# Inhaled Nitric Oxide Does Not Reduce Mortality in Patients With Acute Respiratory Distress Syndrome Regardless of Severity: Systematic Review and Meta-Analysis*

Neill K. J. Adhikari, MDCM, MSc[1]; R. Phillip Dellinger, MD[2]; Stefan Lundin, MD, PhD[3]; Didier Payen, MD, PhD[4]; Benoit Vallet, MD, PhD[5]; Herwig Gerlach, MD, PhD[6]; Kwang Joo Park, MD, PhD[7]; Sangeeta Mehta, MD[8]; Arthur S. Slutsky, MD[9]; Jan O. Friedrich, MD, DPhil[10]

*See also p. 472.

[1]Department of Critical Care Medicine and Sunnybrook Research Institute, Sunnybrook Health Sciences Centre and University of Toronto, Toronto, ON, Canada.

[2]Division of Critical Care Medicine, Department of Medicine, Cooper University Hospital, Camden, NJ.

[3]Department of Anesthesia and Intensive Care, Sahlgrenska University Hospital, Gothenburg, Sweden.

[4]Department of Critical Care and Anesthesiology and SAMU, Hôpital Lariboisière, Université Paris 7 Denis Diderot, Paris, France.

[5]Department of Anesthesiology and Intensive Care Medicine, University Hospital of Lille, Lille, France.

[6]Departments for Anesthesia, Intensive Care Medicine, and Pain Management, Vivantes–Klinikum Neukoelln, Berlin, Germany.

[7]Department of Pulmonary and Critical Care Medicine, Ajou University School of Medicine, Suwon, South Korea.

[8]Department of Medicine, Mount Sinai Hospital and University of Toronto, Toronto ON, Canada.

[9]The Keenan Research Centre in the Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto ON, Canada.

[10]Departments of Critical Care and Medicine, The Keenan Research Centre in the Li Ka Shing Knowledge Institute, St. Michael's Hospital and University of Toronto, Toronto, ON, Canada.

Ikaria provided subgroup data for three trials (references [49], [52], [56]) and reviewed and commented on a draft manuscript approved by all authors before journal submission; Ikaria did not have the right to force changes to the manuscript. Ikaria did not provide financial or other in-kind support. Ikaria had no role in the design or conduct of the study; management, analysis, or interpretation of data; or preparation or approval of the manuscript.

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For information regarding this article, E-mail: j.friedrich@utoronto.ca



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**Objective:** Treatment with inhaled nitric oxide improves oxygenation but not survival in mechanically ventilated patients with acute respiratory distress syndrome, but the effect may depend on the severity of hypoxemia. Our objective was to determine whether nitric oxide reduces hospital mortality in patients with severe acute respiratory distress syndrome ($Pa_{O_2}/F_{I_{O_2}} \leq 100$ mm Hg) but not in patients with mild-moderate acute respiratory distress syndrome ($100 < Pa_{O_2}/F_{I_{O_2}} \leq 300$ mm Hg) at the time of randomization.

**Data Sources:** Data were collected from Medline, Embase, and Cochrane CENTRAL electronic databases (inception to May 2013); proceedings from five conferences (to May 2013); and trial registries (http://www.clinicaltrials.gov and http://www.controlled-trials.com). No language restrictions were applied.

**Study Selection:** Two authors independently selected parallel-group randomized controlled trials comparing nitric oxide with control (placebo or no gas) in mechanically ventilated adults or postneonatal children with acute respiratory distress syndrome.

**Data Extraction:** Two authors independently extracted data from included trials. Trial investigators provided subgroup data. Meta-analyses used within-trial subgroups and random-effects models.

**Data Synthesis:** Nine trials ($n = 1{,}142$ patients) met inclusion criteria. Overall methodological quality was good. Nitric oxide did not reduce mortality in patients with severe acute respiratory distress syndrome (risk ratio, 1.01 [95% CI, 0.78–1.32]; $p = 0.93$; $n = 329$, six trials) or mild-moderate acute respiratory distress syndrome (risk ratio, 1.12 [95% CI, 0.89–1.42]; $p = 0.33$;

$n = 740$, seven trials). Risk ratios were similar between subgroups (interaction $p = 0.53$). There was no between-trial heterogeneity in any analysis ($I^2 = 0\%$). Varying the $Pa_{O_2}/F_{I_{O_2}}$ threshold between 70 and 200 mm Hg, in increments of 10 mm Hg, did not identify any threshold at which the nitric oxide–treated patients had lower mortality relative to controls.

**Conclusions:** Nitric oxide does not reduce mortality in adults or children with acute respiratory distress syndrome, regardless of the degree of hypoxemia. Given the lack of related ongoing or recently completed randomized trials, new data addressing the effectiveness of nitric oxide in patients with acute respiratory distress syndrome and severe hypoxemia will not be available for the foreseeable future. (*Crit Care Med* 2014; 42:404–412)

**Key Words:** acute respiratory distress syndrome; meta-analysis; nitric oxide; systematic review

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The acute respiratory distress syndrome (ARDS) is characterized by the acute onset of hypoxemia and bilateral radiographic opacities not explained by cardiac failure or volume overload and arises in response to various direct and indirect pulmonary insults (1, 2). These clinical features stem from inflammation and increased permeability of the alveolar-capillary membrane (3) that leads to alveolar filling and collapse. Hypoxemia results from ventilation-perfusion mismatching; pulmonary hypertension is an important associated finding. Use of inhaled nitric oxide (NO)—a selective pulmonary vasodilator with anti-inflammatory properties (4, 5)—was anticipated to improve oxygenation and clinical outcomes. However, meta-analyses of randomized controlled trials (RCTs) in adults and postneonatal children have shown that NO, despite improving $Pa_{O_2}/F_{I_{O_2}}$ by approximately 5–13% for the first 4 days of treatment (6), does not reduce mortality and increases the risk of renal failure (6–8). Long-term follow-up of one RCT found no beneficial effect of NO on other outcomes, including hospital costs, workload in the ICU, discharge location, hospital readmissions, functional status, or quality of life (9).

Despite the lack of evidence for NO and the high daily cost of USD 1,500–3,000 (10–12), it continues to be used for approximately 7% of all patients with ARDS (13) and for 10% of other mechanically ventilated patients with refractory hypoxemia (14). During the recent H1N1 influenza pandemic, NO was administered to a substantial minority of mechanically ventilated patients in academic and community hospitals: 8% in South Korea (15), 12% in Europe (16), and 14% in Canada (17). Ongoing use of NO for severely hypoxemic patients may be explained by their underrepresentation in RCTs. Such patients would be expected to be at high short-term risk of death due to hypoxemia and therefore likely to benefit from NO-mediated improvement in oxygenation.

The objective of this systematic review, performed in collaboration with investigators who led the seminal trials of NO, was to determine whether NO reduces mortality in patients with severe ARDS. The primary a priori hypothesis was that NO would reduce mortality in patients with severe ARDS ($Pa_{O_2}/F_{I_{O_2}} \leq 100$ mm Hg) but not in patients with mild-moderate ARDS ($100 < Pa_{O_2}/F_{I_{O_2}} \leq 300$ mm Hg) at the time of randomization. We also planned a priori to conduct similar comparisons of the more versus less hypoxemic subgroups using $Pa_{O_2}/F_{I_{O_2}}$ thresholds ranging from 70 to 200 mm Hg, in increments of 10 mm Hg, to determine whether there is a threshold for which NO reduces mortality in the more hypoxemic subgroup.

## MATERIALS AND METHODS

### Search Strategy

We (N.K.J.A., J.O.F.) updated our previous search (6) by electronically searching Medline, Embase, and The Cochrane Central Database of Controlled Trials (CENTRAL) from inception to May 2013 for RCTs comparing NO with control (placebo or no gas) in mechanically ventilated patients with ARDS. The Medline search strategy retrieved citations containing 1) the subject headings *endothelium-dependent relaxing factors* or *nitric oxide* or the text words *endothelium dependent relax: factor*, *endothelium derived relax: factor:* or *nitric oxide* and 2) the subject headings *respiratory insufficiency* or *respiratory distress syndrome, adult* or *lung transplantation* or the text words *(acute adj lung adj injur:) or (shock adj lung) or ARDS* or *(acute or adult) and (respiratory adj distress)* or *lung transplant.* Terms were modified as needed for other databases. Medline citations were limited to RCTs using a sensitive strategy (18) that was modified for other databases. Details of the search strategies are available in **Appendix 1** (Supplemental Digital Content 1, http://links.lww.com/CCM/A734).

We searched reference lists from included studies and review articles. We also updated searches of conference proceedings of the American Thoracic Society (1994–2013), Society of Critical Care Medicine (1994–2013), European Society of Intensive Care Medicine (1994–2012), American College of Chest Physicians (1994–2012), and the International Symposium on Intensive Care and Emergency Medicine (1999–2013) and contacted primary investigators. Finally, we searched for unpublished and ongoing trials in http://www.clinicaltrials.gov and http://www.controlled-trials.com. No language restrictions were applied.

### Study Selection

Two reviewers (N.K.J.A., J.O.F.) independently screened studies for inclusion, retrieved potentially relevant studies, and decided on study eligibility. We selected parallel-group RCTs enrolling adults or children (excluding neonates), with more than or equal to 80% of patients, or a separately reported subgroup, having ARDS (using authors' definitions). Included trials compared NO with control (placebo or no gas) for treatment (not prevention) of ARDS, reported all-cause mortality at any time, and had less than 50% of patients crossing over from control to NO arms. We included trials with cointerventions (such as prone ventilation or recruitment maneuvers)

applied equally in NO and control groups. We did not consider cause-specific mortality (e.g., refractory hypoxemia vs multiple organ failure).

### Data Abstraction and Validity Assessment

From included trials, two reviewers had previously independently abstracted trial data and methodology, including method of randomization and allocation concealment; blinding of caregivers and outcomes assessors; number of post-randomization withdrawals; and standardization or similar application of mechanical ventilation, weaning, and sedation in treatment groups (6). Disagreements were resolved by consensus. For the current review, authors of included trials provided previously unpublished trial data for subgroups of patients defined by $Pa_{O_2}/F_{IO_2}$ ratio. Two reviewers (N.K.J.A., J.O.F.) verified outcomes data against previously published data from the same trials, where possible.

### Quantitative Data Synthesis

The primary outcome was mortality in the subgroup of patients with severe ARDS ($Pa_{O_2}/F_{IO_2} \leq 100$ mm Hg) compared with that in patients with mild-moderate ARDS ($100 < Pa_{O_2}/F_{IO_2} \leq 300$ mm Hg) at the time of randomization. We selected these categories based on the recent Berlin consensus conference (2) that categorized ARDS severity based on degree of hypoxemia as mild ($200 < Pa_{O_2}/F_{IO_2} \leq 300$ mm Hg), moderate ($100 < Pa_{O_2}/F_{IO_2} \leq 200$ mm Hg), and severe ($Pa_{O_2}/F_{IO_2} \leq 100$ mm Hg). We also conducted similar analyses of mortality in more versus less hypoxemic subgroups using $Pa_{O_2}/F_{IO_2}$ thresholds ranging from 70 to 200 mm Hg in increments of 10 mm Hg. For one trial, the numbers of deaths and randomized patients were only available in groups defined by less than $Pa_{O_2}/F_{IO_2}$ threshold and more than or equal to $Pa_{O_2}/F_{IO_2}$ threshold, rather than less than or equal to threshold and more than threshold (19).

Mortality was taken at hospital discharge, or if not available, at discharge from the ICU or at 28 or 30 days after randomization. Our analyses adhered to the intention-to-treat principle. In studies with two or more NO groups receiving different doses, we combined data from all doses to determine an overall effect for the NO group.

Two investigators (N.K.J.A., J.O.F.) performed all calculations independently. We used standard equations for random-effects models (20) in Excel 2007 (Microsoft, Redmond, WA) and verified analyses with outcome events in at least one treatment arm of each study with Review Manager 5.1 (The Cochrane Collaboration, Oxford, UK). We also verified analyses for the primary outcome using R version 2.15.2 (R Foundation for Statistical Computing, Vienna, Austria). We reported binary outcomes as risk ratios (RRs) with 95% CI and considered $p$ value of less than or equal to 0.05 (two-sided) as statistically significant.

For the primary outcome, we performed a $z$ test of interaction between the RR for mortality in the subgroup of patients with $Pa_{O_2}/F_{IO_2}$ less than or equal to 100 mm Hg and the RR in the subgroup of patients with $Pa_{O_2}/F_{IO_2}$ more than 100 mm Hg, which tests the null hypothesis that the treatment effects in each subgroup are the same. We also conducted similar comparisons of the more versus less hypoxemic subgroups using other $Pa_{O_2}/F_{IO_2}$ thresholds as defined above. At each $Pa_{O_2}/F_{IO_2}$ threshold in the primary analyses, we included all trials with a calculable RR in either the hypoxemic or less hypoxemic subgroup. At each $Pa_{O_2}/F_{IO_2}$ threshold in secondary analyses, we only included trials with calculable RRs in both subgroups. Trials without a calculable RR in a particular subgroup (e.g., in the subgroup of patients with $Pa_{O_2}/F_{IO_2} \leq 80$ mm Hg) were those that randomized no patients to either NO or control in that subgroup. Trials that randomized patients to both NO and control in a particular subgroup and had zero deaths in both treatment arms were included by adding 0.5 to each cell, as described previously (21).

We assessed between-study heterogeneity for each outcome using the $I^2$ measure (22, 23), with suggested thresholds for low (25–49%), moderate (50–74%), and high (≥ 75%) values of $I^2$. To assess for publication bias, we examined a funnel plot of treatment effect versus study precision.

## RESULTS

### Literature Search, Study Characteristics, and Methodologic Quality

We identified 2,221 citations from searches of electronic bibliographic databases and six citations from conference proceedings. We retrieved 35 records for detailed evaluation, of which 21 citations were excluded for the following reasons (**Fig 1**): no mortality data (confirmed after author contact) (24), review (25), not randomized (26–29), not for treatment of ARDS (NO used postcardiac surgery (30) or lung transplantation (31–36), with left ventricular assist device (37), or for acute sickle cell pain crisis) (38), crossover trial (39), not ARDS and crossover trial (40), duplicate (41) or partial duplicate (confirmed after author contact) (42), or longer term follow-up of included trials (9, 43). Four additional trials that otherwise met selection criteria were excluded because more than or equal to 50% patients crossed over from control to NO (44–47); data from one of these trials were distributed in two articles (46, 48). We found no trials actively recruiting patients or recently terminated in trial registries.

Nine trials enrolling 1,142 patients (19, 49–56) met criteria for inclusion in our review (Fig. 1; **Table 1**). Data from one study were presented in two abstracts (19, 57). No new trials have been published since our previous review (6), which provides a detailed description of the study characteristics. Four trials used a fixed NO dose of 5 (55, 56) or 10 ppm (19, 54), one trial randomized patients to different doses (1.25–80 ppm) (49), and the remaining trials used the lowest dose to achieve an oxygenation response (mean dose, 5.3 [51], 9 [52], 13 [50], or 5–10 ppm [53]). Trials continued NO until criteria for improvement (generally in oxygenation or requirement for positive end-expiratory pressure) were met. Overall methodological quality of included trials was good (**Supplemental**

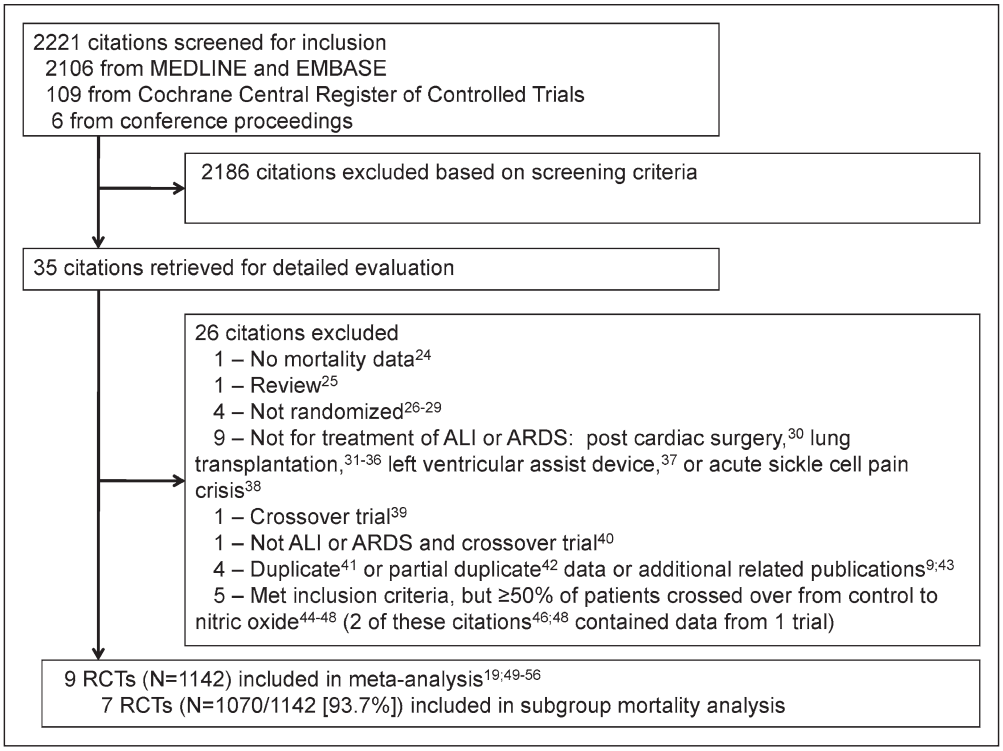


**Figure 1.** Flow of trials through the systematic review and meta-analysis. ALI = acute lung injury, ARDS = acute respiratory distress syndrome, RCT = randomized controlled trial.

**Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/A734) (6).

We obtained patient-level data on $Pa_{O_2}/F_{IO_2}$ ratio and mortality for seven trials. For one trial, we obtained overall and subgroup data on the 177 patients reported in the original publication (49) as well as 56 randomized patients that had treatment gas (NO or placebo nitrogen) prematurely discontinued before meeting oxygenation threshold criteria. The authors of one trial were unable to locate the original data files (51), and we were unable to establish contact with the corresponding author of another trial (50).

### Quantitative Data Synthesis

Considering all patients (19, 49–56), regardless of severity of hypoxemia, NO had no effect on mortality (RR, 1.10 [95% CI, 0.94–1.29]; $p = 0.24$; $n = 1{,}142$; nine trials). Seven trials with 1,070 patients (93.7% of all randomized patients) contributed to the analysis of mortality based on baseline $Pa_{O_2}/F_{IO_2}$ (19, 49, 52–56). Subgroup analysis showed that NO did not reduce mortality in patients with baseline $Pa_{O_2}/F_{IO_2}$ less than or equal to 100 mm Hg (RR, 1.01 [95% CI, 0.78–1.32]; $p = 0.93$; $n = 329$; six trials) or those with baseline $Pa_{O_2}/F_{IO_2}$ more than 100 mm Hg (RR, 1.12 [95% CI, 0.89–1.42]; $p = 0.33$; $n = 740$; seven trials) (**Fig. 2**). The test for interaction was not statistically significant ($p = 0.53$), indicating that treatment effects were similar in subgroups with severe and mild-moderate ARDS. If the trial with a calculable RR in the $Pa_{O_2}/F_{IO_2}$ more than 100 mm Hg subgroup but not in the $PaO_2/F_{IO_2}$ less than or equal to 100 mm Hg subgroup (55) is excluded, the results do not change ($Pa_{O_2}/F_{IO_2} \leq 100$ mm Hg subgroup: RR as above and $Pa_{O_2}/F_{IO_2}$ more than 100 mm Hg subgroup: RR, 1.13 [95% CI, 0.89–1.43]; $p = 0.31$; $n = 724$, six trials; interaction $p = 0.54$).

Substituting $Pa_{O_2}/F_{IO_2}$ thresholds from 70 to 200 mm Hg, in increments of 10 mm Hg, did not identify any cut-point at which mortality improved in NO-treated patients relative to controls, in either the more or less hypoxemic subgroups (**Fig. 3**). Secondary analyses that excluded data from all trials without a calculable RR in both subgroups at each threshold resulted in negligible changes. There was no evidence of statistical heterogeneity in any analyses ($I = 0\%$). Visual inspection of the funnel plot did not suggest publication bias.

## DISCUSSION

### Main Findings

The main finding of this systematic review and meta-analysis is that NO does not reduce hospital mortality in patients with ARDS, regardless of the severity of hypoxemia. The effect of NO did not differ between more hypoxemic and less hypoxemic patients, regardless of the threshold of $Pa_{O_2}/F_{IO_2}$ ratio used to demarcate these subgroups. Given that no relevant ongoing or recently completed RCTs are currently registered, new data addressing the effectiveness of NO in patients with ARDS and severe hypoxemia will not be available for the foreseeable future.

### Comparison With Other Studies

Other recent meta-analyses of NO found no improvement in mortality and an increased risk of renal failure despite modest improvements in oxygenation (7, 8). Compared with these

## TABLE 1. Details of Randomized Trials of Nitric Oxide

| Author | Patients/Centers (*n*/*n*) | Main Selection Criteria | NO Dose and Duration[a] | Control Group |
|---|---|---|---|---|
| Dellinger et al (49) | 177 adults/30 | AECC criteria for ARDS and $F_{IO_2} \geq 0.5$, PEEP ≥ 8 cm $H_2O$ | 1.25, 5, 20, 40, or 80 ppm until 28 d or oxygenation and PEEP criteria met | Placebo gas (nitrogen) |
| Michael et al (50) | 37 adults, 3 children/1 | AECC criteria for ARDS except $Pa_{O_2}/F_{IO_2} \leq$ 150 mm Hg and $F_{IO_2} \geq 0.8$ for ≥ 12 hr or ≥ 0.65 for ≥ 24 hr | 5, 10, 15, 20 ppm every 6 hr for 24 hr then clinically adjusted; tapered if oxygenation not improved by 72 hr; mean dose ~13 ppm | Usual care |
| Troncy et al (51) | 30 adults/1 | Lung injury score[b] ≥ 2.5 | Initial titration (2.5, 5, 10, 20, 30, 40 ppm every 10 min) and daily retitration until oxygenation and PEEP criteria met; mean dose, 5.3 ppm; mean, 8 d (SD, 5 d) | Usual care |
| Lundin et al (52) | 180 adults/43 | Any CXR infiltrates, $Pa_{O_2}/F_{IO_2} \leq$ 165 mm Hg, PEEP ≥ 5 cm $H_2O$, mean airway pressure > 10 cm $H_2O$<br>NO responder[c] | 1–40 ppm (lowest effective dose) until reversal of ALI or severe respiratory failure, up to 30 d; mean dose, 9 ppm (SD, 8 ppm); mean, 9 d (SD, 6 d) | Usual care |
| Payen et al (19) | 203 adults/23 | AECC criteria for ARDS, lung injury score[b] 2–3 after 24 hr of "therapeutic optimization" | 10 ppm, until oxygenation and PEEP criteria met; median, 5 d | Placebo gas (nitrogen) |
| Mehta et al (53) | 14 adults/1 | Bilateral CXR infiltrates, $Pa_{O_2}/F_{IO_2} <$ 200 mm Hg, PEEP ≥ 8 cm $H_2O$, PAOP < 18 mm Hg | Daily titration (5, 10, 20 ppm every 30 min) for 4 d, then until oxygenation criteria met; most received 5–10 ppm on days 2–4; mean, 8 d (SD, 9 d) | Usual care |
| Gerlach et al (54) | 40 adults/1 | Bilateral CXR infiltrates, $Pa_{O_2}/F_{IO_2} \leq$ 150 mm Hg, PEEP ≥ 10 cm $H_2O$, PAOP ≤ 18 mm Hg<br>Duration of ventilation ≥ 48 hr with $F_{IO_2} \geq 0.6$ | 10 ppm (with daily dose-response analysis) until weaning initiated | Usual care |
| Park et al (55) | 17 adults/1 | AECC criteria for ARDS | 5 ppm for mean 3.5 d (SD, 1.5 d); all received one lung recruitment maneuver (same as control group)[c] | One lung recruitment maneuver (inflation pressure of 30–35 cm $H_2O$ for 30 s) |
| Taylor et al (56) | 385 adults/46 | AECC criteria for ALI except $Pa_{O_2}/F_{IO_2} \leq$ 250 mm Hg, $0.5 \leq F_{IO_2} \leq 0.95$ on PEEP ≥ 8 cm $H_2O$ | 5 ppm for 28 d or until oxygenation and PEEP criteria met | Placebo gas (nitrogen) |

NO = nitric oxide, AECC = American-European Consensus Conference (1), ARDS = acute respiratory distress syndrome, PEEP = positive end-expiratory pressure, CXR = chest radiograph, ALI = acute lung injury, PAOP = pulmonary artery occlusion pressure.

[a]Patients in the study by Dellinger et al (49) were randomized to the doses listed. In the remaining trials with different doses, each patient underwent dose titration.

[b]For details of the lung injury score, see Murray JF, Matthay MA, Luce JM, et al: An expanded definition of the adult respiratory distress syndrome [Erratum, *Am Rev Respir Dis* 1989; 139:1065]. *Am Rev Respir Dis* 1988; 138:720–723.

[c]Patients were given NO 0, 2, 10, 40 ppm every 10 min and response defined as relative increase in $Pa_{O_2}$ of 25% (n = 140) or 20% (n = 40). Responders were randomized.

[c]Third group (*n* = 6) received NO 5 ppm alone for 8.2 d (SD, 4.7 d) and was not included in the meta-analysis.

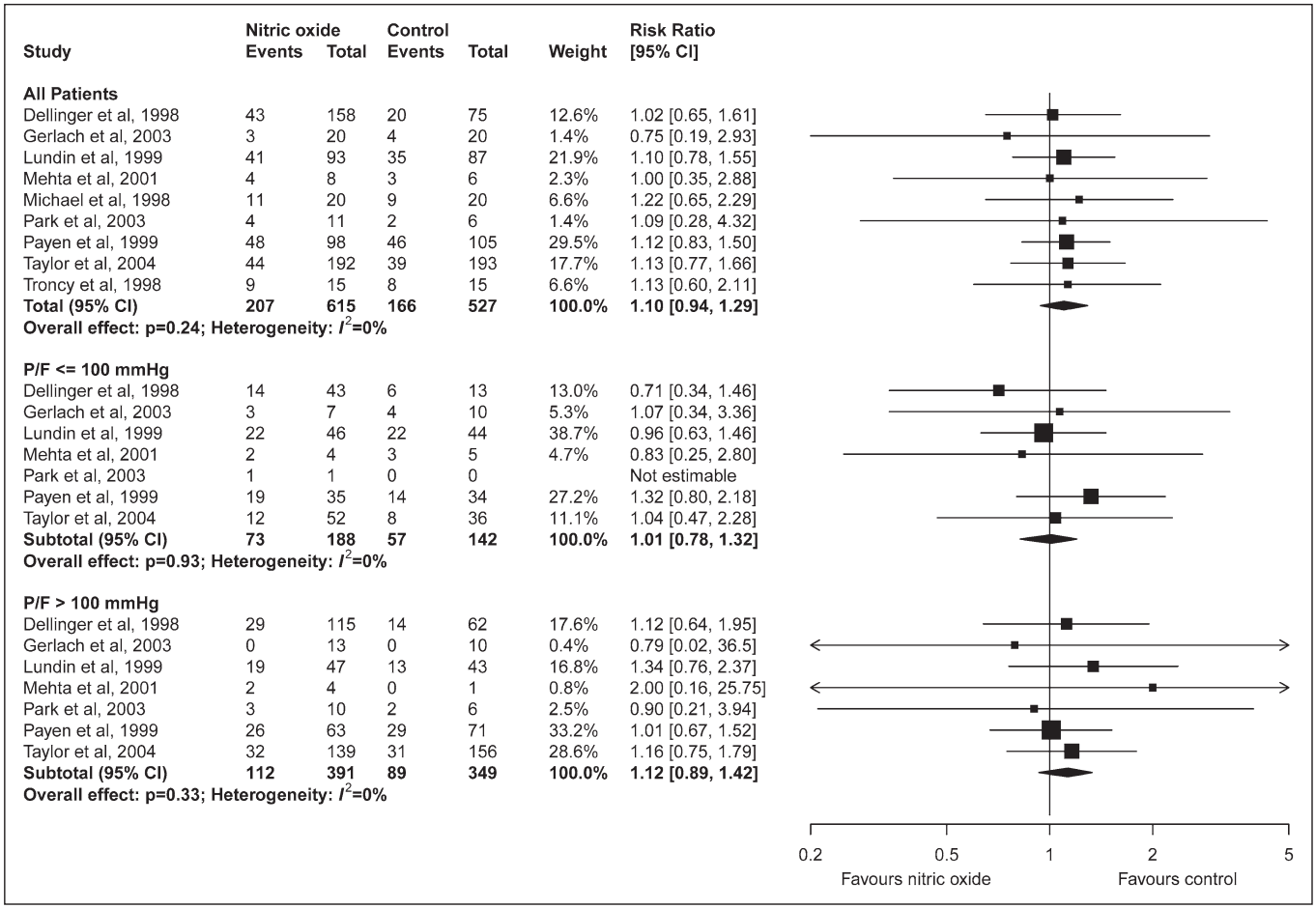


**Figure 2.** Effect of nitric oxide (NO) versus control on mortality, expressed as the risk ratio (RR), with values more than 1 indicating increased mortality with NO. The *z* test for subgroup interaction was not statistically significant ($p = 0.53$). Total patient numbers differed from the original publication for one trial (49). Baseline $Pao_2/Fio_2$ values were unavailable for one NO and one control patient in one trial (56). In another trial, the numbers of deaths and randomized patients were available as less than $Pao_2/Fio_2$ threshold and more than or equal to threshold, and mortality status was unavailable for two NO and five control patients (19). Finally, the number of deaths in the control group in one trial (53) differs from our previous meta-analysis (6), in which one very late death (68 d) was not counted. Weight is the contribution of each study to the overall RR. For the $Pao_2/Fio_2$ more than 100 mm Hg subgroup, weights do not add to 100% due to rounding. $I^2$ = percentage of total variation across studies from between-study heterogeneity rather than chance, Each *black square* and *horizontal line* denotes the point estimate and 95% CI for each trial's RR. The *diamond* signifies the pooled RR for all trials and for each subgroup. The diamond's center denotes the point estimate and the width denotes the 95% CI.

reviews, we excluded one trial (42) confirmed to have most patients co-enrolled in a larger included trial (52), another trial (24) confirmed after author contact not to have mortality data, and trials in which more than or equal to 50% of patients crossed over from control to NO (44–47). For one trial (55) also included in previous reviews (7, 8), we included the two randomized groups that both received a recruitment manoeuvre but differed in the use of NO, and we excluded the third group that received NO alone. We used 30-day mortality instead of 90-day mortality for one trial (52). Finally, we verified data in collaboration with primary trial investigators, and our meta-analysis is the first to use within-trial subgroup analysis to examine the effect of NO by baseline severity of hypoxemia.

Our analytic approach was similar to a previous meta-analysis (58) of ventilation in the prone position, which may also be considered for severely hypoxemic patients with ARDS. In that study, pooled mortality data from subgroups of patients with acute hypoxemic respiratory failure showed that prone ventilation reduced mortality in patients with severe hypoxemia ($Pao_2/Fio_2 < 100$ mm Hg) but not mild-moderate hypoxemia ($Pao_2/Fio_2 \geq 100$ mm Hg); this subgroup effect was statistically significant (58).

There are several possible reasons why improvements in oxygenation are not linked to improved mortality in the case of NO. The prolonged fixed-dosing regimen used in most trials may have attenuated benefit over time because of increased sensitization (54), dampening the oxygenation benefit while continuing to expose patients to possible toxic effects such as oxidative damage (59). Even among the most severely hypoxemic patients, who may be expected to die of primary respiratory failure rather than multiple nonlung organ failure (60), the small improvements in oxygenation due to inhaled NO may have been overwhelmed by injurious effects from a mechanical ventilation strategy used in most trials that did not strictly limit tidal volume or airway pressure. It is possible that the subgroup of patients with ARDS and cor pulmonale,

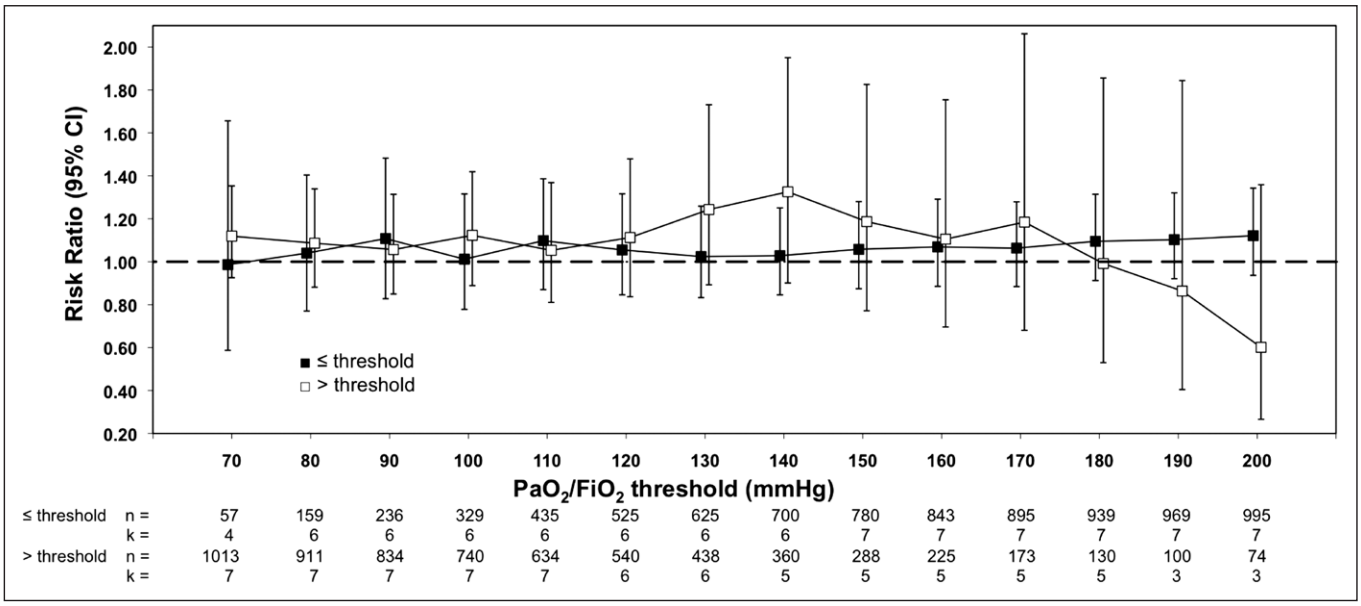


**Figure 3.** Effect of nitric oxide (NO) versus control on mortality in subgroups of more severe (*closed squares*) and less severe (*open squares*) baseline hypoxemia, defined by a range of $Pa_{O_2}/F_{IO_2}$ threshold values, and expressed as the risk ratio (RR), with values more than 1 indicating increased mortality with NO. Error bars denote 95% CIs. In one trial, baseline $Pa_{O_2}/F_{IO_2}$ values were unavailable for one NO and one control patient (56). In another trial, the numbers of deaths and randomized patients were available as less than $Pa_{O_2}/F_{IO_2}$ threshold and more than or equal to threshold, and mortality status was unavailable for two NO and five control patients (19). Weight is the contribution of each study to the overall RR. *n* (*k*) = number of randomized patients (trials) included for each subgroup at the $Pa_{O_2}/F_{IO_2}$ threshold. At $Pa_{O_2}/F_{IO_2}$ threshold values of 120 and 130 mm Hg, there are six trials in each subgroup, of which five trials are the same in both subgroups and one is different. As discussed in the text, secondary analyses at each threshold that excluded data from trials without a calculable RR in both subgroups resulted in negligible changes.

for whom clinicians may prioritize treatment with NO (61), would benefit from additional study in randomized trials.

Although NO does not improve mortality, follow-up of one trial (56) included in this review suggested that 6-month survivors who received NO had small improvements on some pulmonary function tests compared with those who received placebo (43). However, the internal validity of the study was limited by loss to follow-up of approximately 70% of survivors and by the lack of information on smoking status. In addition, the functional implications of these data are unclear, given that 6-minute walk distance was not measured and other data showing that pulmonary function in ARDS survivors returns to normal at 1 year (62).

## Strengths and Limitations

An important strength of our study is the inclusion of 93.7% of eligible patients in the subgroup analysis after confirmation of data from primary trial authors. The primary hypothesis that NO would reduce mortality in patients with severe hypoxemia was prespecified, biologically plausible, and analyzed using appropriate tests for subgroup effects (63). The trials included in this meta-analysis exhibited some methodological diversity (different inclusion criteria and different NO dosing and duration). However, for our primary comparison, we used patient-level subgroups within trials, which produce similar distributions of trial-specific characteristics in the more and less hypoxemic subgroups.

Our review has limitations. First, we conducted a subgroup analysis based on baseline $Pa_{O_2}/F_{IO_2}$ ratio, which is commonly reported and is used to define the severity of ARDS (2). However, $Pa_{O_2}/F_{IO_2}$ is influenced by ventilator settings and hemodynamic management that were not standardized across trials. Unfortunately, most trials did not measure oxygenation index, an alternative measure of hypoxemia that incorporates mean airway pressure as a marker of the intensity of mechanical ventilation. Second, the number of patients in the severe ARDS subgroup was relatively small, limiting the statistical power of our analysis to detect true differences in mortality between subgroups. Third, clinicians may argue that the dose used in included studies was insufficient to improve gas exchange in the most severely hypoxemic patients, who would be expected to be at highest risk from imminent death due to hypoxemia. However, the trials included in this review suggest otherwise. Of the trials that titrated NO to achieve improved oxygenation (50–53), the lowest and most effective dose was 5–10 ppm in three trials (51–53) and ~13 ppm in the fourth trial (50). These findings are consistent with a detailed dose-response study that found that the average increase in $Pa_{O_2}$ was maximal at 5 ppm (64). Another trial in our review found that as the duration of NO treatment increased, a lower dose (1 ppm) than initially prescribed (10 ppm) was associated with the best improvement in oxygenation (54). In the one trial that randomized patients to doses ranging from 1.25 to 80 ppm, the proportion of patients with an immediate oxygenation response was approximately 60%, with no significant differences among dose arms (49). This trial also found day 28 survival without mechanical ventilation to be highest in the 5 ppm group, which was therefore chosen as the dose in a subsequent large trial (56).

Finally, compared with a meta-analysis based on within-trial subgroups, individual patient data meta-analysis is more robust, since it can adjust for patient-level confounders and can explore effects of NO dose and duration. However, such an analysis is more statistically complex and would face challenges of ensuring complete availability and comparability of data among trials (65, 66). In the case of NO, recent observational data (13–17) suggest that clinicians reserve NO primarily for severe hypoxemia, suggesting that this is the most clinically relevant factor to consider in subgroup analysis. Furthermore, given our findings, it seems unlikely that a more complex analysis would identify subgroups in which NO reduced mortality.

## CONCLUSIONS

In conclusion, our systematic review and meta-analysis extend previous work by finding no beneficial effect of NO on mortality among patients with ARDS, regardless of the severity of hypoxemia at randomization. This subgroup analysis was prespecified, included data verified by primary trial investigators, and included almost all randomized patients eligible for analysis. Although wide CIs preclude the conclusion that NO has absolutely no clinical benefit among severely hypoxemic patients with ARDS, other evidence argues against its use even in this limited population. Such evidence includes an increased risk of renal dysfunction (6), the high cost of NO (10–12), and the existence of alternative approaches (prone ventilation [58] and extracorporeal support [67]) that have stronger evidence for clinical benefit. Given the evidence to date, it is highly unlikely that additional randomized trials of NO in severely hypoxemic patients, using different dosing strategies or duration, will be performed. Therefore, as currently dosed and administered, the routine use of NO in patients with ARDS, regardless of severity, should therefore be abandoned. In rare circumstances in which patients appear to be at great risk of imminent death from hypoxemia despite all other available treatments, NO could be considered.

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