# Efficacy and Safety of High-Flow Nasal Cannula vs. Other Oxygenation Techniques in Cardiogenic Pulmonary Edema: A Systematic Review and Meta-Analysis

AHA Scientific Sessions 2026
Chicago, IL. November 7, 2026

Poster Sa2077

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## 1 Background & Objective

Acute cardiogenic pulmonary edema (ACPE) is a life-threatening manifestation of acute heart failure requiring prompt respiratory support. Although non-invasive ventilation (NIV) remains the standard first-line treatment in significant respiratory distress, mask intolerance, air leaks and claustrophobia may limit its use. High-flow nasal cannula (HFNC) delivers heated, humidified oxygen and is often better-tolerated; however, its comparative efficacy and safety remain uncertain.

**OBJECTIVE**

To compare HFNC with conventional oxygen, helmet CPAP or NIV in adults with ACPE, for 60-minute physiology, intubation (24h) and mortality (7d)

- **P** Adults with ACPE
- **I** High-flow nasal cannula (HFNC)
- **C** Conventional oxygen (COT), helmet CPAP or NIV
- **O** $SpO_2$, RR, pH, HR, MAP, Intubation, and mortality

## 2 Methods

This review follows PRISMA 2020 standards with prospective registration and formal inter-reviewer agreements at every stage.

- PROSPERO CRD420261444589
- PubMed/MEDLINE from inception to May 2026; RCTs in adults with ACPE
- Two reviewers independently screened studies and extracted data; disagreements were resolved by consensus or a third reviewer
- Risk of bias assessed using Cochrane RoB 2 tool
- RevMan 5.4.1 random-effects model with leave-one-out sensitivity analysis

## 3 Study Selection

**55** Records screened → **17** Full texts assessed → **5** RCTs included

**38 excluded at screening:** case reports/series 15, wrong population 12, systematic reviews 7, reviews 4

**12 excluded at full text:** non-randomized 3, no HFNC arm 3, insufficient data 2, mixed population 2, wrong population 1, narrative review 1

## 4 Included Trials & Risk of bias

| Trial | Comparator | n | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|---|---|
| Ci 2025 | COT | 124 | + | ! | ! | + | ! | ! |
| Ko 2020 | COT | 67 | ! | + | + | ! | + | ! |
| Makdee 2017 | COT | 128 | + | + | + | + | + | + |
| Osman 2021 | Helmet CPAP | 188 | + | + | ! | ! | + | ! |
| Maia 2025 | NIV | 272 | + | + | + | + | + | + |

*Ci 2025 (Front Oncol); Ko 2020 (J Clin Med); Makdee 2017 (Ann Emerg Med); Osman 2021 (Eur Heart J); Maia 2025 (JAMA)*

**Domains:** D1 Randomization, D2 Deviations from intended intervention, D3 Missing data, D4 Outcome measurement, D5 Selective reporting. **Included trials:** Five randomized trials involving 779 participants across three comparator categories, patients aged 53-77. Assessed by ITT (Maia, Ko, Makdee) or Per-protocol (Osman, Ci). **Judgement:** + = Low Risk, ! = Some Concerns

**MAIN FINDING**

**HFNC improved oxygen saturation at 60 minutes compared to conventional oxygen therapy (MD +2.53 percentage points), while no statistical differences in 24-hour intubation or 7-day mortality were demonstrated**

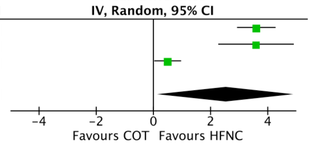
**5** Randomized trials | **779** Participants | **3** Comparators: COT, helmet CPAP, NIV

## 5 Results: Oxygenation and Clinical Outcomes

### $SpO_2$ at 60 minutes; MD +2.53 points (P=0.04)

| Study or Subgroup | HFNC Mean [%] | HFNC SD [%] | HFNC Total | COT Mean [%] | COT SD [%] | COT Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Ci 2025 | 97.8 | 2.1 | 60 | 94.2 | 1.7 | 64 | 34.0% | 3.60 [2.92, 4.28] |
| Ko 2020 | 97.71 | 2.14 | 34 | 94.12 | 3.25 | 33 | 31.5% | 3.59 [2.27, 4.91] |
| Makdee 2017 | 99.2 | 1.2 | 63 | 98.7 | 1.5 | 65 | 34.5% | 0.50 [0.03, 0.97] |
| **Total (95% CI)** | | | **157** | | | **162** | **100.0%** | **2.53 [0.15, 4.91]** |

Heterogeneity: $Tau^2 = 4.22$; $Chi^2 = 63.32$, df = 2 (P < 0.00001); $I^2 = 97\%$
Test for overall effect: Z = 2.08 (P = 0.04)

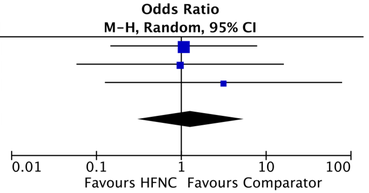



*All 3 trials compared HFNC with conventional oxygen; Considerable heterogeneity was observed ($I^2$ = 97%)*

### Intubation within 24 hours; OR 1.30 (P=0.73)

| Study or Subgroup | HFNC Events | HFNC Total | Comparator Events | Comparator Total | Weight | Odds Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Ci 2025 | 2 | 60 | 2 | 64 | 53.1% | 1.07 [0.15, 7.84] |
| Ko 2020 | 1 | 34 | 1 | 33 | 26.6% | 0.97 [0.06, 16.17] |
| Makdee 2017 | 1 | 63 | 0 | 65 | 20.3% | 3.14 [0.13, 78.63] |
| **Total (95% CI)** | | **157** | | **162** | **100.0%** | **1.30 [0.30, 5.54]** |
| Total events | 4 | | 3 | | | |

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.37$, df = 2 (P = 0.83); $I^2 = 0\%$
Test for overall effect: Z = 0.35 (P = 0.73)

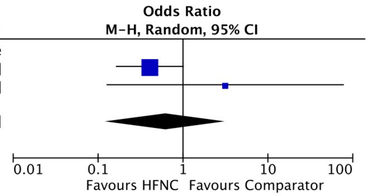



*3 trials (all COT): Ci 2025, Ko 2020, Makdee 2017. $I^2$ =0%. Maia 2025 (HFNC vs NIV) measured intubation at 7d rather than 24h and was not pooled: 12/136 vs 27/136*

### Death within 7 days; OR 0.62 (P=0.56)

| Study or Subgroup | HFNC Events | HFNC Total | Comparator Events | Comparator Total | Weight | Odds Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Ci 2025 | 0 | 60 | 0 | 64 | | Not estimable |
| Maia 2025 | 7 | 136 | 16 | 136 | 79.5% | 0.41 [0.16, 1.02] |
| Makdee 2017 | 1 | 63 | 0 | 65 | 20.5% | 3.14 [0.13, 78.63] |
| **Total (95% CI)** | | **259** | | **265** | **100.0%** | **0.62 [0.12, 3.13]** |
| Total events | 8 | | 16 | | | |

Heterogeneity: $Tau^2 = 0.64$; $Chi^2 = 1.44$, df = 1 (P = 0.23); $I^2 = 30\%$
Test for overall effect: Z = 0.58 (P = 0.56)




*3 trials: Maia 2025 (vs NIV) and Ci 2025, Makdee 2017 (vs COT). Point estimate favors HFNC; Small event count limits precision. Low heterogeneity ($I^2$ =30%)*

## 6 Other Physiology at 60 Minutes

| Outcome | Trials (n) | MD [95% CI] | P | $I^2$ |
|---|---|---|---|---|
| Respiratory rate (/min) | 4 (507) | -1.76 [-3.87, 0.35] | 0.10 | 93% |
| Arterial pH | 3 (379) | 0.00 [-0.04, 0.03] | 0.81 | 75% |
| Heart rate (bpm) | 2 (312) | -1.29 [-9.42, 6.84] | 0.76 | 92% |
| MAP (mmHg) | 2 (316) | -0.22 [-7.67, 7.23] | 0.95 | 75% |

*MD = mean difference. None of these four additional physiologic outcomes differed significantly*

## 7 Interpretation of Results & Sensitivity Analysis

- HFNC improved $SpO_2$ at 60 minutes by 2.5 percentage points compared with conventional oxygen (MD 2.53, 95% CI 0.15-4.91; P=0.04), a statistically significant short-term oxygenation benefit
- Intubation and mortality showed no significant difference. Event counts were small in both analyses, limiting precision
- Respiratory rate, pH, heart rate and MAP showed no significant difference at 60 minutes, consistent with HFNC's physiologic profile
- Leave-one-out sensitivity analyses confirmed a consistent direction of effect; precision remained limited by the small number of studies

## 8 Limitations & Next Steps

The evidence base this review draws on remains limited to 5 trials, with heterogeneity in comparators and short follow-up windows. These gaps define the questions worth answering next:

- A powered head-to-head HFNC vs CPAP/NIV trial in ACPE, with escalation and ICU admission as primary outcomes
- Standardized measurement timing across trials, enabling true meta-analytic pooling
- Identification of patient subgroups (mild respiratory distress, mask intolerance, hypoxemia without hypercapnia) most likely to benefit from HFNC

**CONCLUSION**

**HFNC demonstrated a significant short-term oxygenation benefit compared with conventional oxygen therapy in patients with ACPE. Although reductions in intubation and mortality were not established, HFNC may represent a valuable alternative respiratory support option in selected patients, particularly when conventional oxygen is insufficient or NIV is poorly tolerated. Further large-scale trials directly comparing HFNC with NIV/CPAP are warranted**

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**Disclosures:** The authors report no conflicts of interest and no specific funding
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