JAMA | Original Investigation

Association of Noninvasive Ventilation Strategies With Mortality and Bronchopulmonary Dysplasia Among Preterm Infants
A Systematic Review and Meta-analysis

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IMPORTANCE Various noninvasive ventilation strategies are used to prevent bronchopulmonary dysplasia (BPD)of preterm infants; however, the best mode is uncertain.

OBJECTIVE To compare 7 ventilation strategies for preterm infants including nasal continuous positive airway pressure (CPAP) alone, intubation and surfactant administration followed by immediate extubation (INSURE), less invasive surfactant administration (LISA), noninvasive intermittent positive pressure ventilation, nebulized surfactant administration, surfactant administration via laryngeal mask airway, and mechanical ventilation.

DATA SOURCES MEDLINE, EMBASE, CINAHL, and Cochrane CENTRAL from their inceptions to June 2016.

STUDY SELECTION Randomized clinical trials comparing ventilation strategies for infants younger than 33 weeks' gestational age within 24 hours of birth who had not been intubated.

DATA EXTRACTION AND SYNTHESIS Data were independently extracted by 2 reviewers and synthesized with Bayesian random-effects network meta-analyses.

MAIN OUTCOMES AND MEASURES A composite of death or BPD at 36 weeks' postmenstrual age was the primary outcome. Death, BPD, severe intraventricular hemorrhage, and air leak by discharge were the main secondary outcomes.

RESULTS Among 5598 infants involved in 30 trials, the incidence of the primary outcome was 33% (1665 of 4987; including 505 deaths and 1160 cases of BPD). The secondary outcomes ranged from 6% (314 of 5587) for air leak to 26% (1160 of 4455) for BPD . Compared with mechanical ventilation, LISA had a lower odds of the primary outcome (odds ratio [OR], 0.49; 95% credible interval [CrI], 0.30-0.79; absolute risk difference [RD], 164 fewer per 1000 infants; 57-253 fewer per 1000 infants; moderate quality of evidence), BPD(OR, 0.53; 95% CrI, 0.27-0.96; absolute RD, 133 fewer per 1000 infants; 95% CrI, 9-234 fewer per 1000 infants; moderate-quality), and severe intraventricular hemorrhage (OR, 0.44; 95% CrI, 0.19-0.99; absolute RD, 58 fewer per 1000 births; 95% CrI, 1-86 fewer per 1000 births; moderate-quality). Compared with nasal CPAP alone, LISA had a lower odds of the primary outcome (OR, 0.58; 95% CrI, 0.35-0.93; absolute RD, 112 fewer per 1000 births; 95% CrI, 16-190 fewer per 1000 births; moderate quality), and air leak (OR, 0.24; 95% CrI, 0.05-0.96; absolute RD, 47 fewer per 1000 births; 95% CrI, 2-59 fewer per 1000 births; very low quality). Ranking probabilities indicated that LISA was the best strategy with a surface under the cumulative ranking curve of 0.85 to 0.94, but this finding was not robust for death when limited to higher-quality evidence.

CONCLUSIONS AND RELEVANCE Among preterm infants, the use of LISA was associated with the lowest likelihood of the composite outcome of death or BPD at 36 weeks' postmenstrual age. These findings were limited by the overall low quality of evidence and lack of robustness in higher-quality trials.

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Despite the substantial improvement in survival of preterm infants over the last 2 decades, complications of preterm birth remain among the leading contributors to loss of health in the United States.[1] Bronchopulmonary dysplasia (BPD) has the highest prevalence of all the major complications of prematurity,[2,3] and the incidence is increasing, as shown in 1 study,[3] from 32% in 1993 to 45% in the years 2008 through 2012. Bronchopulmonary dysplasia has life-long effects on patients and health care systems due to increased risks of death,[4] long-term respiratory problems, and serious neurodevelopmental impairment requiring educational and social support.[5,6]

Although the pathogenesis of BPD is multifactorial, ventilator-induced barotrauma and volutrauma on the premature lung are major factors.[7] Hence, various noninvasive ventilation strategies have been growing in popularity. Although previous randomized clinical trials and systematic reviews reported benefits from these strategies,[8-13] clinicians remain uncertain about which strategy to choose, perhaps because conventional systematic reviews and meta-analyses have focused on head-to-head comparison of 2 interventions without assessing multiple interventions as a whole. Network meta-analyses (or multiple treatment comparison meta-analyses) provide a framework for analyzing and interpreting more than 2 interventions (network of multiple interventions) to understand the evidence of the network of multiple interventions as a whole.[14] This systematic review summarizes available evidence from randomized clinical trials using a Bayesian network meta-analysis to compare multiple ventilation strategies simultaneously to identify the best strategy to prevent BPD of preterm infants.

BPD *bronchopulmonary dysplasia*

CPAP *continuous positive airway pressure*

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

INSURE *intubation and surfactant administration followed by immediate extubation*

LISA *less invasive surfactant administration*

NPPV *noninvasive intermittent positive pressure ventilation*

SUCRA *surface under the cumulative ranking curve*

Key Points

Question What is the best noninvasive ventilation strategy for preventing death or bronchopulmonary dysplasia in the first 24 hours of life in spontaneously breathing preterm infants with or at risk of respiratory distress syndrome?

Findings In this meta-analysis, less invasive surfactant administration was the strategy associated with the lowest odds of the composite outcome of death or bronchopulmonary dysplasia compared with either nasal continuous positive airway pressure or mechanical ventilation.

Meaning Less invasive surfactant administration should be considered as a first-line ventilation strategy for spontaneously breathing preterm infants with respiratory distress syndrome.

Methods

Literature Searches

Four electronic databases, MEDLINE, EMBASE, CINAHL, and Cochrane CENTRAL, were systematically searched from their inceptions to June 7, 2016, and supplemented by searching the World Health Organization International Clinical Trials Registry Platform[15] and reference lists of eligible studies and review articles. (For search strategies, see eTable 1 in the Supplement.) The protocol of this systematic review was registered before the literature search in PROSPERO (Prospero 2015 CRD42015023403).[16] Several differences in study methods between the protocol and this article are presented in eTable 2 in the Supplement.

Criteria for Study Inclusion

This systematic review included randomized or quasi-randomized clinical trials fulfilling the following 4 criteria: (1) published as a full report in a peer-reviewed journal, (2) enrolled spontaneously breathing preterm infants born at less than 33 weeks' gestational age (with or at risk of respiratory distress syndrome) who had never been intubated before randomization, which occurred within 24 hours of birth, (3) compared 2 or more of the predetermined 7 ventilation strategies, and (4) reported at least 1 event of the primary or secondary outcomes. Trials in which some of the infants were 33 weeks gestational age or older were included if the mean or median gestational age was less than 33 weeks. Studies enrolling infants within 72 hours of birth were included if a mean or median age was less than 24 hours at study entry. If subgroups of infants fulfilled all the inclusion criteria and their data were available, the studies were included.

The 7 eligible ventilation strategies were (1) nasal continuous positive airway pressure (CPAP) alone, in which infants continued nasal CPAP with surfactant selectively given only when infants met a certain criteria of nasal CPAP failure; (2) intubation and surfactant administration followed by immediate extubation (INSURE), in which infants were intubated, given surfactant, and extubated within 1 hour received nasal CPAP[13]; (3) less invasive surfactant administration (LISA), in which infants continued nasal CPAP without intubation and surfactant was given via thin diameter tubes or catheters (eg, feeding tubes, vascular catheters) directly placed into infants' tracheas using laryngoscopes with or without Magill forceps[17]; (4) noninvasive intermittent positive pressure ventilation (NPPV), defined as any noninvasive strategy that provided intermittent increased airway pressure in addition to nasal CPAP including biphasic nasal CPAP[18]; (5) nebulized surfactant administration while receiving nasal CPAP; (6) surfactant administration via laryngeal mask airway, in which surfactant was given via a laryngeal mask airway as a conduit without intubation after which infants received nasal CPAP; and (7) mechanical ventilation via endotracheal tube. Because the use of positive end-expiratory pressure or nasal CPAP was considered standard respiratory management, ventilation strategies without it were excluded.[19,20] No language restrictions were applied.

Primary and Secondary Outcomes

Nine outcomes were selected a priori and rated on a 1-to-9 scale (7-9, critical; 4-6, important; and 1-3, of limited importance) based on their importance for patients and clinicians according to a method proposed by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) group.[21] A composite outcome of death or BPD at 36 weeks' postmenstrual age (a critical outcome rated 8) was selected as the primary outcome because BPD is the most important respiratory morbidity of preterm infants and death is a competing risk. Because several similar but slightly different definitions exist for BPD and because some studies used more than 1 definition, the order of priority for selecting a definition of BPD in each trial was decided a priori as follows, in descending order: (1) oxygen use, positive pressure support, or both at 36 weeks' postmenstrual age; (2) oxygen use at 36 weeks' postmenstrual age; (3) oxygen use, pressure support, or both at 36 weeks' postmenstrual age along with oxygen use at 28 days of age; and (4) oxygen use at 36 weeks' postmenstrual age along with oxygen use at 28 days of age.

Bronchopulmonary dysplasia at 36 weeks' postmenstrual age (a critical outcome rated 7), death at 36 weeks' postmenstrual age or before discharge (a critical outcome rated 9), severe intraventricular hemorrhage (grade 3 or 4 based on the Papile criteria,[22] a critical outcome rated 7), and air leak including pneumothorax or pulmonary interstitial emphysema before discharge (an important outcome rated 5) were selected as the 4 main secondary outcomes because previous studies indicated that early ventilation strategies might affect these outcomes.[23,24] Other secondary outcomes included necrotizing enterocolitis (stage 2 or higher based on the Bell criteria,[25] a critical outcome rated 7) and severe retinopathy of prematurity (stage 3 or higher based on the international classification, or treated disease,[26] a critical outcome rated 7) before discharge; neurodevelopmental impairment at 18 months or later (a critical outcome rated 8); and a composite outcome of death or neurodevelopmental impairment at 18 months or later (a critical outcome rated 8).

Data Extraction and Risk of Bias Assessment

Two reviewers (T.I. and H.I.) independently screened all titles and abstracts identified in the literature search, reviewed full texts of eligible articles, and extracted data from the selected articles using a pretested data extraction form. The 2 reviewers independently assessed the risk of bias of each trial for each outcome including selection bias (inadequate random sequence generation, failure to conceal allocation), performance bias (inadequate blinding of patients and personnel), detection bias (failure to blind outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting), and other bias (publication bias, stopping early for apparent benefit, etc) according to the Cochran Handbook.[27] If 1 or more components of the risk of bias assessment were judged high risk, the trial was judged high risk of bias. Any disagreement between the reviewers was resolved by discussion or consultation with the third author (S.M.).

Data Synthesis and Analysis

Bayesian hierarchical random-effects network meta-analysis was conducted to compare all interventions simultaneously using Markov chain Monte Carlo simulation with noninformative prior distribution. Network meta-analyses generate direct pair-wise effects estimates (eg, *A* vs *B*) and also indirect effects estimates (eg, *A* vs *C* via *B* using 2 comparisons of *A* vs *B* and *B* vs *C*) to estimate network effects (or mixed effects) combining direct and indirect effects and rank the interventions, enabling selection of the best intervention.[14,28,29] The method estimates relative effects of multiple interventions simultaneously whether or not they have been directly compared with each other in previous trials.[14] The analyses used generalized linear models with a logit link function with 4 chains and 100 000 iterated simulations discarding the initial 5000 iterations as burn-in. Convergence was assessed using the Brooks-Gelman-Rubin statistic.[30] Model fit was assessed by comparing the mean sum of residual deviance to the number of independent trial groups. Odds ratios (ORs) and 95% credible intervals (95% CrIs) were estimated from the medians and 2.5th and 97.5th percentile of the posterior distributions in the simulations, respectively. A network absolute risk difference (RD) was calculated from the network OR estimates using an assumed control risk[27] that was the average risk in the control group in the network derived by dividing the total event number by the total infant number in the control groups in the network. The I^2 statistic and Cochran *Q* test were used to assess heterogeneity of trials within each direct comparison. Node-splitting was used to assess incoherence between direct and indirect comparisons.[31]

Rank probabilities that interventions were the best, second best, third best, etc were calculated from proportions of Markov chain cycles in which the interventions had the lowest, second lowest, third lowest odds ratios (ORs), respectively. Surface under the cumulative ranking curve (SUCRA) for each intervention was calculated from a cumulative ranking probability that an intervention is above a certain ranking.[32] SUCRA is a simple summary index indicating the degree to which an intervention is better or worse than others, taking a value between 0 (certainly the worst intervention) and 1 (certainly the best intervention).[32] All the analyses were conducted using R version 3.1.2 (R Project for Statistical Computing) with R packages (gemtc, metafor, and rjags), and JAGS version 3.4.0.

Quality-of-Evidence Assessment

The quality of evidence of each direct, indirect, and network effects estimate was evaluated for the primary and main secondary outcomes according to the GRADE method.[33,34] The quality of evidence of direct-effects estimates started as high and was decreased to moderate, low, or very low based on risk of bias, imprecision, heterogeneity, indirectness, and publication bias.[33] For the assessment of precision, a sample size required to detect a 25% relative risk reduction, called *optimal information size*, was calculated for each comparison for each outcome based on a total event rate in the control group[35] using the PS Power and Sample Size Calculation

software version 3.0.[36] Publication bias was assessed by inspecting asymmetry of funnel plots visually. The quality of evidence of indirect and network effects estimates were derived from those of direct- effects estimates by evaluating network geometry, intransitivity, and incoherence (for details, see the eText and eFigure 1 in the Supplement).

Sensitivity Analyses

For the primary and main secondary outcomes, 2 preplanned sensitivity analyses were conducted: excluding trials with high risk of bias and combining INSURE and LISA as 1 strategy.

Subgroup Analyses

Four preplanned subgroup analyses were conducted for the primary outcome, stratifying by potential effects modifiers including mean (or median) gestational age at birth (≤28 or >28 weeks), timing of interventions (≤1 or >1 hour after birth), thresholds of fraction of inspired oxygen (≤40% or >40%), and backup measures (mechanical ventilation or INSURE and LISA) for treatment failure of noninvasive ventilation strategies. Between-subgroup differences in effects estimates were assessed by the *Z* test.

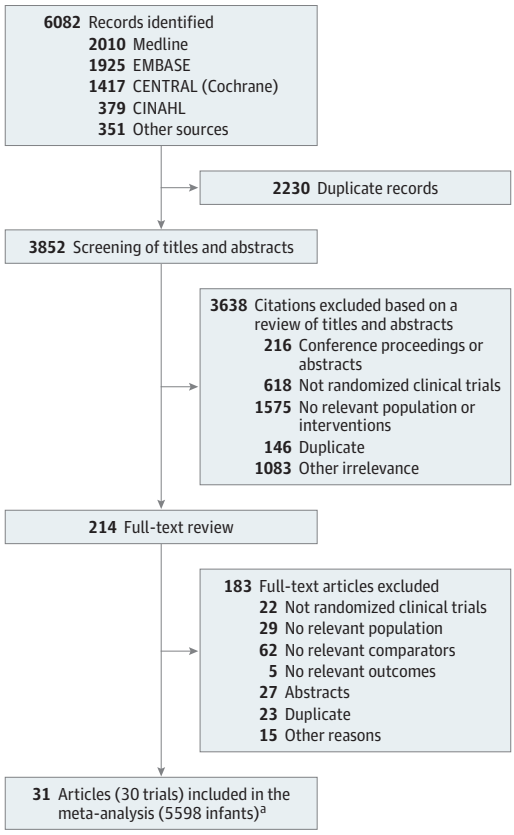
Results

Among 6082 records identified in the literature search, 31 articles of 30 trials met inclusion criteria and involved 5598 infants[8-10,18,37-63] (**Figure 1**). One article[62] was a follow-up study of an included trial.[8] Sample sizes ranged from 24 to 1316 infants; mean or median gestational age at birth, 25 to 32 weeks; mean or median timing of enrollment, less than 24 hours; antenatal corticosteroid exposure, 15% to 99%; and threshold for backup measures in the nonventilation group of fraction of inspired oxygen (F_{IO_2}; 0.3 to 1.0 (**Table**). Except for one 3-group trial,[37] all others were 2-group trials. Noninvasive positive-pressure ventilation was only compared with nasal CPAP alone. There was only 1 eligible trial for nebulized surfactant administration[58] and surfactant administration via laryngeal mask airway.[63] The authors of 17 trials provided additional information or data for this systematic review (eTable 3 in the Supplement) (References 9, 18, 38, 42, 50-53, 56, 57, 59-61). The authors of 5 trials provided data on a subset of infants who were eligible for the review.[18,51,53,57,63]

Risk of Bias of Included Studies

Seven trials did not report or conduct allocation concealment and were considered at high risk of bias.[39,40,54,55,57,60,61] Three trials were stopped early due to significant findings in interim analyses. Because early stopping may overestimate intervention effects, the trials were considered high risk of bias (eTable 4 in the Supplement).[38,42,43] High risk of attrition bias (missing data >10%) was found in 1 trial for both the primary outcome and for BPD,[48] 3 trials for severe intraventricular hemorrhage,[43,48,53] and 2 trials for retinopathy of prematurity.[8,53] Among 30 trials included, 16 trials were at low risk of bias for all outcomes assessed, (References 9, 10, 18, 37, 41, 44-47, 50-52, 56, 58, 59, 63) and 3 trials were at low risk of bias for some outcomes (eTable 4 in the Supplement).[8,48,53]

Figure 1. Flow Diagram of Literature Search and Trial Selection



[a] One article was a follow-up study reporting neurodevelopmental outcomes of a trial (SUPPORT 2010[62]) included in this systematic review.

Primary Outcome

A total of 21 trials including 4987 infants reported the primary composite outcome of death or BPD (**Figure 2**). The incidence of the primary outcome was 33% (1665 of 4987 infants) with 505 infant deaths and 1160 infants with BPD. LISA was associated with a lower likelihood of the primary outcome than was mechanical ventilation (OR, 0.49; 95% CrI; 0.30-0.79; absolute RD, 164 fewer per 1000 infants; 95% CrI, 57-253 fewer per 1000 infants; moderate quality of evidence) and nasal CPAP alone (OR, 0.58; 95% CrI, 0.35-0.93; absolute RD, 112 fewer per 1000 infants; 95% CrI, 16-190 fewer per 1000 infants; moderate quality of evidence) (**Figure 3**). INSURE was associated with a lower likelihood of the primary outcome than was mechanical ventilation (OR, 0.71; 95% CrI, 0.50-0.98; absolute RD, 83 fewer per 1000 infants; 95% CrI, 5-160 fewer per 1000 infants]; moderate quality-of-evidence). The individual trial-level outcome data are in eFigure 2 in the Supplement.

Secondary Outcomes

The network meta-analyses for the 4 main secondary outcomes included 19 to 30 trials involving 4455 to 5587 infants

Table. Baseline Characteristics of Included Trials

Trials	Country	Enrollment Years	No. of Hospitals	No. of Infants	Gestational Age at Birth, Mean, Median, or Range, wk	Infant Age at Enrollment, h	Respiratory Distress at Enrollment	Antenatal Steroid, No. (%)	FIO_2 Threshold for Backup[a]	Backup Measures for Noninvasive Strategies[a]
3-Group Trial										
Nasal CPAP vs INSURE vs MV										
Dunn et al,[37] 2011	United States, Canada	2003-2009	27	648	28	0	No	639 (99)	0.4	MV
2-Group Trials										
INSURE vs MV										
Dani et al,[38] 2004	Italy	2001-2003	1	27	28	<6	Yes	21 (78)	0.5	MV
Huang et al,[39] 2013	China	2010-2012	1	64	31	<12	Yes	27 (42)	NA	NA
Nayeri et al,[40] 2014	Iran	NA	1	42	30	<2	Yes	NA	0.7	MV
LISA vs MV										
Kribs et al,[10] 2015	Germany	2009-2012	13	211	25	0.17-2	Yes	207 (98)	0.35	LISA
nasal CPAP vs MV										
Morley et al,[41] 2008	9 Countries[b]	1999-2006	17	610	26	0.08	Yes	NA (94)[c]	0.6	MV
Finer NM et al,[8,62] 2010	United States	2005-2009	23	1316	26	0	No	1265 (96)[d]	0.5	MV
INSURE vs nasal CPAP										
Verder et al,[42] 1994	Denmark, Sweden	1991-1992	11	68	29-30[e]	2-72[f]	Yes	34 (50)	0.75[g]	MV
Verder et al,[43] 1999	Denmark	1995-1997	11	60	27-28[e]	0.5-72[f]	Yes	48 (80)	0.55[g]	Mixed[h]
Reininger et al,[44] 2005	United States	1995-2002	1	105	32	<72[f]	Yes	54 (51)	0.3	MV
Rojas et al,[45] 2009	Columbia	2004-2006	8	278	29	0.25-1	Yes	240 (88)[d]	0.75	MV
Sandri et al,[46] 2010	6 countries[b]	2007-2008	24	208	27	<0.5	No	202 (97)	0.4	Mixed[h]
Kandraju et al,[47] 2013	India	2008-2011	1	153	30	<2	Yes	144 (94)	0.5	INSURE
Dilmen et al,[48] 2014	Turkey	2009-2010	6	159	28	0	No	NA (65)[c]	0.4	INSURE
Nakhshab et al,[49] 2015	Iran	2011-2012	1	60	31	<6	Yes	54 (90)	0.7	MV
NPPV vs nasal CPAP										
Kugelman et al,[50] 2007	Israel	2004-2006	1	84	30	<1[i]	Yes	NA (71)[c]	0.5	MV
Sai Sunil Kishore et al,[51] 2009	India	2007-2008	1	29	31	<6	Yes	15 (52)	0.7	INSURE
Lista et al,[52] 2010	Italy	2007-2008	1	40	30	<1	Yes	6 (15)	0.4	INSURE
Meneses et al,[53] 2011	Brazil	2007-2009	1	182	29	1[j]	Yes	137 (75)	0.5	INSURE
Kong et al,[54] 2012	China	2010-2011	1	67	32	<6	Yes	52 (78)	0.5	MV

(continued)

Table. Baseline Characteristics of Included Trials (continued)

Trials	Country	Enrollment Years	No. of Hospitals	No. of Infants	Gestational Age at Birth, Mean, Median, or Range, wk	Infant Age at Enrollment, h	Respiratory Distress at Enrollment	Antenatal Steroid, No. (%)	FIO_2 Threshold for Backup[a]	Backup Measures for Noninvasive Strategies[a]
Kirpalani et al,[18] 2013	10 countries[b]	2007-2011	34	145	27	<24	Yes	139 (96)	No limitation	MV
Armanian et al,[55] 2014	Iran	2013-2014	1	98	29	At NICU admission	Yes	NA	0.3	INSURE
Aguiar et al,[56] 2015	Portugal	2011-2013	2	220	31	At NICU admission	Yes	214 (97)	0.5	INSURE
Oncel et al,[9] 2016	Turkey	2012-2013	1	200	29	<0.5	Yes	171 (86)	0.4	LISA
Salama et al,[57] 2015	Jordan	2011	1	42	32	1-2[j]	Yes	31 (74)	1.0	MV
NEBU vs nasal CPAP										
Berggren et al,[58] 2000	Sweden	Not reported	6	32	31	2-36	Yes	24 (75)	0.75[g]	MV
LISA vs INSURE										
Kanmaz et al,[59] 2013	Turkey	2010-2011	1	200	28	<2	Yes	154 (77)	0.4	Mixed[k]
Mirnia et al,[60] 2013	Iran	2010-2012	3	136	29	4[j]	Yes	88 (65)	NA	NA
Bao et al,[61] 2015	China	2012	1	90	29	<2	Yes	82 (90)[d]	0.6	MV
LMA vs INSURE										
Pinheiro et al,[63] 2016	United States	2010 - 2012	1	24	31	4-24	Yes	16 (67)	≥0.5[l]	Mixed[m]

Abbreviations: BW, birth weight; FIO_2, fraction of inspired oxygen; INSURE, intubation and surfactant administration; LISA, less invasive surfactant administration; LMA, laryngeal mask airway; MV, mechanical ventilation; NA, nonavailable; NEBU, nebulized surfactant administration on nasal CPAP; NICU, neonatal intensive care units; NPPV, noninvasive intermittent positive pressure ventilation.

[a] Backup measures were rescue measures to take for infants assigned to noninvasive ventilation strategies in trials when these infants did not tolerate the assigned noninvasive strategies (eg, nasal CPAP). The FIO_2 threshold for backup indicated when these rescue measures had to be taken. For example, in the study of Kandraju 2013,[47] when infants did not tolerate nasal CPAP and required FIO_2 of more than 0.5 (FIO_2 threshold), these infants were rescued by INSURE (a backup measure) in both the INSURE and nasal CPAP–alone groups.

[b] Morley et al[41] was conducted in Australia, the United States, Norway, Germany, France, Belgium, Greece, New Zealand, and Canada. Sandri et al[46] was conducted in the Czech Republic, Italy, France, Spain, Portugal. Kirpalani et al[18]was conducted in Canada, the United States, Qatar, the United Kingdom, Sweden, Singapore, Ireland, the Netherlands, Belgium, and Austria.

[c] The trial reported only the percentages of infants who received antenatal corticosteroids and did not report the number of infants.

[d] The total number of infants for calculating the INSURE rate were reduced due to missing antenatal data.

[e] Median gestational age in each group was reported in the original articles. Median (or mean) gestational age in all study infants was between the 2 values.

[f] Although the upper limit of the timing of enrollment was 72 hours, the mean or median timing of enrollment of these trials was less than 24 hours (10-13 hours for Verder et al,[42] 4.1-4.5 hours for Verder et al,[43] and 6.5 hours for Reininger et al[44]).

[g] The arterial:alveolar oxygen tension ratio values of 0.15 and 0.22 were considered corresponding to fraction of inspired oxygen values of 0.55 and 0.77, respectively, assuming arterial oxygen tension is 75 mm Hg and arterial carbon dioxide tension is 50 mm Hg.

[h] The backup measures were mechanical ventilation for infants in the INSURE group and INSURE for infants in the nasal CPAP–alone group.

[i] Most of the infants were randomized within 1 hour of birth.

[j] These hours are approximate times of enrollment.

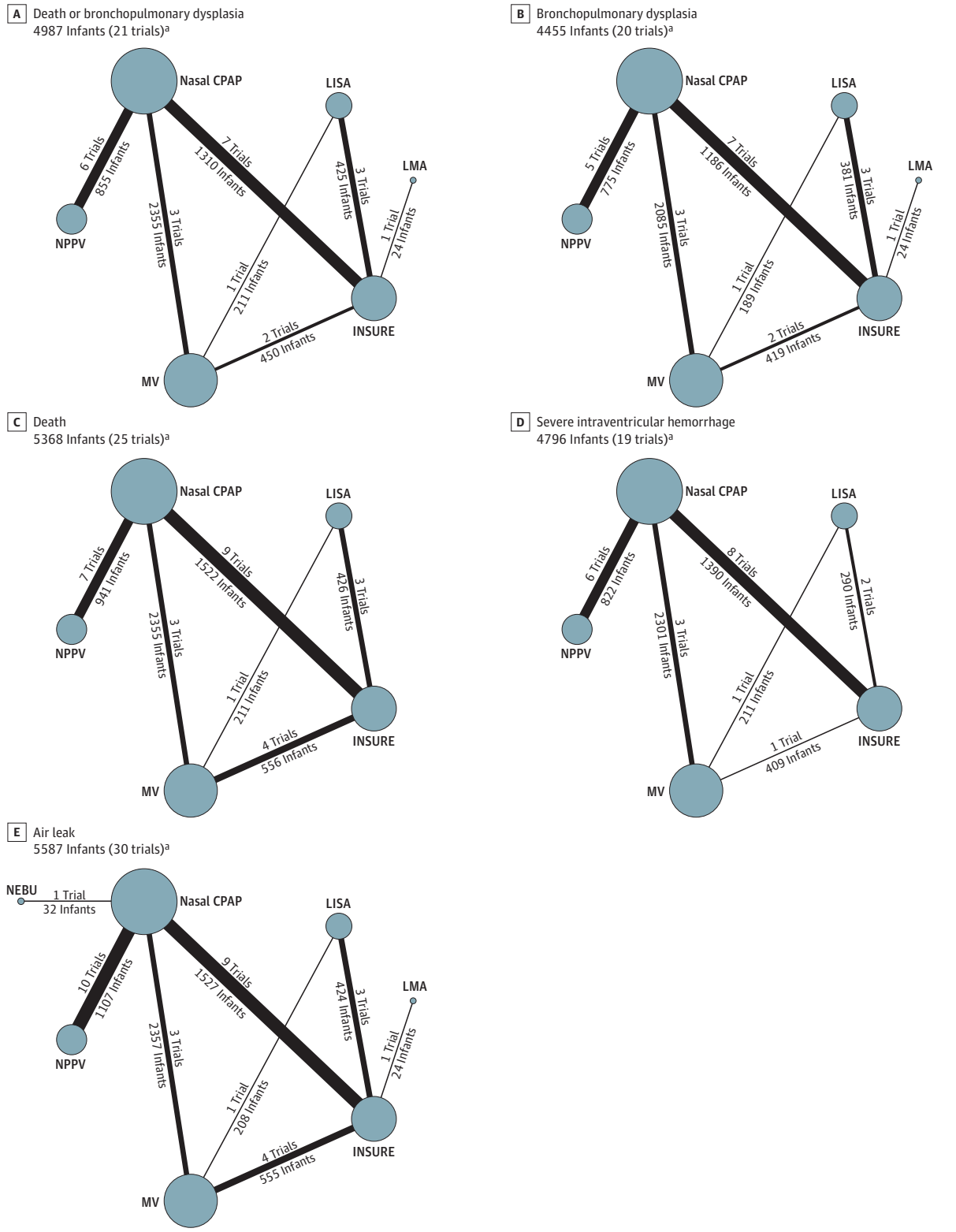
[k] The backup measures were LISA for infants in the LISA group and INSURE for infants in the INSURE group.

[l] The FIO_2 threshold was at least 0.5. Within 8 hours of birth, the FIO_2 threshold was 0.2 higher than the initial FIO_2 at randomization. After 8 hours, the FIO_2 threshold was FIO_2 of 0.6 or higher or FIO_2 of 0.3 or higher with worsening clinical signs of respiratory distress syndrome.

[m] The backup measures were INSURE for infants in the INSURE group. The backup measure for the LMA group was INSURE except for the first rescue dose after 8 hours of birth and surfactant administration via LMA for which LMA was used as a backup measure.

(Figure 2). The incidence of BPD was 26% (1160 of 4455); death, 10% (542 of 5368 eFigure 2 in the Supplement); severe intraventricular hemorrhage, 8% (389 of 4796); and air leak, 6% (314 of 5587). LISA was associated with a lower likelihood of BPD and severe intraventricular hemorrhage than was mechanical ventilation (moderate quality-of-evidence) (**Figure 4**). LISA and INSURE were associated with a lower likelihood of air leak than was nasal CPAP alone (very low-quality of evidence). There were no other significant differences between interventions in the likelihood of the main secondary outcomes (Figure 3 and Figure 4) or other secondary outcomes (eTable 7 in the Supplement).

Figure 2. Network Geometry for Outcomes in Network Meta-analysis of Noninvasive Ventilation Strategies for Preterm Infants



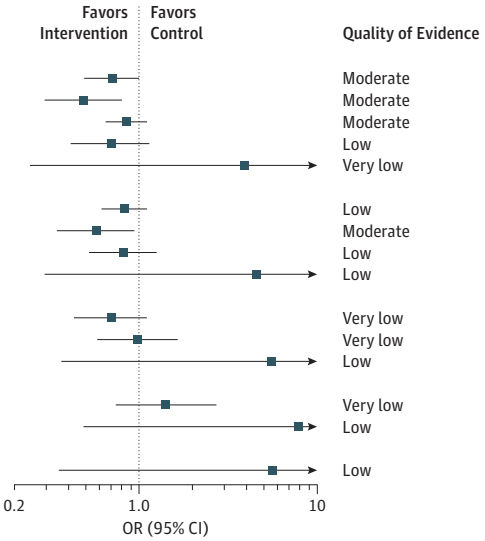
Each node indicates a ventilation strategy and is sized proportional to the number of infants who received the ventilation strategy. Each line connecting 2 nodes indicates a direct comparison between 2 strategies, and the thickness of each is proportional to the number of trials directly comparing the 2 strategies.

[a] The total numbers of trials and infants were not the same as the sum of the numbers of infants and trials in pairwise comparisons because one 3-group trial was included. See Table 1 footnotes for abbreviation expansions.

Figure 3. Primary Outcome of Bronchopulmonary Dysplasia or Death in Preterm Infants

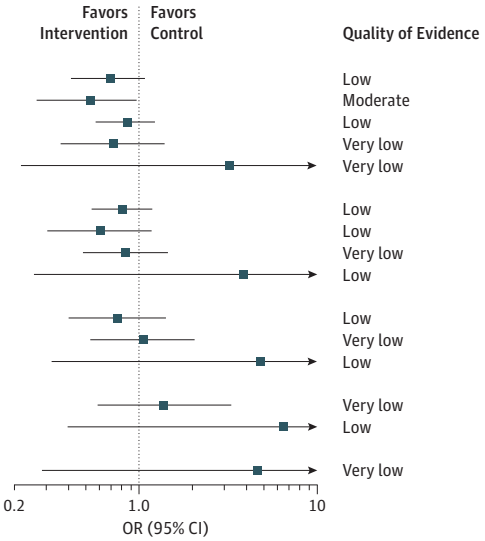
A Death or bronchopulmonary dysplasia (composite outcome)

Source	No. of Infants	No. of Trials	Network Absolute RD per 1000 (95% CI)	Network OR (95% CI)	Quality of Evidence
MV (control)					
INSURE	419	2	83 Fewer (5 fewer-160 fewer)[a]	0.71 (0.50-0.98)	Moderate
LISA	189	1	164 Fewer (57 fewer-253 fewer)[a]	0.49 (0.30-0.79)	Moderate
Nasal CPAP	2085	3	40 Fewer (24 more-99 fewer)	0.85 (0.66-1.10)	Moderate
NPPV			86 Fewer (30 more-194 fewer)	0.70 (0.42-1.13)	Low
LMA			311 More (280 fewer-539 more)	3.90 (0.25-119.88)	Very low
Nasal CPAP (control)					
INSURE	1186	7	41 Fewer (22 more-96 fewer)	0.83 (0.63-1.10)	Low
LISA			112 Fewer (16 fewer-190 fewer)[a]	0.58 (0.35-0.93)[a]	Moderate
NPPV	775	5	44 Fewer (50 more-127 fewer)	0.82 (0.53-1.24)	Low
LMA			362 More (210 fewer-639 fewer)	4.58 (0.30-141.08)	Low
INSURE (control)					
LISA	381	3	65 Fewer (17 more-131 fewer)	0.70 (0.44-1.09)	Very low
NPPV			4 Fewer (91 fewer-105 more)	0.98 (0.59-1.62)	Very low
LMA	24	1	402 More (150 fewer-713 more)	5.53 (0.37-167.35)	Low
LISA (control)					
NPPV			62 More (43 fewer-205 more)	1.41 (0.75-2.69)	Very low
LMA			467 More (94 fewer-778 more)	7.91 (0.49-244.67)	Low
NPPV (control)					
LMA			348 More (89 fewer-821 more)	5.68 (0.36-177.56)	Low



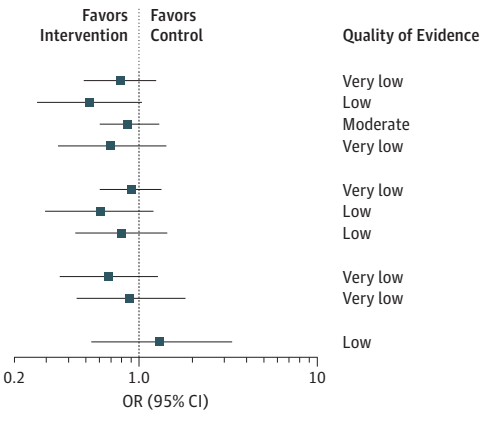
B Bronchopulmonary dysplasia

Source	No. of Infants	No. of Trials	Network Absolute RD per 1000 (95% CI)	Network OR (95% CI)	Quality of Evidence
MV (control)					
INSURE	419	2	82 Fewer (14 more-169 fewer)	0.69 (0.42-1.06)	Low
LISA	189	1	133 Fewer (9 fewer-234 fewer)[a]	0.53 (0.27-0.96)	Moderate
Nasal CPAP	2085	3	35 Fewer (46 more-116 fewer)	0.86 (0.58-1.21)	Low
NPPV			73 Fewer (78 more-192 fewer)	0.72 (0.37-1.38)	Very low
LMA			291 More (257 fewer-612 more)	3.32 (0.22-105.87)	Very low
Nasal CPAP (control)					
INSURE	1186	7	40 Fewer (34 more-103 fewer)	0.81 (0.55-1.18)	Low
LISA			87 Fewer (31 more-170 fewer)	0.61 (0.31-1.16)	Low
NPPV	775	5	33 Fewer (80 more-119 fewer)	0.84 (0.49-1.45)	Very low
LMA			321 More (186 fewer-703 more)	3.88 (0.26-123.62)	Low
INSURE (control)					
LISA	381	3	39 Fewer (56 more-104 fewer)	0.76 (0.41-1.39)	Low
NPPV			8 More (79 fewer-134 more)	1.05 (0.54-2.03)	Very low
LMA	24	1	342 More (120 fewer-780 more)	4.81 (0.33-150.76)	Low
LISA (control)					
NPPV			42 More (51 fewer-204 more)	1.37 (0.59-3.26)	Very low
LMA			366 More (77 fewer-834 more)	6.39 (0.40-207.74)	Low
NPPV (control)					
LMA			238 More (68 fewer-846 more)	4.63 (0.29-155.21)	Very low



C Death

Source	No. of Infants	No. of Trials	Network Absolute RD per 1000 (95% CI)	Network OR (95% CI)	Quality of Evidence
MV (control)					
INSURE	556	4	25 Fewer (23 More-60 fewer)	0.78 (0.49-1.22)	Very low
LISA	211	1	56 Fewer (2 More-88 fewer)	0.52 (0.27-1.02)	Low
Nasal CPAP	2355	3	16 Fewer (30 More-46 fewer)	0.86 (0.60-1.28)	Moderate
NPPV			36 Fewer (42 More-77 fewer)	0.68 (0.35-1.40)	Very low
Nasal CPAP (control)					
INSURE	1522	9	9 Fewer (26 More-37 fewer)	0.90 (0.61-1.30)	Very low
LISA			37 Fewer (16 More-68 fewer)	0.61 (0.30-1.18)	Low
NPPV	941	7	20 Fewer (37 More-54 fewer)	0.79 (0.44-1.42)	Low
INSURE (control)					
LISA	426	3	28 Fewer (21 More-56 fewer)	0.67 (0.36-1.26)	Very low
NPPV			10 Fewer (48 fewer-62 more)	0.88 (0.45-1.80)	Very low
LISA (control)					
NPPV			23 More (36 fewer-144 more)	1.31 (0.54-3.28)	Low

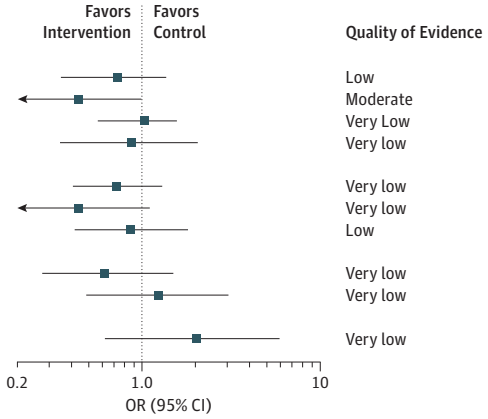


Network absolute risk difference (RD) was calculated from the network odds ratio (OR) estimates with an assumption that an assumed control risk was the average risk in a control group in the network. The assumed control risk values are presented in eTable 6 in the Supplement. See Table 1 footnotes for abbreviation expansions.

Figure 4. Main Secondary Outcomes of Severe Intraventricular Hemorrhage and Air Leak in Preterm Infants

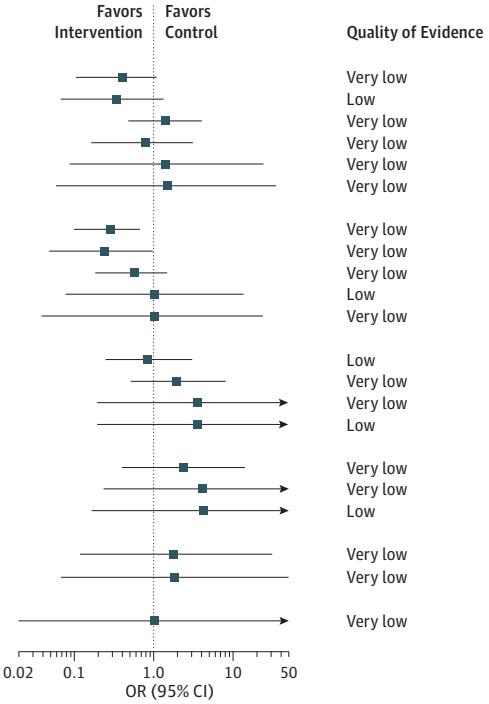
A Severe intraventricular hemorrhage

Source	No. of Infants	No. of Trials	Network Absolute RD per 1000 (95% CI)	Network OR (95% CI)	Quality of Evidence
MV (control)					
INSURE	409	1	28 Fewer (33 More-68 fewer)	0.72 (0.35-1.35)	Low
LISA	211	1	58 Fewer (1 Fewer-86 fewer)[a]	0.44 (0.19-0.99)	Moderate
Nasal CPAP	2301	3	2 More (44 Fewer-50 more)	1.02 (0.57-1.55)	Very Low
NPPV			13 Fewer (68 Fewer-90 more)	0.87 (0.35-2.03)	Very low
Nasal CPAP (control)					
INSURE	1390	8	23 Fewer (20 More-47 fewer)	0.71 (0.41-1.27)	Very low
LISA			46 Fewer (7 More-66 fewer)	0.43 (0.19-1.09)	Very low
NPPV	822	6	11 Fewer (47 Fewer-56 more)	0.86 (0.42-1.78)	Low
INSURE (control)					
LISA	290	2	19 Fewer (21 More-35 fewer)	0.61 (0.28-1.47)	Very low
NPPV			10 More (24 fewer-85 more)	1.22 (0.49-3.00)	Very low
LISA (control)					
NPPV			73 More (30 fewer-270 more)	2.01 (0.63-5.85)	Very low



B Air leak

Source	No. of Infants	No. of Trials	Network Absolute RD per 1000 (95% CI)	Network OR (95% CI)	Quality of Evidence
MV (control)					
INSURE	555	4	38 Fewer (5 more-58 fewer)	0.41 (0.11-1.08)	Very low
LISA	208	1	43 Fewer (19 more-61 fewer)	0.34 (0.07-1.31)	Low
Nasal CPAP	2357	3	23 More (33 fewer-154 more)	1.39 (0.49-4.00)	Very low
NPPV			12 Fewer (54 fewer-116 more)	0.80 (0.17-3.14)	Very low
NEBU			24 More (60 fewer-560 more)	1.40 (0.09-23.71)	Very low
LMA			27 More (62 fewer-643 more)	1.45 (0.06-34.42)	Very low
Nasal CPAP (control)					
INSURE	1527	9	43 Fewer (20 fewer-56 fewer)[a]	0.29 (0.10-0.66)	Very low
LISA			47 Fewer (2 fewer-59 fewer)[a]	0.24 (0.05-0.96)	Very low
NPPV	1107	10	26 Fewer (26 more-50 fewer)	0.57 (0.19-1.46)	Very low
NEBU	32	1	1 More (57 fewer-409 more)	1.01 (0.08-13.44)	Low
LMA			2 More (60 fewer-545 more)	1.04 (0.04-23.34)	Very low
INSURE (control)					
LISA	424	3	6 Fewer (27 fewer-68 more)	0.83 (0.26-3.03)	Low
NPPV			34 More (18 fewer-206 more)	1.95 (0.53-8.05)	Very low
NEBU			83 More (29 fewer-680 more)	3.45 (0.25-63.43)	Very low
LMA	24	1	87 More (31 fewer-718 more)	3.58 (0.20-76.94)	Low
LISA (control)					
NPPV			70 More (35 fewer-413 more)	2.34 (0.40-14.04)	Very low
NEBU			150 More (45 fewer-788 more)	4.17 (0.24-87.62)	Very low
LMA			155 More (49 fewer-820 more)	4.29 (0.17-114.32)	Low
NPPV (control)					
NEBU			21 More (25 fewer-446 more)	1.77 (0.12-30.60)	Very low
LMA			23 More (27 fewer-566 more)	1.83 (0.07-49.55)	Very low
NEBU (control)					
LMA			9 More (243 fewer-700 more)	1.05 (0.02-56.94)	Very low



Network absolute risk difference (RD) was calculated from the network odds ratio (OR) estimates with an assumption that an assumed control risk was the average risk in a control group in the network. The assumed control risk values are presented in eTable 6 in the Supplement. See Table 1 footnotes for abbreviation expansions.

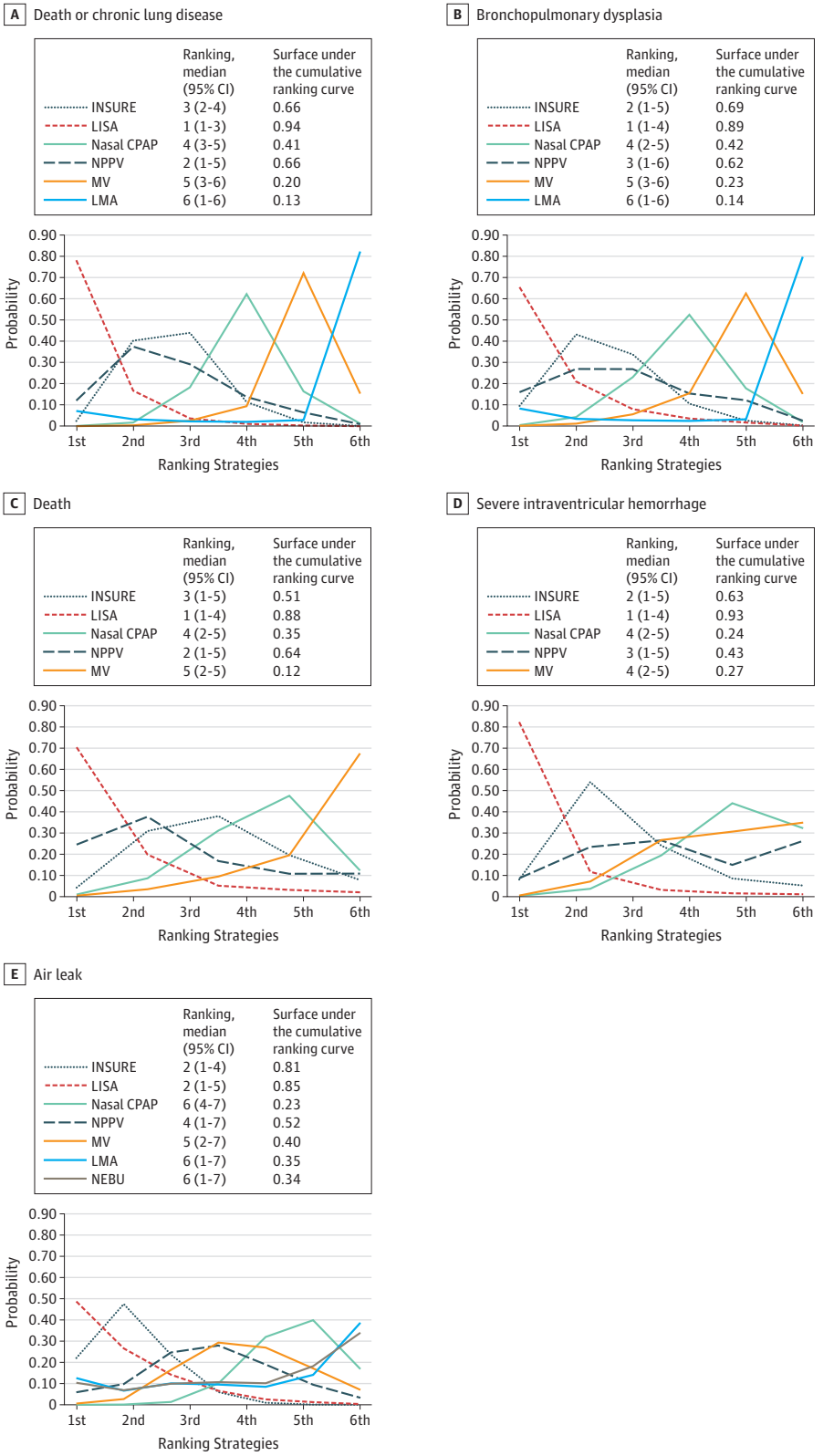
Ranking Probability

For the main outcomes, LISA had the highest probability of being the best strategy for supporting respiration in preterm infants with or at risk of respiratory distress syndrome (**Figure 5**). Additionally, LISA was the best strategy for all outcomes based on SUCRA (SUCRA, 0.85-0.94). INSURE was the second best strategy for the primary outcome (tied with NPPV), BPD, air leak, and severe intraventricular hemorrhage (SUCRA, 0.63-0.81).

Quality of Evidence Assessment

Among a total of 34 direct comparisons for the primary and main secondary outcomes, the quality of evidence was down rated for serious risk of bias in 10 comparisons, for serious heterogeneity in 10 comparisons, and for serious or very serious imprecision in all 34 comparisons (eTable 5 in the Supplement). The sample size of the meta-analyses did not reach the optimal information size in most direct comparisons (31 of 34) resulting in down rating due to imprecision (eTable 5 and eTable 6 in the Supplement). Node splitting found no significant incoherence in comparisons for any outcomes (eTable 6 in the Supplement). The inspection of effects modifiers found potential intransitivity in 3 comparisons (NPPV vs mechanical ventilation for death, LISA vs INSURE for severe intraventricular hemorrhage, and INSURE vs mechanical ventilation for air leak), and the quality of evidence for their

Figure 5. Ranking Probability of Strategies and Surface Under the Cumulative Ranking Curve in the Network Meta-analysis of Noninvasive Ventilation Strategies for Preventing Bronchopulmonary Dysplasia or Death in Preterm Infants



Each line indicates a ventilation strategy. The horizontal x-axis represents the ranking of strategies in which the first through sixth strategies are ranked in numerical order, with the first representing the best strategy. The vertical y-axis represents the probability of each ranking. CI indicates credible interval. The surface under the cumulative ranking curve is a simple summary index with values ranging between 0 (certainly the worst intervention) and 1 (certainly the best intervention).[32] See Table 1 footnotes for abbreviation expansions.

indirect effects estimates was down rated (eTable 6 in the Supplement). Based on these results, the quality of evidence for network effects estimates was judged as moderate in 7, low in 26, and very low in 38 comparisons (Figure 3, eTable 6 in the Supplement).

Sensitivity Analyses

Excluding studies with high risk of bias, the lower odds of the primary outcome and severe intraventricular hemorrhage in LISA compared with mechanical ventilation remained significant (eTable 8 in the Supplement). The other significant findings in the primary analyses became nonsignificant (eTable 8 in the Supplement). As in the primary analysis, LISA had the highest probability of being the best strategy and had the highest SUCRA among all strategies for all the main outcomes except for death (eTable 8F in the Supplement), for which NPPV had the highest SUCRA.

LISA and INSURE together were associated with lower odds of the primary outcome and BPD than was mechanical ventilation and lower odds of air leak than nasal CPAP alone (eTable 9 in the Supplement). LISA and INSURE had the highest probability of being the best strategy and had the highest SUCRA among all strategies for all the main outcomes except for death (eTable 9F in the Supplement).

Subgroup Analyses

The 4 preplanned subgroup analyses did not find any significant differences between subgroups for the primary outcome (eTable 10 in the Supplement).

Discussion

This network meta-analysis including 30 trials with 5598 nonventilated spontaneously breathing preterm infants with or at high risk of respiratory distress syndrome simultaneously estimated relative effects of 7 currently used noninvasive or invasive ventilation strategies. The use of LISA was associated with a lower likelihood of the primary outcome of death or BPD and secondary outcomes of BPD and severe intraventricular hemorrhage than mechanical ventilation and lower likelihood of the primary outcome and air leak than nasal CPAP alone. INSURE was associated with a lower likelihood of the primary outcome than mechanical ventilation and lower likelihood of air leak than nasal CPAP alone. Ranking probabilities supported that LISA was the best strategy among all strategies for all outcomes assessed. INSURE was the second best strategy to prevent the primary outcome (tied with NPPV), BPD, air leak, and severe intraventricular hemorrhage. Although significant findings for the primary outcome had moderate quality of evidence, the evidence for the secondary outcomes was, overall, of low quality. When limited to high-quality trials, the best strategy remained LISA for all main outcomes except for death, for which NPPV was the best strategy.

Previous Studies and Important Differences From This Study

Several systematic reviews have evaluated various noninvasive ventilation strategies using conventional pair-wise comparisons. Three systematic reviews reported that early nasal CPAP use, avoiding intubation, reduced the composite outcome of death or BPD compared with early intubation with or without early surfactant administration.[11,12,23] Because these systematic reviews did not differentiate between INSURE (or LISA) and mechanical ventilation in their intubation groups,[11,12,23] they did not address the important question of whether early surfactant administration with INSURE or LISA, avoiding prolonged mechanical ventilation, is more effective than nasal CPAP alone.

Among noninvasive strategies with early surfactant administration, INSURE has been most intensively investigated. Since Verder and colleagues[42,43] originally reported 2 randomized clinical trials during the 1990s, several other trials evaluated the efficacy of INSURE. A recent systematic review found no significant differences in efficacy or safety between early INSURE and nasal CPAP alone in preterm infants.[13] LISA has been developed as an alternative to INSURE, with potential benefits including maintenance of spontaneous breathing of infants while receiving nasal CPAP during the procedure,[17,64] complete avoidance of intermittent positive-pressure ventilation via endotracheal tubes,[17,64] and reduction of traumatic airway injuries caused by intubation with semi-rigid endotracheal tubes.[65] A previous systematic review[64] evaluating LISA that included 4 observational studies and 2 randomized clinical trials reported that all 6 studies demonstrated that LISA reduced the need for mechanical ventilation, and 1 study reported a reduction in BPD incidence.[59] The study however did not conduct a meta-analysis of the data.

To our knowledge, our study is the first systematic review conducting meta-analyses to evaluate the outcomes and adverse effects associated with LISA. Other modes of surfactant administration, via either laryngeal mask airway or nebulizer, have suggested promise.[64] However, there was only 1 eligible small trial for each of these strategies, and their effectiveness has yet to be adequately assessed.

Noninvasive positive-pressure ventilation is another noninvasive alternative to nasal CPAP alone. A previous systematic review comparing NPPV and nasal CPAP in ventilated and nonventilated preterm infants[66] found a reduction of the need for mechanical ventilation in the NPPV group but no differences in the rates of BPD and other major outcomes. This review focused on infants who had never been intubated before study entry, which is essential to evaluate the effect of avoiding ventilator-induced lung injury. Although this systematic review found no significant differences in outcomes between NPPV and other strategies, sample sizes did not reach the optimal information size and NPPV was only compared with nasal CPAP alone.

The overall inferiority of mechanical ventilation to other strategies found in this systematic review suggests that routine use of this strategy should not be recommended. However, because previous studies reported that substantial proportions of infants initially managed with LISA,[67] INSURE,[68] or nasal CPAP alone[69] required mechanical ventilation later, it may be reasonable to use mechanical ventilation strategies if noninvasive strategies are expected to fail.[68,69]

The American Academy of Pediatrics recommends early nasal CPAP as an alternative to routine intubation and surfac-

tant administration.[19] The European consensus guidelines recommend early routine use of nasal CPAP along with early rescue surfactant administration for infants with respiratory distress syndrome.[20] Both the American and European guidelines recommend the use of INSURE for rescue surfactant administration if infants seem to tolerate immediate extubation; however, neither include a recommendation for the use of LISA.[19,20] The lowest likelihood of adverse outcomes associated with LISA found in this systematic review could inform future updates of these clinical guidelines.

Strengths and Limitations

This study has several strengths, especially the use of network meta-analysis to enable comparisons among currently used respiratory strategies, while increasing statistical power by taking advantage of indirect network pathways. This systematic review used robust methods, guided by the Cochrane Handbook[27] and the GRADE approach for network meta-analyses.[34] The Bayesian statistical methods provided ranking probabilities and allowed comparison of all the strategies simultaneously using SUCRA. Two sensitivity analyses assessed the robustness of the study findings. The authors of 17 original articles provided data to help assess the study designs, reduce missing data, clarify outcome definitions, and enable inclusion of clinically important subgroups.

This study has some limitations. Although this systematic review is the largest yet performed, most of the direct comparisons had smaller sample sizes than the optimal information sizes. The wide 95% CrIs of the network ORs in many comparisons, especially those including NPPV and surfactant administration via nebulizers or laryngeal airway mask, indicate that further trials are needed to obtain more precise effects estimates. There were some differences in baseline characteristics of included trials that could lead to biased results.[34] This issue was incorporated in the quality-of-evidence assessment by evaluating the I^2 statistic and Cochrane Q test for heterogeneity within each direct comparison, inspecting differences in effects modifiers for transitivity between comparisons, and conducting node splitting to assess incoherence between direct and indirect comparisons.[34] Furthermore, differences in the infants' baseline characteristics indicate variations in severity of respiratory distress syndrome in the included trials. Because the severity of respiratory distress was reported to predict nasal CPAP failure,[69] the strategies with early surfactant administration (LISA, INSURE, and surfactant administration via nebulizer or laryngeal mask airway) may be more effective for those with severe respiratory distress. The preplanned subgroup analyses assessed this possibility; however, the small sample sizes in subgroups limited the assessment. Therefore, which infants need early surfactant administration via LISA or INSURE is yet to be addressed. Because the lack or delay of surfactant administration is a drawback of the nasal CPAP-alone and NPPV strategies, it is possible that the nasal CPAP alone and NPPV with early, appropriate but selective surfactant administration may be as or more effective than LISA and INSURE. Also, there are potential cointerventions that may affect primary ventilation strategies, such as premedications before LISA, INSURE, or surfactant administration via laryngeal mask airway (eg, atropine, sedatives)[17] and prophylaxis with methylxanthines (eg, caffeine) to prevent apnea.[70] Because many of the included trials did not report cointerventions (eTable 11 in the Supplement), future trials should describe them. When limited to high-quality trials, some of the study findings changed. This study incorporated the fragility of these results by rating down their quality of evidence.

Implications for Clinicians and Researchers

Based on the best available evidence, this systematic review found that early surfactant administration via LISA was the best management strategy, and INSURE likely the second best, for nonventilated spontaneously breathing preterm infants with or at high risk of respiratory distress syndrome, along with early nasal CPAP application. However, when limited to high-quality evidence, some significant findings for LISA compared with other strategies became nonsignificant, and the lower likelihood of death associated with LISA was not robust. Therefore, to confirm the overall lower likelihood of the primary and secondary outcomes associated with LISA found in this systematic review, further well-designed trials with large sample sizes comparing LISA with nasal CPAP alone are warranted, and some are currently under way.[71] Because LISA and INSURE are similar procedures, INSURE can be an alternative to LISA, especially for clinicians not familiar with LISA.

Conclusions

Among preterm infants, the use of LISA was associated with the lowest likelihood of the composite outcome of death or BPD at 36 weeks' postmenstrual age. These findings were limited by the overall low quality of evidence and lack of robustness in higher quality trials.

ARTICLE INFORMATION

Correction: This article was corrected September 13, 2016, to change the corresponding author's address.

Author Contributions: Dr Isayama 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.
Concept and design: Isayama, McDonald, Beyene.
Acquisition, analysis, or interpretation of data: Isayama, Iwami, Beyene.
Drafting of the manuscript: Isayama.
Critical revision of the manuscript for important intellectual content: All Authors.
Statistical analysis: Isayama, Beyene.
Study supervision: McDonald, Beyene.
No additional contributions: Iwami.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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Hospital, School of Medicine, Zhejiang University, Zhejiang, China],[62] Sourabh Dutta, PhD [The Postgraduate Institute of Medical Education and Research, Chandigarh, India],[52] Gianluca Lista, MD [V. Buzzi Children's Hospital, Milan, Italy],[53] Jucille Meneses, PhD [Instituto de Medicina Integral Professor Fernando Figueira, Recife, Brazil],[54] Gozde Kanmaz, MD [Zekai Tahir Burak Maternity Teaching Hospital, Ankara, Turkey],[60] Kayavan Mirnia, MD [Tabriz Medical University, Alzahra Teaching Hospital, Tabriz, Iran],[61] Mohammad Heidarzadeh, MD [Tabriz Medical University, Alzahra Teaching Hospital, Tabriz, Iran],[61] Ghassan Salama, MD [Jordanian Royal Medical Services, Amman, Jordan],[58] Carlo Dani, MD [Careggi University Hospital of Florence, Florence, Italy],[39] Amir Kugelman, MD [Bnai Zion Medical Center, Haifa, Israel],[51] Michael Dunn, MD [Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada],[38] Hemasree Kandraju, MD [Fernandez Hospital, Hyderabad, Telangana, India],[48] Srinivas Murki, DM [Fernandez Hospital, Hyderabad, Telangana, India],[48] Carl D'Angio, MD [Golisano Children's Hospital, University of Rochester School of Medicine and Dentistry, Rochester, New York],[45] Henrik Axel Verder, DMSc [Holbaek University Hospital, Region Zealand, Denmark],[43] Mehmet Yekta Oncel, MD [Zekai Tahir Burak Maternity Teaching Hospital, Ankara, Turkey],[9] Teresa Aguiar, MD [Hospital Prof Doutor Fernando Fonseca, Amadora, Portugal],[57] Joaquim M. B. Pinheiro, MPH [Albany Medical College, Albany, New York]).[64] We also thank Russell de Souza, ScD (McMaster University, Hamilton, Ontario, Canada) for reviewing the study protocol and manuscript and providing comments; Yue Yao, MD (Hospital for Sick Children, Toronto, Ontario, Canada) for translating the Chinese articles. Neither Dr de Souza nor Yao received financial compensation for their contribution to this manuscript.

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