	ICU LOS, hospital LOS, hypoxia, escalation of respiratory therapy, reintubation, mean PF ratio in first 48 hours, complications

			visualization or bleeding; or > 80 years of age			
Zochios, 2018	Birmingham, UK	100	**Inclusion:** elective cardiac surgery; aged>18 years with one or more patient-related risk factors for post-operative pulmonary complications (COPD, asthma, lower respiratory tract infection in preceding four weeks, BMI≥35, current heavy smokers) and capable of performing a 6-minute walk test **Exclusion:** Patients in whom high-flow nasal oxygen was contraindicated, those who needed CPAP pre-operatively or those who did not meet tracheal extubation criteria by 10.00 the day after surgery	(OptiFlow, Fisher & Paykel Healthcare) Flow: Started at 30 L/min, and titrated to sats and comfort Duration: First 24 hours	Nasal prongs or a soft face mask Duration: First 24 hours	Hospital mortality, ICU LOS, hospital LOS, complications, escalation of respiratory care, reintubation, post op day 1 FEV1, post op 6MWT

HFNC = high flow nasal cannula

6MWT = 6 minute walk test

FEV1 = forced expiratory volume in 1 second

LOS = length of stay

BMI = Body mass index

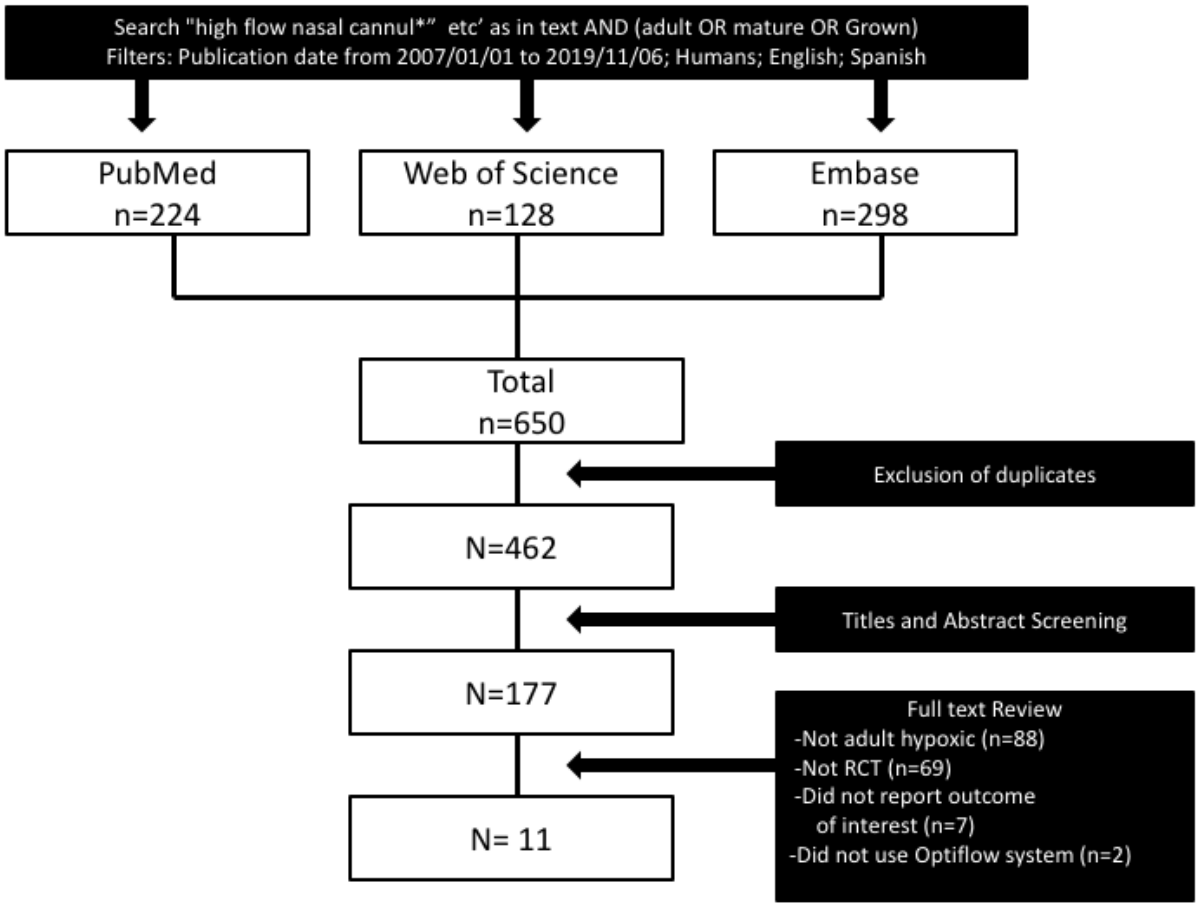
PF = PaO_2:FiO_2 ratio

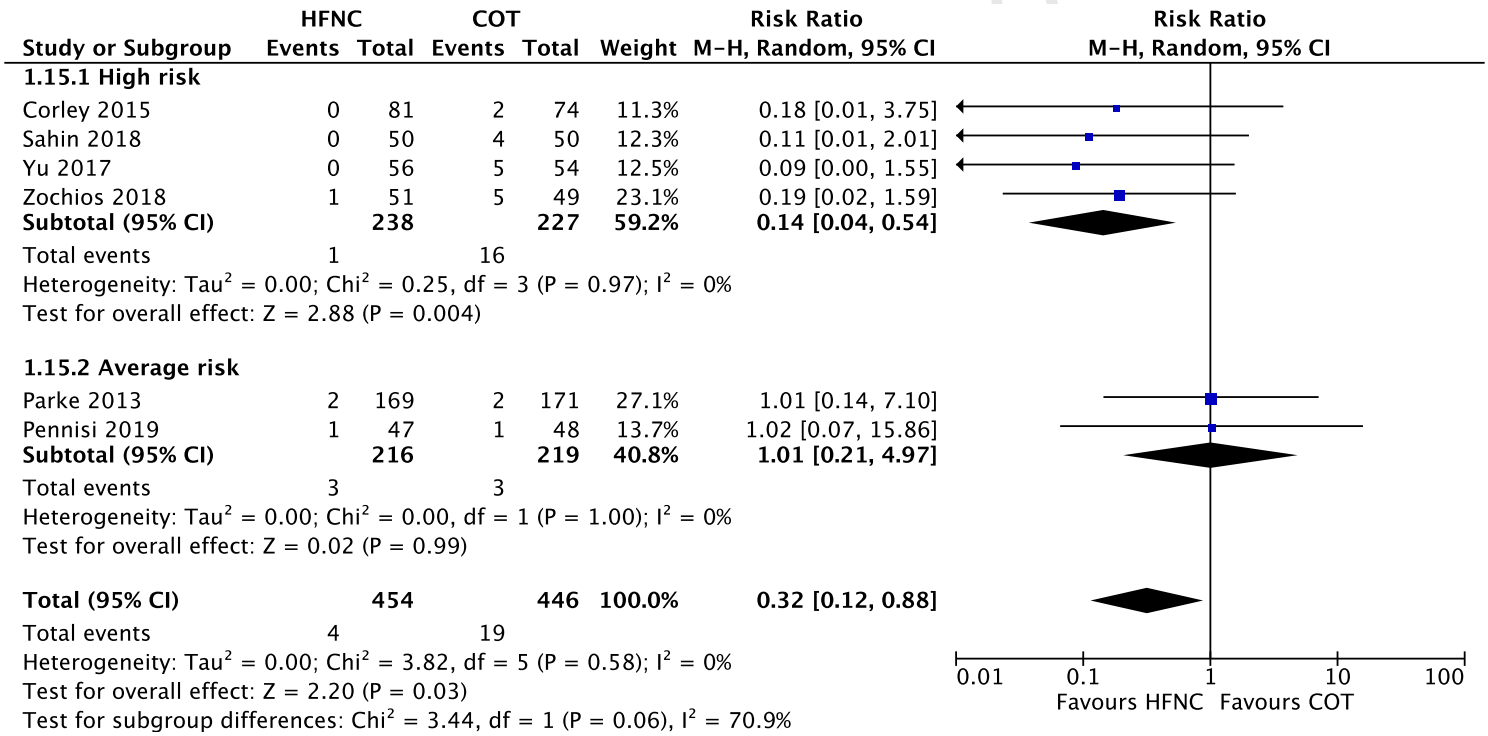
NIV = Non-invasive ventilation

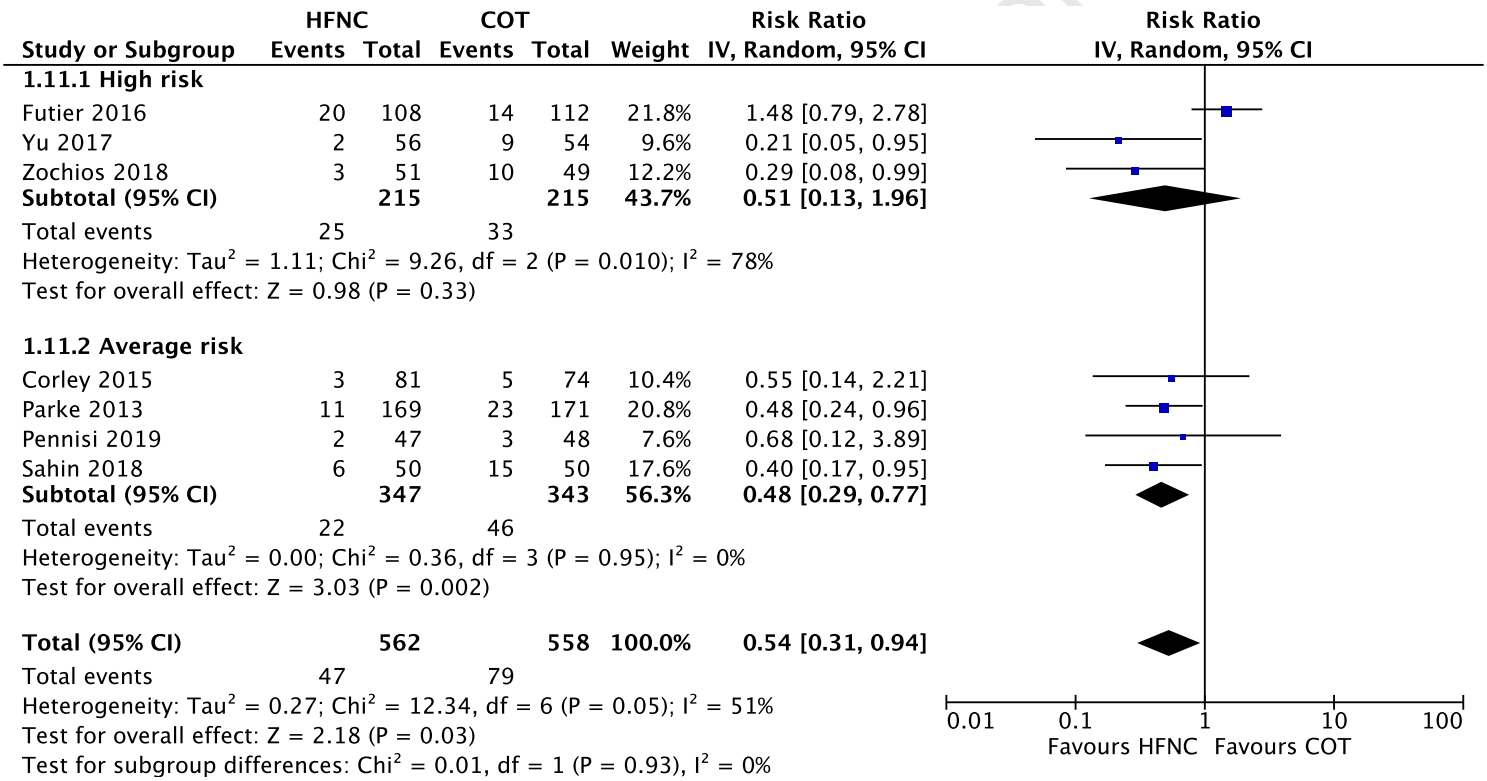
CABG = coronary artery bypass graft

COPD = chronic obstructive pulmonary disease

CPAP = continuous positive airway pressure


Search "high flow nasal cannul*" etc' as in text AND (adult OR mature OR Grown)
Filters: Publication date from 2007/01/01 to 2019/11/06; Humans; English; Spanish
PubMed
n=224
Web of Science
n=128
Embase
n=298
Total
n=650
Exclusion of duplicates
N=462
Titles and Abstract Screening
N=177
Full text Review
-Not adult hypoxic (n=88)
-Not RCT (n=69)
-Did not report outcome
of interest (n=7)
-Did not use Optiflow system (n=2)
N= 11


HFNC
COT
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
1.15.1 High risk
Corley 2015 0 81 2 74 11.3% 0.18 [0.01, 3.75]
Sahin 2018 0 50 4 50 12.3% 0.11 [0.01, 2.01]
Yu 2017 0 56 5 54 12.5% 0.09 [0.00, 1.55]
Zochios 2018 1 51 5 49 23.1% 0.19 [0.02, 1.59]
Subtotal (95% CI) 238 227 59.2% 0.14 [0.04, 0.54]
Total events 1 16
Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 3 (P = 0.97); I² = 0%
Test for overall effect: Z = 2.88 (P = 0.004)
1.15.2 Average risk
Parke 2013 2 169 2 171 27.1% 1.01 [0.14, 7.10]
Pennisi 2019 1 47 1 48 13.7% 1.02 [0.07, 15.86]
Subtotal (95% CI) 216 219 40.8% 1.01 [0.21, 4.97]
Total events 3 3
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.02 (P = 0.99)
Total (95% CI) 454 446 100.0% 0.32 [0.12, 0.88]
Total events 4 19
Heterogeneity: Tau² = 0.00; Chi² = 3.82, df = 5 (P = 0.58); I² = 0%
Test for overall effect: Z = 2.20 (P = 0.03)
Test for subgroup differences: Chi² = 3.44, df = 1 (P = 0.06), I² = 70.9%
0.01
0.1
1
10
100
Favours HFNC
Favours COT


HFNC
COT
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight IV, Random, 95% CI
IV, Random, 95% CI
1.11.1 High risk
Futier 2016 20 108 14 112 21.8% 1.48 [0.79, 2.78]
Yu 2017 2 56 9 54 9.6% 0.21 [0.05, 0.95]
Zochios 2018 3 51 10 49 12.2% 0.29 [0.08, 0.99]
Subtotal (95% CI) 215 215 43.7% 0.51 [0.13, 1.96]
Total events 25 33
Heterogeneity: Tau² = 1.11; Chi² = 9.26, df = 2 (P = 0.010); I² = 78%
Test for overall effect: Z = 0.98 (P = 0.33)
1.11.2 Average risk
Corley 2015 3 81 5 74 10.4% 0.55 [0.14, 2.21]
Parke 2013 11 169 23 171 20.8% 0.48 [0.24, 0.96]
Pennisi 2019 2 47 3 48 7.6% 0.68 [0.12, 3.89]
Sahin 2018 6 50 15 50 17.6% 0.40 [0.17, 0.95]
Subtotal (95% CI) 347 343 56.3% 0.48 [0.29, 0.77]
Total events 22 46
Heterogeneity: Tau² = 0.00; Chi² = 0.36, df = 3 (P = 0.95); I² = 0%
Test for overall effect: Z = 3.03 (P = 0.002)
Total (95% CI) 562 558 100.0% 0.54 [0.31, 0.94]
Total events 47 79
Heterogeneity: Tau² = 0.27; Chi² = 12.34, df = 6 (P = 0.05); I² = 51%
Test for overall effect: Z = 2.18 (P = 0.03)
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.93), I² = 0%
0.01
0.1
1
10
100
Favours HFNC
Favours COT

Study or Subgroup	HFNC Events	HFNC Total	COT Events	COT Total	Weight	Risk Ratio IV, 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]
Sahin 2018	0	50	2	50	15.9%	0.20 [0.01, 4.06]
Zochios 2018	1	49	1	45	19.2%	0.92 [0.06, 14.25]
Total (95% CI)		**376**		**378**	**100.0%**	**0.64 [0.19, 2.14]**
Total events	4		7			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.75$, df = 3 (P = 0.86); $I^2 = 0\%$

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