

# ***High-flow nasal cannula and interface- or mode-specific noninvasive ventilation in acute hypoxemic respiratory failure: an endpoint-harmonized systematic review and Bayesian network meta-analysis of randomized trials***

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**Abstract:** Previous meta-analyses of noninvasive respiratory support for acute hypoxemic respiratory failure (AHRF) have often treated noninvasive ventilation (NIV) as a single intervention and have pooled non-comparable intubation outcomes. We updated the randomized evidence base and reassessed comparative effectiveness after harmonizing standalone intubation endpoints and separating NIV according to interface and ventilation mode. Embase, PubMed, the Cochrane Library, and Web of Science were searched from inception to March 7, 2026 for randomized controlled trials in adults with AHRF. The primary outcome was short-term standalone endotracheal intubation reported during the index hospitalization or by day 28-30; composite endpoints, including intubation-or-death, were excluded from the primary efficacy network. Thirty-seven randomized trials involving 6,592 participants were retained in the evidence base, and 28 trials involving 5,583 participants informed the primary endpoint-harmonized network. Compared with standard oxygen therapy (SOT), short-term standalone intubation was reduced with helmet NIV (odds ratio [OR] 0.20, 95% credible interval [CrI] 0.09-0.43), high-flow nasal cannula (HFNC; OR 0.54, 95% CrI 0.34-0.80), and face-mask NIV (OR 0.56, 95% CrI 0.37-0.79). In the prespecified 6-node network, helmet bilevel NIV showed the largest estimated effect versus SOT (OR 0.12, 95% CrI 0.05-0.29). Restriction to strict day-28/day-30 standalone intubation attenuated effect sizes but did not change the direction of effect. No active strategy was associated with a credible reduction in day-28/day-30 mortality. In adults with AHRF, HFNC, face-mask NIV, and helmet NIV each reduced short-term standalone intubation compared with SOT after endpoint harmonization; the apparent helmet benefit was driven mainly by helmet bilevel NIV. Mortality data remain too sparse for firm comparative conclusions.

## 1. Introduction

Acute hypoxemic respiratory failure (AHRF) is a common reason for escalation of respiratory support. Avoiding endotracheal intubation is clinically important because invasive mechanical ventilation is associated with sedation exposure, ventilator-associated complications, ventilator-induced lung injury, and prolonged intensive care unit stay [1-3]. Consequently, noninvasive respiratory support has become an important component of care in selected patients with de novo hypoxemic respiratory failure.

HFNC and NIV act through different physiological mechanisms. HFNC delivers heated, humidified oxygen at high flow rates, reduces anatomic dead space, and generates modest positive airway pressure [4,5]. NIV can provide higher and more controllable positive end-expiratory pressure and, in bilevel mode, inspiratory pressure support. Effects may vary by interface and mode: compared with face masks, helmet interfaces may allow longer continuous use and more stable pressure delivery, whereas CPAP and bilevel modes may differ in inspiratory unloading, comfort, and the ability to mitigate patient self-inflicted lung injury [1-3,6].

Earlier randomized trials and meta-analyses suggested that active noninvasive support reduces intubation compared with standard oxygen therapy (SOT) in selected patients with AHRF [7-10]. However, prior syntheses have often grouped NIV into a single category and have pooled outcome definitions that are not directly comparable. Contemporary platform trials also frequently report composite endpoints such as intubation or death rather than standalone intubation. We therefore updated the randomized evidence base, harmonized endpoint definitions, and compared HFNC, face-mask NIV, helmet NIV, and SOT. A prespecified device-level network further separated CPAP and bilevel NIV according to interface to better reflect bedside treatment selection.

## 2. Methods

### 2.1 Design and search strategy

This systematic review and Bayesian network meta-analysis followed the PRISMA extension for network meta-analyses and PRISMA 2020 reporting guidance [11,12]. The protocol was registered prospectively in PROSPERO (CRD420261325050). Embase, PubMed, the Cochrane Library, and Web of Science were searched from inception through March 7, 2026. Full search strategies are reported in the Supplementary Appendix.

### 2.2 Eligibility criteria, endpoint harmonization, and data handling

We included randomized controlled trials in adults with AHRF that compared SOT, HFNC, or NIV-based respiratory support strategies. Studies focused on sleep-disordered breathing, acute exacerbations of chronic obstructive pulmonary disease, acute cardiogenic pulmonary edema, perioperative respiratory support, pediatric populations, or nonrandomized designs were excluded. Two reviewers independently selected studies and extracted intervention definitions, study characteristics, arm-level sample sizes, event counts, and follow-up windows; disagreements were resolved by consensus or third-reviewer adjudication. All arm and outcome tables were reaudited against source reports before model fitting, and missing extractable outcomes were restored when verifiable. Risk of bias was assessed with the Cochrane RoB 2 framework [13].

The primary efficacy endpoint was short-term standalone endotracheal intubation. Reports were eligible for the primary network only if actual intubation events could be isolated from composite endpoints such as intubation-or-death, generic treatment failure, escalation to other support modes, or clinical deterioration criteria alone. For the primary analysis, standalone intubation reported

during the index hospitalization or by day 28 or 30 was pooled as a clinically coherent short-term outcome; a strict day-28/day-30 standalone-intubation analysis was prespecified as sensitivity analysis.

This rule directly affected contemporary platform and adaptive trials. RECOVERY-RS contributed only when standalone intubation could be extracted separately from the composite primary endpoint [9]. In RENOVATE, standalone intubation was explicitly extractable only at day 7 in the relevant non-immunocompromised hypoxemic AHRF population [14]. Because day 7 lay outside the prespecified primary window, that record was reserved for the day-7 sensitivity analysis. Trials that evaluated relevant respiratory supports but reported only physiological outcomes or inseparable composite outcomes were retained in the broader evidence base but did not contribute to the primary efficacy network.

### 2.3 Network structure and statistical analysis

The primary class-level network contained four nodes: SOT, HFNC, face-mask NIV, and helmet NIV. A prespecified 6-node network separated face-mask CPAP, face-mask bilevel NIV, helmet CPAP, and helmet bilevel NIV while retaining SOT and HFNC. The 4-node analysis was intended to inform broad treatment selection, whereas the 6-node analysis explored within-NIV heterogeneity that may be relevant to bedside device choice.

For each eligible outcome, Bayesian hierarchical network meta-analysis models with binomial likelihoods and a logit link were fitted using *gemtc* and *rjags* [15,16]. Multi-arm studies were modeled while preserving within-trial correlation. Fixed-effect and random-effects models were both fitted, and model choice was guided by deviance information criterion [17]. Weakly informative priors were assigned to trial baselines, treatment effects, and variance parameters. Four Markov chains were run with 20,000 adaptation iterations and 100,000 sampling iterations, thinned by 10. Relative effects are reported as odds ratios with 95% credible intervals (CrIs) versus SOT and were translated into absolute risk differences per 1,000 using the pooled SOT baseline risk. Convergence was assessed with Gelman-Rubin diagnostics and effective sample size [18], and SUCRA values were treated as descriptive summaries rather than proof of superiority [19].

Supplementary frequentist quality-control models were fitted with *netmeta* [20] to estimate heterogeneity, explore design-by-treatment inconsistency, and assess small-study effects with comparison-adjusted funnel plots and Egger regression [21-23]. Clinical transitivity across direct comparisons was examined using baseline PaO<sub>2</sub>/FiO<sub>2</sub>, crossover rate, do-not-intubate prevalence, and publication year. Exploratory subgroup networks were prespecified for severe hypoxemia (PaO<sub>2</sub>/FiO<sub>2</sub> ≤150 mmHg), COVID-19, and immunocompromised populations, and confidence in estimates was interpreted with CINeMA-informed principles [24].

## 3. Results

### 3.1 Study set and evidence geometry

Thirty-seven randomized trials involving 6,592 participants formed the canonical AHRF evidence base; 17 of these 37 studies were published from 2021 onward [6,9,14,25-58]. Among the 37 canonical trials, 31 reported standalone intubation at at least one adjudicated time window. Twenty-eight studies involving 5,583 participants informed the primary endpoint-harmonized short-term standalone-intubation network. Of these 28 studies, 15 contributed in-hospital standalone intubation and 13 contributed day-28/day-30 standalone intubation. Three additional canonical trials informed only the day-7 sensitivity analysis, and a fourth day-7 record derived from RENOVATE was retained as sensitivity-only rather than counted in the canonical evidence base. The strict day-

28/day-30 standalone-intubation sensitivity network included 13 studies with 4,575 participants, and the day-28/day-30 mortality network included 6 studies with 2,369 participants (Table 1).

Direct evidence in the primary network was dominated by SOT-centered comparisons, although active-comparator evidence was also available. The network included 13 studies of face-mask NIV versus SOT, 10 of face-mask NIV versus HFNC, 6 of HFNC versus SOT, 3 of face-mask NIV versus helmet NIV, and 2 of helmet NIV versus HFNC. Most studies were judged as having some concerns for overall risk of bias, largely reflecting the unavoidable absence of blinding for respiratory-device interventions.

Table 1. Evidence networks, endpoint definitions, and selected models

Outcome network	Studies	Participants	Follow-up definition	Selected model	Baseline SOT risk
Primary short-term intubation (4-node)	28	5583	In-hospital or day 28-30 actual intubation	Random-effects	44.1%
Primary short-term intubation (6-node)	28	5583	In-hospital or day 28-30 actual intubation	Random-effects	44.1%
Strict day-28/day-30 intubation	13	4575	Day 28-30 actual intubation only	Fixed-effect	43.7%
Day-7 intubation	4	899	Day 7 actual intubation only	Fixed-effect	20.4%
Day-28/day-30 mortality	6	2369	Day 28-30 all-cause mortality	Fixed-effect	25.5%

### 3.2 Primary 4-node network

For the primary short-term standalone-intubation network, the random-effects model was preferred over the fixed-effect model (DIC 109.0 vs 136.5). Compared with SOT, helmet NIV was associated with the largest reduction in short-term standalone intubation (OR 0.20, 95% CrI 0.09-0.43), followed by HFNC (OR 0.54, 95% CrI 0.34-0.80) and face-mask NIV (OR 0.56, 95% CrI 0.37-0.79) (Table 2). The pooled baseline intubation risk in SOT arms was 44.1%, corresponding to approximately 302 fewer intubations per 1,000 patients for helmet NIV, 143 fewer for HFNC, and 135 fewer for face-mask NIV.

Head-to-head comparisons among active strategies were directionally informative but considerably less precise than contrasts versus SOT. The network therefore supports superiority of active noninvasive support over SOT for intubation reduction, but it does not establish definitive pairwise superiority among all active modalities.

Table 2. Class-level effect estimates versus standard oxygen therapy

Outcome	Intervention	Model	OR (95% CrI)	ARD per 1,000 (95% CrI)
Primary short-term standalone intubation	Face-mask NIV	Random-effects	0.56 (0.37-0.79)	-135 (-214 to -57)
Primary short-term standalone intubation	Helmet NIV	Random-effects	0.20 (0.09-0.43)	-302 (-375 to -187)
Primary short-term standalone intubation	HFNC	Random-effects	0.54 (0.34-0.80)	-143 (-228 to -55)

Strict day-28/day-30 intubation	Face-mask NIV	Fixed-effect	0.73 (0.61-0.88)	-76 (-117 to -32)
Strict day-28/day-30 intubation	Helmet NIV	Fixed-effect	0.54 (0.32-0.91)	-142 (-240 to -22)
Strict day-28/day-30 intubation	HFNC	Fixed-effect	0.81 (0.70-0.94)	-50 (-84 to -14)
Day-28/day-30 mortality	Face-mask NIV	Fixed-effect	0.88 (0.62-1.25)	-23 (-80 to 44)
Day-28/day-30 mortality	Helmet NIV	Fixed-effect	0.77 (0.26-2.20)	-47 (-172 to 174)
Day-28/day-30 mortality	HFNC	Fixed-effect	0.97 (0.78-1.22)	-5 (-45 to 39)

### 3.3 Prespecified device-level network

The 6-node disaggregated network also favored the random-effects model (DIC 108.8 vs 128.4) and demonstrated clinically relevant heterogeneity within NIV. Helmet bilevel NIV had the strongest association with lower short-term standalone intubation versus SOT (OR 0.12, 95% CrI 0.05-0.29), corresponding to approximately 353 fewer intubations per 1,000 patients at the observed baseline risk. Face-mask CPAP (OR 0.50, 95% CrI 0.26-0.89), HFNC (OR 0.55, 95% CrI 0.36-0.79), and face-mask bilevel NIV (OR 0.59, 95% CrI 0.39-0.86) also favored active treatment, whereas helmet CPAP showed a point estimate in the same direction but remained imprecise (OR 0.54, 95% CrI 0.16-1.73) (Table 3).

Table 3. Prespecified 6-node device-level effect estimates versus standard oxygen therapy

Intervention	OR (95% CrI)	ARD per 1,000 (95% CrI)	Clear difference vs SOT
Face-mask bilevel NIV	0.59 (0.39-0.86)	-122 (-207 to -38)	Yes
Face-mask CPAP	0.50 (0.26-0.89)	-157 (-271 to -28)	Yes
Helmet bilevel NIV	0.12 (0.05-0.29)	-353 (-405 to -255)	Yes
Helmet CPAP	0.54 (0.16-1.73)	-142 (-331 to 137)	No
HFNC	0.55 (0.36-0.79)	-138 (-221 to -58)	Yes

This device-level analysis suggests that the apparent benefit of helmet-based support is not evenly distributed across helmet strategies. Pooling helmet CPAP and helmet bilevel NIV under a single helmet-NIV label may therefore obscure clinically relevant within-class variation.

### 3.4 Sensitivity analyses and mortality

Restricting the analysis to strict day-28/day-30 standalone intubation attenuated effect sizes but did not reverse the direction of benefit. Compared with SOT, helmet NIV had an OR of 0.54 (95% CrI 0.32-0.91), HFNC an OR of 0.81 (95% CrI 0.70-0.94), and face-mask NIV an OR of 0.73 (95% CrI 0.61-0.88) (Table 2). The day-7 standalone-intubation network was sparse and inconclusive: the estimated OR was 1.99 (95% CrI 0.81-5.08) for HFNC and 2.35 (95% CrI 0.90-6.40) for face-mask NIV versus SOT. Given the very small network and wide intervals, these estimates should not be interpreted as evidence of early harm.

For day-28/day-30 mortality, the fixed-effect model was preferred (DIC 19.1 vs 21.1). None of the active strategies showed a credible reduction in mortality versus SOT: face-mask NIV OR 0.88 (95% CrI 0.62-1.25), helmet NIV OR 0.77 (95% CrI 0.26-2.20), and HFNC OR 0.97 (95% CrI 0.78-1.22) (Table 2). Although the pooled baseline mortality risk in SOT arms was 25.5%, the mortality network was substantially sparser and less informative than the intubation network.

### 3.5 Model convergence, consistency checks, and exploratory subgroups

Convergence diagnostics were reassuring across the selected models; the largest upper R-hat was 1.002, and effective sample sizes were high for monitored parameters. Transitivity checks did not suggest major imbalance in baseline PaO<sub>2</sub>/FiO<sub>2</sub>, crossover rate, or do-not-intubate prevalence, but publication year differed across direct comparisons, consistent with temporal evolution in practice and intubation thresholds. In frequentist quality-control analyses, heterogeneity was moderate (I<sup>2</sup> 60.1%), and the between-design Q statistic suggested possible incoherence (p = 0.0019), whereas the random-effects design-by-treatment interaction model was less definitive (p = 0.0540). Comparison-adjusted funnel plotting and Egger regression did not show strong statistical evidence of small-study effects (p = 0.2042).

Exploratory subgroup networks were directionally concordant with the main analysis. Active noninvasive support generally favored SOT in studies limited to severe hypoxemia, COVID-19, and immunocompromised populations, although several subgroup networks were small and not suitable for formal interaction testing. These subgroup results should therefore be viewed as hypothesis generating rather than definitive.

## 4. Discussion

This endpoint-harmonized reanalysis of randomized trials indicates that HFNC, face-mask NIV, and helmet NIV each reduce short-term standalone intubation relative to SOT in adults with AHRF. The largest class-level effect was observed with helmet NIV, and the device-level analysis suggests that this signal is driven primarily by helmet bilevel NIV. When the analysis was restricted to a narrower day-28/day-30 time window, effect sizes were attenuated but remained directionally consistent. By contrast, current mortality data were too sparse to support firm comparative conclusions.

The present study extends earlier meta-analyses [7,10] in two important ways. First, the evidence base was updated through March 2026 and reaudited against source reports. Second, the analysis explicitly separated standalone intubation from composite outcomes such as intubation-or-death, treatment failure, or deterioration criteria. This distinction is not merely semantic. Contemporary trials increasingly report different time windows and composite outcomes, and pooling these endpoints without transparent adjudication can produce misleading precision and reduce clinical interpretability. In this review, the primary pooled outcome was deliberately labeled short-term standalone intubation because the 28-study primary network combined both in-hospital and day-28/day-30 standalone-intubation data rather than a single uniform time point. The persistence of benefit in the stricter day-28/day-30 analysis supports the robustness of the main finding while underscoring the need for clearer endpoint standardization in future trials.

The disaggregated 6-node network also offers a clinically plausible explanation for the helmet signal. Helmet interfaces may permit longer continuous treatment and more stable airway pressure than face masks, while bilevel support may better reduce inspiratory effort and improve respiratory-muscle unloading [1-3,6,59]. This interpretation accords with physiological studies showing lower inspiratory effort and more favorable lung mechanics with helmet-based support in selected patients [59]. At the same time, direct active-comparator evidence remains limited. The current literature

therefore supports helmet bilevel NIV as a promising strategy in experienced centers, but it does not justify assuming that all helmet configurations are uniformly superior to HFNC or face-mask NIV. Similarly, while HENIVOT and Nagata suggested benefits for helmet NIV or CPAP over HFNC in selected populations [42,50], HELMET-COVID did not demonstrate a clear mortality advantage for helmet NIV over usual respiratory support [60].

The divergence between intubation and mortality findings warrants caution. Avoiding intubation is clinically meaningful, but benefit depends on whether invasive ventilation is truly prevented rather than simply delayed in patients who ultimately require it. Mortality in AHRF is influenced by many downstream factors, including clinician thresholds for intubation, crossover to rescue modalities, sedation exposure, nosocomial complications, and ICU co-interventions [1-3]. The absence of a statistically clear mortality effect in this review should therefore be interpreted primarily as imprecision rather than therapeutic equivalence. The sparse day-7 network reinforces this point by showing how unstable estimates can become when event windows are short and data are limited.

Several limitations should be acknowledged. The review was restricted to English-language reports and did not include exhaustive grey-literature retrieval. Even after harmonization, the primary endpoint combines in-hospital and day-28/day-30 standalone intubation and therefore represents a clinically coherent short-term construct rather than a single uniform time point. Included trials were almost universally open label, and intubation thresholds, crossover rules, and do-not-intubate policies varied across studies. Publication year was imbalanced across direct comparisons, indicating that the network bridges trials conducted under different practice environments, rescue strategies, and pandemic contexts. Mortality data and some device-level nodes remained sparse, and pooled data precluded detailed analyses of patient-level effect modifiers and time-to-event patterns. These limitations do not invalidate the central signal, but they argue against overly categorical treatment rankings.

From a clinical perspective, the results suggest that SOT should not be the default strategy when HFNC or NIV can be applied safely in adults with AHRF. HFNC remains a broadly applicable option with a consistent class-level signal across multiple settings. Helmet bilevel NIV appears particularly promising where staff are familiar with the interface, ventilator settings, and close monitoring needed for timely escalation decisions. Future randomized trials should report standalone intubation separately from composite endpoints, prespecify harmonized short-term windows, document crossover and do-not-intubate prevalence transparently, and directly compare the most clinically relevant active strategies, especially helmet bilevel NIV, HFNC, and face-mask CPAP.

## 5. Conclusion

In adults with AHRF, HFNC, face-mask NIV, and helmet NIV each reduced short-term standalone intubation compared with SOT after endpoint harmonization. The largest device-level effect was observed with helmet bilevel NIV. Mortality data remain insufficient to determine whether the observed intubation benefit translates into improved survival.

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**Data availability:** The datasets extracted for this study are available from the corresponding author on reasonable request.

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