Acute respiratory distress syndrome (ARDS) is a fulminant disease characterized by impaired oxygenation, pulmonary congestion and decreased lung compliance following a direct pulmonary insult, such as aspiration or pneumonia, or a systemic injury, such as sepsis or trauma. In many patients with ARDS, mechanical ventilation can further injure damaged lungs, leading to long-term morbidity and mortality. Although minimizing tidal volumes and optimizing positive end-expiratory pressure (PEEP) may reduce lung injury, mortality associated with ARDS remains high.

Placing patients in the prone position for a portion of time each day during mechanical ventilation, first suggested in 1974, is sometimes used as a protective lung strategy in patients with ARDS. Alveolar distension varies regionally because of gravity and anatomic relationships with the chest wall and heart. In the prone position, the volume of lung collapsed under its own weight and that of the heart is decreased relative to the supine position. Because pulmonary perfusion is preserved in both the ventral and dorsal lung regions, ventilation–perfusion matching is improved in the prone position. More homogenous dispersion of tidal volume in the prone position may minimize alveolar stretch and strain. Improvements in oxygenation may reduce the risk of death from hypoxia.

Early randomized controlled trials (RCTs) of prone positioning did not show reductions in mortality. However, these trials included patients with mild ARDS, the duration of prone positioning each day was short, and protective lung ventilation was not used. A subsequent meta-analysis suggested that prone positioning reduces mortality among patients with severe hypoxemia. Because of the availability of new data, we undertook a systematic review and meta-analysis, in collaboration with the Canadian Critical Care Trials Group, to determine the effect of prone positioning on mortality among patients with ARDS receiving protective lung ventilation.
tion with all of the primary investigators, to determine whether a strategy incorporating the prone position for a portion of each day, compared with supine position alone, decreases mortality among patients with ARDS receiving protective lung ventilation.

**Methods**

**Literature search**

We conducted a systematic review using a previously described protocol with prespecified selection criteria, outcome measures and analysis plan. Amendments to the protocol for the current review are described in Appendix 1 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.140081/-/DC1). We systematically searched multiple sources to identify RCTs that compared prone positioning with supine positioning during mechanical ventilation in patients with ARDS. To identify relevant trials published since the earlier systematic review, we searched the electronic databases MEDLINE, Embase and CENTRAL (the Cochrane Central Register of Controlled Trials) for articles published from June 2009 to August 2013. We also searched the bibliographies of included studies and review articles, as well as the conference proceedings of the American Thoracic Society (1994–2013), the Society of Critical Care Medicine (1994–2013) and the European Society of Intensive Care Medicine (1994–2013). Finally, we searched the ClinicalTrials.gov registry and the Current Controlled Trials database for unpublished and ongoing trials. No language restrictions were applied. Details of our search strategy are described in Appendix 2 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.140081/-/DC1).

**Study selection**

Three of us (S.S., J.O.F. and M.S.), who were not blinded to the study authors or results, independently evaluated the studies for inclusion and resolved differences through consensus.

We included RCTs and quasi-randomized trials (e.g., trials allocating patients in alternating fashion or by hospital registry number) if they met the following criteria: they enrolled adults or postneonatal children with ARDS supported by mechanical ventilation; they used prone positioning in the experimental group and supine positioning alone in the control group; and they reported any of the primary or secondary outcomes described in the next section. We included trials that used either the older or more recent definition of ARDS. For trials that enrolled patients with other forms of hypoxic respiratory failure, we asked the primary investigators to supply mortality data for patients who had ARDS at the time of enrolment.

We excluded crossover trials. We also excluded physiologic studies lasting 48 hours or less, reasoning that a brief intervention period would not affect clinical outcomes.

**Data extraction and quality assessment**

The 3 of us involved in selecting the studies also independently abstracted data on study methods, details of prone positioning and mechanical ventilation, and study outcomes. Disagreements were resolved through consensus.

The primary outcome was all-cause mortality. For each study, mortality was determined at hospital discharge or, if not available, the longest duration of follow-up. For the primary analysis, we included only trials in which all patients received protective lung ventilation (defined as tidal volume < 8 mL/kg of predicted body weight), because we felt studies that did not use protective ventilation might bias results to the null and would be less relevant to current clinical practice. Studies that did not mandate protective lung ventilation were included in the analyses of secondary outcomes.

Secondary outcomes included change in oxygenation and adverse events (ventilator-associated pneumonia, pressure ulcers, obstruction of endotracheal tube, unplanned extubation, unplanned removal of central venous catheters or arterial lines, unplanned removal of chest tubes, pneumothorax and cardiac arrest).

For the assessment of methodologic quality and risk of bias, we abstracted the following data: randomization methods and allocation concealment; number of withdrawals and losses to follow-up after randomization; crossovers between assigned groups; blinding of outcome assessors; and whether the trial was stopped early because of evidence of benefit. We assessed risk of bias using a modified version of the Cochrane risk-of-bias instrument. Because blinding of caregivers, patients and family members was not possible in the trials, we determined whether important co-interventions (e.g., weaning, sedation and paralysis) were standardized or applied equally in the treatment and control groups. We assessed the quality of evidence for our primary outcome using the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation).

Primary investigators collaborated in this systematic review by confirming original trial data, providing previously unpublished data for subgroups of patients, and clarifying data and methods.

**Data synthesis**

We performed 2 subgroup analyses. First, we hypothesized that maximizing the daily duration
of prone positioning would optimize lung protection. We compared trials in which prone positioning was prolonged (≥16 h/d) with those in which the duration was shorter. Second, we hypothesized that prone positioning would be of greater benefit in patients with more severe hypoxemia at baseline. We compared the effect of prone positioning on mortality among patients who had severe hypoxemia (baseline ratio of partial pressure of arterial oxygen to fraction of inspired oxygen [PaO₂/FIO₂ < 100 mm Hg]) with mortality among patients who had moderate hypoxemia (PaO₂/FIO₂ ratio 100–199 mm Hg) and those who had mild hypoxemia (PaO₂/FIO₂ ratio 200–299 mm Hg). 19

Finally, we analyzed the effect of prone positioning on oxygenation by obtaining data on the mean PaO₂/FIO₂ ratios on the first, second and third day after randomization for each treatment group.

We analyzed all outcomes using the intention-to-treat approach. We aggregated outcomes data at the trial level and performed statistical calculations using Review Manager software (RevMan version 5.1; Nordic Cochrane Centre, Cochrane Collaboration, 2011) and Stata software (Stata Statistical Software, release 9.2; StataCorp, 2006). For the pooled analyses, we used random-effects models, which incorporate between-study variation and generally result in wider confidence intervals than fixed-effects models do when heterogeneity is present. We reported continuous outcomes as ratios of means (a measure of relative change) and binary outcomes as risk ratios (RRs). For each subgroup analysis, we tested for interaction between the RR for mortality in each subgroup, which tests the null hypothesis that the treatment effect in each subgroup is the same. All statistical tests were 2-sided. We considered a p value of less than 0.05 to be statistically significant and reported individual trial and summary results with 95% confidence intervals (CIs).

We assessed between-study heterogeneity for each outcome using the F statistic. 21 We considered statistical heterogeneity to be low if the F value was 25%–49%, moderate if 50%–74% and high if 75% or greater.

We assessed publication bias using the Begg rank correlation test 26 and the Peters regression test. 27 Given the low power of these tests, we considered a p value less than 0.1 to indicate publication bias.

Results

Search results and study characteristics

In addition to the 15 RCTs from the previous meta-analysis, 13 we identified 238 potentially eligible reports through searching electronic bibliographic databases. After screening the titles and abstracts and removing duplicate records, we reviewed 22 articles in full. We excluded 11 trials, 6 of which had intervention periods that lasted 48 hours or less, 8–10 which left 11 trials 14–17, 34–40 for the meta-analysis (Figure 1). Reviewers were in total agreement about the included studies.

The characteristics of the 11 included trials are summarized in Table 1 and in Appendix 3 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.140081/-/DC1). A total of 2341 patients were enrolled (median 102, range 16–802); children were included in 1 trial (n = 102). Overall, the median PaO₂/FIO₂ ratio at enrolment was 118 (range 100–326) mm Hg, the median FIO₂ was 73% (range 49%–88%), and the median PEEP was 10 (range 7–13) cm H₂O. The duration of ARDS before enrolment was less than 72 hours in 8 trials; 14,17,34–36 2 studies did not limit the duration before enrolment. 15,16 One trial included 802 patients with acute hypoxemic respiratory failure, of whom 413 had ARDS. Another included 53 patients with a Glasgow Coma Score of 9 or less, of whom 7 had ARDS. All of the RCTs, except one small study, defined ARDS according to the American–European Consensus Conference definition, with varying thresholds for the PaO₂/FIO₂ ratio. Prone positioning was used a median of 17 hours per day (range 4–24 h) for 4.6 days (range 4–10 d) and continued until prespecified criteria for clinical improvement were met (9 trials 14,16,17,34–39) or

![Figure 1: Selection of randomized controlled trials (RCTs) for the meta-analysis. ARDS = acute respiratory distress syndrome.](CMAJ, July 8, 2014, 186(10) E383)
Table 1: Characteristics of randomized controlled trials included in the systematic review*

| Study                  | No. of patients | Enrolment criteria                                                                 | Details of prone positioning | Protective lung ventilation† mandated |
|------------------------|-----------------|------------------------------------------------------------------------------------|------------------------------|---------------------------------------|
|                        |                 | Patient characteristics at baseline                                               |                              |                                        |
|                        |                 | Mean PaO2/FIO2 ratio, mm Hg                                           | Mean PEEP, cm H2O       | Mean FIO2, %                          | Duration of ARDS before enrolment     | Mean duration | Criteria for discontinuation |
|                        |                 |                                                                                   |                              |                                        |
| Guérin et al.17, 2013  | 474             | ARDS‡ with PaO2/FIO2 ratio < 150 mm Hg and PEEP ≥ 5 cm H2O after stabilization period of 12–24 h | 100                          | 10                                     | 79                                     | < 36 h        | PaO2/FIO2 ratio ≥ 150 mm Hg, PEEP ≤ 10 cm H2O and FIO2 ≤ 0.6 | Yes |
| Taccone et al.16, 2009 | 344             | ARDS‡ with PEEP ≥ 5 cm H2O                                                      | 113                          | 10                                     | 72                                     | < 72 h        | FIO2 ≤ 40% and PEEP ≤ 10 cm H2O                                      | Yes |
| Fernandez et al.34, 2008 | 42              | ARDS‡                                                                             | 118                          | 11                                     | 85                                     | < 48 h        | PaO2/FIO2 ratio > 250 mm Hg and PEEP ≤ 8 cm H2O for 12 h                   | Yes |
| Chan et al.35, 2007    | 22              | ARDS‡ secondary to community-acquired pneumonia                                | 109                          | 13                                     | 88                                     | < 72 h        | FIO2 ≤ 40% and PEEP ≤ 10 cm H2O                                      | Yes |
| Mancebo et al.36, 2006 | 142             | ARDS‡ with infiltrates in 4 quadrants on chest radiograph                       | 105                          | 7                                      | 82                                     | < 48 h        | FIO2 ≤ 45% and PEEP ≤ 5 cm H2O                                      | No |
| Curley et al.37, 2005  | 102 children (age 2 wk–18 yr) | Acute lung injury or ARDS‡                                                          | 100                          | 9                                      | 60                                     | < 48 h        | Spontaneous breathing and O2 index < 6                                       | Yes |
| Voggenreiter et al.38, 2005 | 40           | Acute lung injury (duration ≥ 24 h or ARDS‡ (duration ≥ 8 h) with PEEP ≥ 5 cm H2O) | 221                          | 11.5                                   | 49                                     | < 48 h        | PaO2/FIO2 ratio > 300 mm Hg for 48 h                                       | Yes |
| Guérin et al.19, 2004  | 802             | Hypoxemic acute respiratory failure (n = 413 with acute lung injury or ARDS‡)    | 152                          | 8                                      | 66                                     | > 12–24 h     | Clinical improvement¶                                                      | No |
| Beuret et al.20, 2002  | 53              | Coma, intubation required (n = 7 with acute lung injury or ARDS‡)              | NR                           | NR                                     | < 24 h       | Able to sit in chair                                                       | No |
| Watanabe et al.21, 2002 | 16              | PaO2/FIO2 ratio < 200 mm Hg, PEEP > 5 cm H2O 5 d after esophagectomy               | 166**                        | NR                                     | NR                                     | < 24 h       | Not prespecified                                                       | No |
| Gattinoni et al.22, 2001 | 304             | Acute lung injury or ARDS‡ with PEEP ≥ 5 cm H2O                                  | 127                          | 10                                     | 73                                     | Not prespecified | 7 h daily for 4.7 d | None |

Note: ARDS = acute respiratory distress syndrome, FIO2 = fractional concentration of inspired oxygen, NR = not reported, PaO2 = partial pressure of arterial oxygen, PEEP = positive end-expiratory pressure.

*Additional details about the study characteristics are available in Appendix 3 (www.cmaj.ca/lookup/supp/doi:10.1503/cmaj.140081/-/DC1).
†Tidal volume < 8 mL/kg of predicted body weight.
‡Defined according to the criteria of the American–European Consensus Conference.¶
§Defined by 1 major criterion (improvement in PaO2/FIO2 ratio ≥ 30% relative to value at randomization, with FIO2 ≤ 60%) and at least 1 minor criterion (PEEP ≤ 8 cm H2O, no sepsis, cause of acute respiratory failure under control [stable or signs of improvement on chest radiograph, and < 3 organ dysfunctions, including lung dysfunction]).
**Proone group only (baseline ratio in supine group not reported).
after a prespecified duration (2 trials\(^14,16\)). Six trials
\((n = 1016)\) mandated protective lung ventilation in both study groups. Six studies\(^14,16,17,34,36,39\) permitted “rescue” prone positioning according to prespecified criteria for life-threatening hypoxemia in patients randomly assigned to the supine position. Protocols or guidelines for mechanical ventilation were used in 6 trials.\(^14,16,17,34,36,39\) Five trials permitted “rescue” prone positioning according to prespecified criteria for life-threatening hypoxemia in patients randomly assigned to the supine position. Protocols or guidelines for mechanical ventilation were used in 6 trials.\(^14,16,17,34,36,39\) Five of the 6 RCTs that mandated protective lung ventilation followed patients until discharge from hospital or a minimum of 90 days; the other trial\(^37\) followed patients until hospital discharge or 28 days, whichever occurred first.

The risk of bias was low in 6 trials, high in 2 and unclear in 3 (Table 2). Using GRADE methodology,\(^23\) we found that the quality of evidence for the primary outcome of all-cause mortality was high (see Appendices 4 and 5, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.140081/-/DC1). All of the RCTs analyzed outcomes by assigned group. Seven studies were ended early because of slow recruitment\(^34,36,38,39\) or on the basis of a stopping rule for futility.\(^37\) One trial at high risk of bias did not report mortality.\(^40\) For the primary outcome, there was no loss to follow-up in 4 trials.\(^17,35,37,38\) In the remaining 6 trials, less than 5% of patients were lost to follow-up (12/802, \(\%\) 6/142, \(\%\) 6/344, \(\%\) 2/42, \(\%\) 2/53 39 and 7/304 \(\%\)). Crossovers occurred in 8 trials\(^14−17,34,36,37,39\) (range 4%–32% of all patients), which involved 0%–41% of patients initially assigned to prone positioning and 0%–21% of those assigned to the supine group.

There was no evidence of publication bias (\(p = 0.4\) with Begg rank correlation test; \(p = 0.5\) with Peters regression test).

| Study                | Adequate sequence generation | Concealment of allocation | Complete outcome reporting | Complete outcome data | Trial ended early (reason) | Overall risk of bias* |
|----------------------|------------------------------|----------------------------|---------------------------|-----------------------|---------------------------|-----------------------|
| Guérin et al., \(^17\) 2013 | Yes                          | Centralized, Web-based     | Yes                       | Yes                   | No                        | Low                   |
| Taccone et al., \(^14\) 2009 | Yes                          | Central                    | Yes                       | No (mortality unknown for 1/175 in supine group, 1/169 in prone group) | No                        | Low                   |
| Fernandez et al., \(^14\) 2008 | Yes                          | Central                    | Yes                       | No (mortality unknown for 1/20 in supine group, 1/22 in prone group) | Yes (slow enrolment)     | Low                   |
| Chan et al., \(^35\) 2007     | Yes                          | No (randomization table visible to person enrolling patients) | Yes                       | Yes                   | Yes (slow enrolment)     | High†                 |
| Mancebo et al., \(^36\) 2006  | Yes                          | Sealed opaque envelopes     | Yes                       | No (mortality unknown for 2/62 in supine group, 4/80 in prone group) | Yes (slow enrolment)     | Unclear†               |
| Curley et al., \(^37\) 2005   | Yes                          | Sealed opaque envelopes     | Yes                       | Yes                   | Yes (futility stopping rule) | Low                   |
| Voggenreiter et al., \(^38\) 2005 | Yes                          | Central                    | Yes                       | Yes                   | Yes (slow enrolment)     | Low                   |
| Guérin et al., \(^16\) 2004   | Yes                          | Sealed opaque envelopes     | Yes                       | No (mortality unknown for 7/385 in supine group, 4/417 in prone group) | No                        | Unclear†               |
| Beuret et al., \(^39\) 2002   | Yes                          | Sealed opaque envelopes     | Yes                       | No (mortality unknown for 2/28 in supine group, 0/25 in prone group) | Yes (slow enrolment)     | Unclear†               |
| Watanabe et al., \(^40\) 2002  | Yes                          | No (alternate allocation)   | No (alternate allocation) | No mortality data     | NA                        | NR                    | High†                 |
| Gattinoni et al., \(^15\) 2001 | Yes                          | Central                    | Yes                       | Yes                   | Yes (slow enrolment)     | Low                   |

Note: NA = not applicable, NR = not reported.

*The Cochrane risk-of-bias tool\(^22\) was used to assess the risk of bias for each study. Low risk = bias, if present, is unlikely to alter the results seriously, unclear risk = bias raises some doubt about the results, high risk = bias may alter the results seriously.

†High risk of bias because of unclear allocation\(^34,36,38,39\) or alternate allocation.\(^40\)

Unclear risk of bias because of multiple possible sources of plausible bias: protective lung ventilation not mandated in both study arms,\(^16,36,39\) incomplete mortality data,\(^16,36,39\) early study termination\(^14,16\) and excessive crossover from prone to supine group (> 40%).\(^16\)
Effect on mortality

The 6 RCTs that mandated protective lung ventilation were included in the primary analysis.14,17,34,35,37,38 They all had a low risk of bias except one trial35 (n = 22), which had a high risk of bias because allocation was not concealed. Mortality was reduced with the use of prone positioning (RR 0.74, 95% CI 0.59–0.95; I² = 29%) compared with use of the supine position alone (Figure 2). Using a random-effects risk-difference model, we estimated that the number needed to treat to save 1 life was 11 (95% CI 6–50). Our findings remained unchanged in several sensitivity analyses that tested alternative assumptions (Table 3).

Conversely, there was no effect of prone positioning on mortality in the 4 trials that permitted higher tidal volumes than currently recommended (RR 0.98, 95% CI 0.86–1.12; I² = 0%), which differed when compared with trials using protective lung ventilation (interaction p = 0.05).

A priori subgroup analyses are summarized in Figure 3. All-cause mortality was reduced when the daily duration of prone positioning was prolonged (RR 0.77, 95% CI 0.64–0.92; I² = 21%) but not when the daily duration was shorter. Only 1 of the 6 trials with a prolonged duration did not use protective lung ventilation.36 Prone positioning reduced all-cause mortality among patients with severe hypoxemia at baseline (RR 0.76, 95% CI 0.61–0.94; F = 0%). In the subgroups of patients with mild and moderate hypoxemia, prone positioning did not significantly reduce mortality, and statistical heterogeneity increased in the group with moderate hypoxemia (F = 42%). The test for interaction was significant for the analyses according to use of protective lung ventilation and daily duration of prone positioning, but not for the analysis according to degree of hypoxemia.

Effect on secondary outcomes

Improvements in oxygenation were greater in the prone group than in the supine group, with PaO₂/FIO₂ ratios increasing by 25%–36% during the first 3 days after randomization (Table 4). Moderate heterogeneity was detected for the analysis of PaO₂/FIO₂ ratio on day 1 (I² = 49%) and day 2 (I² = 27%), but not on day 3 (I² = 0%).

The risk of pressure ulcers, obstruction of the endotracheal tube and dislodgement of the thoracostomy tube was higher among patients placed in the prone position than among those in the supine group. There was no difference in other adverse events between the 2 groups (Table 4).
Interpretation

Our analysis of high-quality evidence showed that prone positioning during mechanical ventilation reduces mortality among patients with ARDS receiving protective lung ventilation. The quality of evidence was high, and the number needed to treat to save one life was 11 (95% CI 6–50). Our findings complement those of a recent positive RCT and showed consistency of effect across previous RCTs and in the sensitivity analyses.

Most RCTs of prone positioning during mechanical ventilation in patients with ARDS failed on their own to show statistically significant reductions in mortality despite improvements in oxygenation. Previous systematic reviews were similarly unable to show reductions in mortality, although some suggested a mortality benefit among sicker patients. Limitations of earlier trials, including use of injurious tidal volumes (> 8 mL/kg of predicted body weight), enrollment of patients with mild ARDS and inadequate duration of prone positioning.

### Table 3: Results of primary and sensitivity analyses for the effect of prone positioning during mechanical ventilation on mortality among patients with acute respiratory distress syndrome (ARDS)

| Analysis* | No. of trials | No. of deaths, n/N | Risk ratio (95% CI) | $I^2$ value, % |
|-----------|---------------|-------------------|---------------------|----------------|
| Primary   |               |                   |                     |                |
| Trials mandating protective ventilation† | 6 | 363/1016 | 0.74 (0.59–0.95) | 29 |
| Sensitivity |               |                   |                     |                |
| Included all trials‡ | 10 | 797/1869 | 0.86 (0.73–1.00) | 42 |
| Assumed patients lost to follow-up lived | 6 | 363/1020 | 0.74 (0.59–0.95) | 28 |
| Assumed patients lost to follow-up died | 6 | 366/1020 | 0.74 (0.59–0.94) | 26 |
| Excluded trial in which allocation was not concealed35 | 5 | 352/994 | 0.73 (0.55–0.98) | 43 |
| Excluded trial with pediatric population37 | 5 | 355/914 | 0.73 (0.56–0.96) | 42 |
| Included trial that used moderate tidal volume (< 10 mL/kg)36 | 7 | 438/1152 | 0.77 (0.65–0.91) | 16 |
| Fixed-effects model | 6 | 363/1016 | 0.74 (0.63–0.87) | 29 |

Note: CI = confidence interval.

*Random-effects models were used for all analyses except in the final sensitivity analysis.
†Tidal volume < 8 mL/kg of predicted or actual body weight.
‡For the 2 trials that enrolled some patients without ARDS16,39 we included only patients whose condition met the authors’ definition of ARDS; when the analysis was redone to include all patients in these trials, the risk ratio changed minimally (0.87, 95% CI 0.74–1.02; $I^2 = 48\%$).

### Figure 3: Effect of prone positioning during mechanical ventilation on all-cause mortality according to prespecified patient-level and trial-level subgroups.

Risk ratios less than 1.0 indicate a decreased risk of death with prone positioning. *Severe hypoxemia = ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (Pao2/Fio2) < 100 mm Hg; moderate = Pao2/Fio2 ratio 100–199 mm Hg; mild = Pao2/Fio2 ratio 200–299 mm Hg. CI = 95% confidence interval, RR = risk ratio. Baseline Pao2/Fio2 ratios were unavailable for 10 patients in 3 trials.17,34,43
Research may have reduced the “signal” and increased “noise.” A recent RCT found a large reduction in mortality among patients with moderate to severe ARDS who were placed in the prone position for 16 hours per day and had protective lung ventilation.17 In our systematic review, we similarly reduced “noise” by limiting the primary analysis to trials mandating low tidal volumes and enrolling patients with moderate to severe ARDS; most trials also used long daily durations of prone positioning, which may have enhanced the “signal.”

Our finding that prone positioning decreased mortality and improved oxygenation is consistent with results of prior observational and experimental studies,9,30,44 which showed that prone ventilation improves recruitment of collapsed alveoli. Use of the prone position reduced mortality in the subgroup of patients who had severe hypoxemia at baseline (PaO2/FIO2 ratio < 100 mm Hg), with minimal statistical heterogeneity, a finding that is consistent with our previous systematic review.13 However, we found no evidence that the prone position had a differential effect according to severity of hypoxemia, acknowledging the limited number of patients with mild to moderate hypoxemia. Future trials may help to clarify the effects of prone positioning in patients with mild to moderate ARDS.

Prone positioning during mechanical ventilation is not without risks. Our study showed that patients in the prone group were at increased risk of pressure ulcers, obstruction of the endotracheal tube and dislodgement of the thoracostomy tube. Although there was no significant difference in the occurrence of other complications between the prone and supine groups, these adverse events may occur more frequently in centres with less experienced personnel who use prone positioning infrequently. Furthermore, the perceived risk of prone positioning and the impact on other aspects of critical care such as enteral feeding and sedation45−47 may prevent implementation of this manoeuvre in centres that do not frequently care for patients with severe ARDS. The increased risk of certain adverse outcomes underscores the need to have protocols for using prone positioning and to have adequate training and, when these are not available, to consider referring patients to centres with expertise. Future research is needed to address whether referring patients with severe ARDS early to experienced centres for prone positioning or other adjunctive therapies improves their outcomes.48,49

Limitations
Although we found high-quality evidence using rigorous methodology, our systematic review has limitations. Several trials were terminated early

| Table 4: Physiologic, clinical and safety outcomes associated with prone positioning during mechanical ventilation |
|---------------------------------|-----------------|-----------------|-------|
| Outcome                        | No. of patients | Measure of effect* | I² value, % |
|--------------------------------|-----------------|-----------------|-------|
| Oxygenation (PaO2/FIO2 ratio)†  | No. of patients | Ratio of means (95% CI) |       |
| Day 1                          | 1283            | 1.36 (1.25–1.47) | 49    |
| Day 2                          | 1171            | 1.29 (1.21–1.37) | 27    |
| Day 3                          | 933             | 1.25 (1.18–1.31) | 0     |
| Clinical and safety outcomes   | No. of events, n/N | Risk ratio (95% CI) |     |
| Ventilator-associated pneumonia| 368/1561        | 0.89 (0.71–1.13) | 0     |
| Pressure ulcers                | 818/1765        | 1.27 (1.16–1.40) | 0     |
| Obstruction of endotracheal tube| 200/1847        | 1.60 (1.27–2.02) | 0     |
| Unplanned extubation or dislodgement of endotracheal tube† | 211/2309        | 1.08 (0.78–1.48) | 16    |
| Unplanned removal of central or arterial lines | 59/886 | 1.49 (0.42–5.27) | 67    |
| Dislodgement of thoracostomy tube | 17/886 | 3.14 (1.02–9.69) | 0     |
| Pneumothorax                   | 95/1663         | 0.84 (0.57–1.25) | 0     |
| Cardiac arrest                 | 211/1527        | 0.73 (0.39–1.38) | 76    |

Note: CI = confidence interval, PaO2/FIO2 ratio = ratio of partial pressure of arterial oxygen to fraction of inspired oxygen.

*Rando**-effects models were used for all analyses.
†We measured effect on oxygenation by comparing the mean PaO2/FIO2 ratio in the prone group to the closest available recorded measurement in the supine group. If more than one measurement was taken, we chose the measurement closest to the end of the session of prone positioning on that day.
‡One trial included all dislodgements of endotracheal tubes, not just unplanned extubations. When we excluded the results of this trial from the meta-analysis, the risk ratio for unplanned extubation was 0.86 (95% CI 0.62–1.20; F = 0%; 9 trials, 1471 patients, 129 events).
because of slow enrolment, which reduced statistical power. However, none of the trials was stopped early because of a beneficial effect.80

The trials were diverse with respect to inclusion criteria, daily duration of prone positioning and use of protocols for other aspects of ventilator management (e.g., weaning and sedation). Trials in which the daily duration of prone positioning was prolonged tended to be recent and overlapped with those that used protective lung ventilation. It was therefore difficult to identify the precise aspect of the patient population or the protocol for prone positioning most responsible for improved survival. Nevertheless, statistical heterogeneity was low for our primary outcome. Five of the 6 trials included in the primary analysis had risk ratios that pointed toward a benefit of prone positioning.

Several trials reported crossover of patients between the prone and supine groups. We analyzed all outcomes on an intention-to-treat basis, which would have underestimated the effect of prone positioning on mortality.

Although we searched for RCTs with either an adult or a pediatric study population, we found only one small trial that had enrolled children. An adequately powered RCT would be helpful to confirm our findings in children with ARDS.

Our findings are based on relatively few trials, some of which enrolled small numbers of patients and accrued few outcome events, which may have reduced precision and underestimated heterogeneity. The duration of follow-up in the included studies was short, and few examined the impact of prone positioning on long-term survival and quality of life.

Finally, all of the studies included in our primary analysis limited the duration of ARDS before enrolment, which made it difficult to ascertain whether prone positioning was beneficial if started late or as a rescue intervention for patients with life-threatening hypoxemia.

Conclusion

Our analysis of high-quality evidence showed that mechanical ventilation in the prone position significantly reduced mortality among patients with ARDS who received protective lung ventilation. This technique was beneficial to patients with moderate to severe ARDS when used for prolonged periods of 16 hours or more each day.

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