REVIEW ARTICLE

Scandinavian clinical practice guideline on mechanical ventilation in adults with the acute respiratory distress syndrome

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Background: The objective of the Scandinavian Society of Anaesthesiology and Intensive Care Medicine (SSAI) task force on mechanical ventilation in adults with the acute respiratory distress syndrome (ARDS) is to formulate treatment recommendations based on available evidence from systematic reviews and randomised trials.

Methods: This guideline was developed according to standards for trustworthy guidelines through a systematic review of the literature and the use of the Grading of Recommendations Assessment, Development and Evaluation system for assessment of the quality of evidence and for moving from evidence to recommendations in a systematic and transparent process.

Results: We found evidence of moderately high quality to support a strong recommendation for pressure limitation and small tidal volumes in patients with ARDS. Also, we suggest positive end-expiratory pressure (PEEP) > 5 cm H2O in moderate to severe ARDS and prone ventilation 16/24 h for the first week in moderate to severe ARDS (weak recommendation, low quality evidence). Volume controlled ventilation or pressure control may be equally beneficial or harmful and partial modes of ventilatory support may be used if clinically feasible (weak recommendation, very low quality evidence). We suggest utilising recruitment manoeuvres as a rescue measure in catastrophic hypoxaemia only (weak recommendation, low quality evidence). Based on high-quality evidence, we strongly recommend not to use high-frequency oscillatory ventilation. We could find no relevant data from randomised trials to guide decisions on choice of FiO2 or utilisation of non-invasive ventilation.

Conclusion: We strongly recommend pressure- and volume limitation and suggest using higher PEEP and prone ventilation in patients with severe respiratory failure.

An electronic version of this guideline can be accessed at www.ssai.info/guidelines/

• What other guideline statements are available on this topic?

Recommendations for mechanical ventilation in ARDS can be found in UpToDate* and the surviving sepsis campaign guidelines†

• Why was this guideline developed?

This guideline was developed as part of a greater programme under SSAI to create a body of evidence-based guidelines relevant to Nordic anaesthesiologists. Guidelines for the management of the most common forms of organ failure in critical care are an important part of this work.

• How does this statement differ from existing guidelines?

This guideline statement aims to provide Nordic anaesthesiologists with recommendations for the mechanical ventilation of patients with ARDS. Available evidence is presented in a transparent manner to stimulate informed decision making in clinical practice. Recommendations are presented in accord with the latest standards developed by the GRADE working group. The items listed may differ from those found in other guideline statements.

• Why does this statement differ from existing guidelines?

The policy endorsed by SSAI is to issue guideline-statements that are informative and largely free of expert opinion.

Editorial comment: what this article tells us

The task force strongly recommends pressure and volume limitation and suggests using higher PEEP and prone ventilation in patients with severe respiratory failure. Recruitment manoeuvres may significantly improve oxygenation and lung aeration, particularly in the acute stage of ARDS, but clinical benefit has yet to be clearly proven except for prone position that may be regarded as a recruitment manoeuvre.

Management of the acute respiratory distress syndrome (ARDS) is of major importance in modern intensive care units (ICUs). According to recent surveys, patients with ARDS constitute 25–50% of patients in European intensive care units and with an associated mortality of 20–50%. Following its identification by Ashbaugh in 1967,[1] ARDS was defined by an American-European Consensus Conference in 1994.[2] This definition was recently revised in what is now known as the Berlin definition.[3] Briefly, ARDS is presently defined as hypoxemic respiratory failure, classified as mild (26.6 kPa < PaO2/FIO2 ≤ 40 kPa), moderate (13.3 kPa < PaO2/FIO2 ≤ 26.6 kPa), and severe (PaO2/FIO2 ≤ 13.3 kPa) (Table 1). The pathophysiology of ARDS is an evolving concept that involves the inflammatory cascade, fluid dynamics, lung mechanics, and the pulmonary circulation.[4] Recently, both phenotypic and genotypic categorisation has added to our understanding of ARDS.[5,6] Apart from lung mechanics, the manner in which pathophysiological insight will influence therapy in ARDS is still unclear.

Consequently, studies of ARDS suffer from heterogeneity regarding the underlying disease process and also the timing of inclusion following ARDS development. Clinical trials of mechanical ventilation have focussed on how to achieve the right balance between adequate oxygenation and ventilation in patients with ARDS, and simultaneously avoiding further damage to the lungs. This guideline is authored by a task force on mechanical ventilation in adults with ARDS. The work was initiated by the Clinical Practice Committee of the Scandinavian Society of Anaesthesia and Intensive Care Medicine (SSAI), and it summarises best current available research evidence and provides recommendations according to new standards for trustworthy guidelines outlined by the Institute of Medicine and the Guideline Inter-

*Siegel MD Acute respiratory distress syndrome: Supportive care and oxygenation in adults. UpToDate. http://www.uptodate.com [Accessed 25 April 2014].

†The surviving sepsis campaign guidelines: Other Supportive Therapy of Severe Sepsis. http://www.survivingsepsis.org/Guidelines/ [Accessed February 2013].

Table 1 The Berlin definition of the Acute Respiratory Distress Syndrome (ARDS)[3].

ARDS is characterised by the following four criteria:

1. Lung injury of acute onset, within 1 week of an apparent clinical insult and with progression of respiratory symptoms
2. Bilateral opacities on chest imaging not explained by other pulmonal pathology (e.g. pleural effusions, lung collapse, or nodules)
3. Respiratory failure not explained by heart failure or volume overload
4. Decreased arterial PO2/FiO2 ratio:
   - Mild ARDS: ratio is 201–300 mmHg (≤ 39.9 kPa)
   - Moderate ARDS: 101–200 mmHg (≤ 26.6 kPa)
   - Severe ARDS: ≤ 100 mmHg (≤ 13.3 kPa)

(A minimum PEEP of 5 cm H2O is required; it may be delivered non-invasively with CPAP to diagnose mild ARDS).

national Network and according to methodology developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group, now endorsed by the board of SSAI.[7–9] Other authoritative sources such as UpToDate and the Surviving Sepsis Campaign have also applied GRADE in their guidelines for mechanical ventilation of adults in acute respiratory distress syndrome.[10,11]

Methods

Guideline task force

Members of the guideline task force were selected by the national societies of anaesthesiology in Denmark, Finland, Iceland, Norway, and Sweden, following invitation from the Clinical Practice Committee of the SSAI.

GRADE

In our development of recommendations, we used the GRADE system for formulating clinical questions, assessing the quality of evidence, generating anticipated absolute effects, and for moving from evidence to recommendations. Briefly, clinical questions were formulated in the so-called PICO format, which identify the relevant patient population and/or clinical problem (P), the intervention (I) under scrutiny as well as the comparator (C), and important outcomes (O) (Table 2).

For literature review, we first searched the McMaster PLUS database to identify high-quality systematic reviews. If no recent high quality systematic reviews were found, we searched the following databases: PubMed, Embase, Google Scholar, and the Cochrane Library for evidence (Online Appendix). When available, published systematic reviews were used to identify relative effect estimates and assess the quality of evidence for the important outcomes. In keeping with the GRADE methodology, the quality of evidence for an intervention (i.e. our confidence in the effect estimates) was rated down for identified risks of bias (e.g. due to lack of blinding, or early termination of studies), inconsistency (i.e. unexplained heterogeneity), and indirectness (e.g. different patient populations or use of surrogate outcomes) and imprecision (wide confidence interval around the effect estimate). Importantly, however, when the outcome in question was death at any stage, we did not downgrade evidence due to lack of blinded outcome assessment. Accordingly, quality of evidence was rated from 'high' to 'very low'. Recommendations were based on the PICO questions where we identified randomised trials, and this guideline does not offer any recommendations that are not defined by these. Also, we do not propose any recommendation based on non-randomised trials, observational studies, or physiological knowledge. When moving from evidence to recommendations, four factors were considered and integrated: Benefits and harms, quality of evidence, values and preferences (of patients or their proxies), and cost considerations. GRADE classifies recommendations as strong when virtually all informed patients or proxies would choose the recommended management strategy. Weak recommendations, which reflect a close call between benefits and harms, uncertainty regarding treatment effects, questionable cost-effectiveness, or variability in values and

Table 2 Clinical problems and PICO questions used to assess evidence relevant to this guideline statement.

	PICO Question			
Informal clinical question	Population (P)	Intervention (I)	Comparator (C)	Outcomes (O)
1. Should pressure and volume limitation (PVL) be used in patients with ARDS? • Should small tidal volumes always be used in ARDS? • Should plateau pressure always be kept low? (i.e. < 31 cm H2O)	Mechanically ventilated adults with acute respiratory distress syndrome (ARDS)	Pressure and volume limitation (PVL) • Small tidal volumes (5–8 ml/kg) • Plateau pressure < 31 cm H2O	Conventional ventilation • Large tidal volumes (10–12 ml/kg) • Plateau pressure = > 31 cm H2O	Mortality • 28/30 days • 60–180 days • ICU • Hospital • Duration of study
2. Should PEEP be set to a high or low level?		High PEEP • > 5 cm H2O	Low PEEP • < = 5 cm H2O	Oxygenation efficiency Barotrauma
3. What FiO2 should be used?		Higher FiO2	Lower FiO2	Length of stay in ICU
4. Should non-invasive ventilation be used in ARDS?		Non-invasive ventilation	Invasive ventilation	Ventilator-free days Days of mechanical ventilation
5a. Should mechanical ventilation be spontaneous or controlled?		Ventilator modes that allow spontaneous breathing	Fully controlled ventilation	Use of rescue therapies
5b. Should mechanical ventilation be pressure controlled or volume controlled?		Pressure controlled ventilation	Volume controlled ventilation	
6. Should patients be ventilated in the prone position?		Prone ventilation during = > 50 % of each ICU-day	Ventilation in the supine position only	
7. Should lung recruitment manoeuvres be utilised in ARDS?		Lung recruitment manoeuvres	No lung recruitment manoeuvres	
8. Should high frequency oscillatory ventilation (HFOV) be used in ARDS?		HFOV	Conventional mechanical ventilation	

preferences, apply when fully informed patients would choose different management strategies.[9,12]

The group agreed upon the recommendations in this document. Strong recommendations were given the wording 'we recommend', and weak recommendations 'we suggest'.

Results

Table 3 gives recommendation statements and key information underlying the recommendations. We provide GRADE evidence profiles and Forest plots of meta-analyses in the Online Appendix. The baseline risk presented in tables was consistently derived from the control arms in the trials included. Recommendations are mainly based on absolute risk of death, being the most critical patient important outcome. Death at some pre-specified time-point following inclusion is also the primary end point of the included studies. Time to follow-up is variable, however, ranging from 28–30 days to 180 days (or ICU and hospital mortality). With respect to secondary end points, these are extremely diverse, inconsistently reported, and often difficult to interpret with any accuracy.

Recommendation 1

Pressure and volume limitation

We recommend use of pressure limitation and small tidal volumes in patients with ARDS (strong recommendation, moderate quality evidence). The rationale for limiting ventilator pressures and volumes in ARDS has been detailed in numerous reviews and is supported by experimental and clinical evidence.[13] A recent Cochrane review was used for our analysis.[14] We found evidence of moderately high quality for a large effect on mortality. Quality of evidence was only downgraded for inconsistency because of significant heterogeneity between trials (effect on mortality mainly observed in trials where mean plateau pressure was > 31 cm H2O in the control groups) (Online Appendix; Table S1, Fig. S1).

Recommendation 2

Positive end-expiratory pressure

We suggest using positive end-expiratory pressure (PEEP) to improve oxygenation and to prevent atelectasis in all mechanically ventilated patients with respiratory failure (weak recommendation, low quality evidence). The evidence summarised in two recent systematic reviews suggests that any mortality benefit of higher PEEP (> 5 cm H2O) is limited to patients with moderate to severe ARDS (GRADE 2B).[15,16] High PEEP is safe and does not impact on length of stay in patients with moderate to severe ARDS (Online Appendix; Table S2, Fig. S2).

Recommendations 3–4

FiO2, non-invasive ventilation

We decided not to issue recommendations for these questions, as we could find no trial data to support firm decisions on choice of fraction of inspired oxygen (FiO2) or non-invasive ventilation. To the best of our knowledge, there are no trials testing the upper and lower limits and potential harms of either the FiO2 or the arterial oxygen content in patients with acute respiratory failure. There are no randomised clinical trials that compare non-invasive ventilation to invasive ventilation in ARDS.[17]

Recommendation 5

Ventilator mode

1. We suggest that both pressure and volume-regulated ventilation may be used in mechanically ventilated patients with ARDS (weak recommendation, low quality evidence). We were able to identify three randomised trials that compared volume controlled ventilation (VC) with pressure controlled ventilation (PC).[18–20] In general, the quality of evidence for the identified outcomes was very low, and precludes any recommendation of one mode over the other, although one study with severe methodological issues (experimental and control different from start; one group sicker) demonstrated lower hospital mortality with PC.[20] We suggest that both modes of ventilation are equally beneficial or detrimental, and that both modes can be used at the discretion of the attending physician.
2. We suggest that partial modes of ventilatory support may be used if clinically feasible (weak recommendation, very low quality

Table 3 Key recommendations and quality of evidence.

Recommendation	Strength of recommendation	Benefits and harms	Quality of evidence Reason(s) for downgrading	Preferences and values	Resources
Pressure and volume limitation (PVL) During mechanical ventilation, we suggest utilisation of: • Small tidal volumes (5–8 ml/kg)* *and* • Plateau pressure < 31 cm H2O	**S**trong due to large effect on mortality	In patients treated with PVL in preference to conventional ventilation, significantly more patients are likely to be alive at hospital discharge, and at up to 180 days of follow-up, without any significant increase in barotrauma or length of mechanical ventilation.	Moderate to high due to inconsistency	All or nearly all patients or proxies would accept the intervention, given the potential survival benefit and the low rate of serious complications.	No issues
High PEEP (> 5 cm H2O)† In patients with moderate to severe ARDS‡, we suggest increasing PEEP to improve oxygenation efficiency	Weak	Higher PEEP improves oxygenation efficiency without any significant increase in barotrauma, but may increase duration of mechanical ventilation and LOS-ICU, and has no demonstrable effect on mortality.	Moderate due to risk of bias, inconsistency, indirectness	Most patients or proxies would accept the intervention, given the low rate of serious complications.	Increased LOS-ICU may divert resources from other patients.
FiO2	No recommendation		No relevant data		
Non-invasive ventilation	No recommendation		No relevant data		
Ventilator modes that allow spontaneous breathing	Weak		Very low		
Ventilator mode We suggest that for controlled ventilation, volume controlled and pressure controlled ventilation is equally beneficial or detrimental.	Weak	Effect estimates on mortality, ventilator-free days, LOS-ICU and barotrauma are uncertain due to a sparsity of data.	Very low Our confidence in the effect-estimates is very low, rated down due to inconsistency, imprecision.		
Prone positioning We suggest that patients with ARDS be treated in the prone position for at least 16 h per day in preference to supine position for the first 7 days.	Weak	In 1000 patients treated with prone position in preference to supine position, 57 more patients are likely to be alive at day 90, without any significant increase in barotrauma or ICU days.	Very low Our confidence in the effect-estimates is very low, rated down due to indirectness, inconsistency, imprecision.	Most patients would accept the prone position, given the potential survival benefit and the low rate of serious complications.	The authors deem the extra cost associated with the intervention negligible compared to the total cost.
Recruitment manoeuvres We suggest that recruitment manoeuvres may be used as a rescue measure in catastrophic hypoxaemia	Weak	Recruitment manoeuvres improves oxygenation efficiency without any significant increase in barotrauma, but has no demonstrable effect on mortality.	Very low Our confidence in the effect-estimates is very low, rated down due to inconsistency, imprecision.	Where hypoxaemia by itself is immediately life threatening, most patients and care-givers would accept any available measure that relieves hypoxemia if not known to increase the risk of death	
High-frequency oscillatory ventilation (HFOV) We suggest that HFOV should not be used in patients with ARDS	Strong	HFOV has no demonstrable effect on mortality. Two recent multi-centre trials show either no effect or increased mortality when compared with pressure and volume limited ventilation. HFOV results in increased length of stay.	High		Costs include purchasing of oscillators and education of personnel.

*Predicted body weight (kg): Male patients: 50 + 0.91 × (centimetres of height – 152.4); female patients 45.5 + 0.91 × (centimetres of height – 152.4).
†We suggest that PEEP is set either (a) from tables of predefined levels of corresponding FiO2 and PEEP, or (b) as high as possible with respect to the principles of lung protective ventilation (higher PEEP), or as low as possible with respect to oxygenation (lower PEEP), respectively.
‡Moderate or severe ARDS (P/F ≤ 26.6 kPa or 200 mmHg): High PEEP. Mild ARDS (26.6 kPa or 200 mmHg < P/F ≤ 40 kPa or 300 mmHg): Conventional (lower) levels of PEEP.[2]
LOS-ICU, length of stay in intensive care unit.

evidence). Partial ventilatory support (i.e. various degrees of spontaneous ventilation) has been investigated in several studies but only few randomised trials. A systematic review by McMullen et al.[21] identified two randomised trials that compared airway pressure release ventilation with pressure controlled ventilation[22] or synchronised intermittent mandatory ventilation with pressure support.[23] Any conclusion is hampered by lack of adequate control groups in the chosen RCTs and also lack of power to assess mortality, but additional data described in the McMullen review, including experimental studies, suggest that partial support modes of ventilation may improve oxygenation, improve haemodynamics, and decrease need for sedation (Online Appendix; Table S3, Fig. S3).

Recommendation 6

Prone ventilation

We suggest use of ventilation in the prone position for 16/24 h for the first week in moderate to severe ARDS (weak recommendation, low quality evidence). This recommendation is based on the review by Abroug et al.[24] with data from Guérin et al.[25] added to the dataset. There is considerable heterogeneity between included trials. Also, the routine use of neuromuscular blockade (NMB) in later trials of prone ventilation has caused us to rate down the quality of the evidence due to *indirectness*. Our reasoning is that NMB may alter lung mechanics sufficiently to caution against a general application of these results to ARDS patients who are ventilated without NMB. However, prone ventilation appears to be safe and may reduce time on mechanical ventilation compared with ventilation in the supine position only (Online Appendix; Table S4, Fig. S4).

Recommendation 7

Recruitment manoeuvres

We suggest utilising recruitment manoeuvres as a rescue measure against catastrophic hypoxaemia (i.e. when hypoxia in itself is considered to be immediately life threatening) (weak recommendation, low quality evidence). Hodgson et al. recently reviewed the evidence for use of recruitment manoeuvres in ARDS.[26] The authors found no evidence that recruitment manoeuvres reduce mortality or length of ventilation in patients with ARDS. However, a more recent meta-analysis showed that recruitment manoeuvres did significantly increase oxygenation above baseline levels for a short period of time in four of the five studies that measured oxygenation[27] (Online Appendix; Table S5, Fig. S5).‡

Recommendation 8

High-frequency oscillatory ventilation

We recommend against the use of high-frequency oscillatory ventilation (HFOV) (strong recommendation, high-quality evidence). This recommendation is based on the systematic review from Sud et al.[28] with the addition of trial data from two new multicentre trials.[29,30] One study included in the systematic review was removed by us because it is a study in paediatric patients.[31] There is considerable heterogeneity between included trials with respect to the primary end point. However, two large, recently published studies that compared HFOV to volume and pressure-limited ventilation found either no effect or harm from HFOV (Online Appendix; Table S6, Fig. S6).[29,30]

Discussion

In adopting the GRADE-system for its guideline development, the SSAI has emphasised that guidelines should inform readers about current best evidence and avoid advice based solely on expert opinion. Also, this guideline statement avoids reference to observational studies, a huge part of the critical care literature. Such studies are well suited for generating hypotheses, and are therefore an important source of information for the Scandinavian Critical Care Trials Group (SCCTG).

We could use existing high-quality systematic reviews of randomised trials for most of this work. However, in assessing the evidence base for ventilation modes and FiO2, no relevant meta-analyses or systematic reviews were found. Also,

‡Following submission of this guideline, Suzumura et al. published an updated systematic review of the evidence for utilisation of recruitment maneuvers in ARDS.[27] These data will be fully incorporated into later versions of this guideline.

we updated and revised a dataset from an existing meta-analysis of high-frequency oscillatory ventilation to include to later high-quality trials. Existing systematic reviews of non-invasive ventilation do not include data relevant to this guideline.[17]

Both primary and secondary end points are inconsistently reported in the ARDS literature. In selecting the most relevant outcomes across several studies, even mortality can be difficult to assess because authors have chosen different length of follow-up, some studies report only percentages (instead of numbers), and even mortality rates adjusted for severity are used in some reports. In such cases, we have sought to present data as simply as possible, using absolute numbers whenever possible and a conservative calculation of numbers when percentages have been used in original papers.

The redefinition of hypoxaemic respiratory failure into mild, moderate, and severe ARDS[3] simplifies study selection. Analysis is complicated, however, due to significant variability between published studies with respect to the severity of illness in patients included in each study, and also by the heterogeneous nature of any underlying disease and the timing of inclusion of patients following development of ARDS. Examples include volume-limited ventilation, where data indicate that survival benefit is only demonstrable in studies where plateau pressures in the control arm exceeded 31 cm H2O (Online Appendix, Fig. S1). Also, PEEP > 5 cm H2O only confers benefit (oxygenation) to patients with moderate to severe ARDS, and any benefit is lost in mild ARDS (Online Appendix; Table S2).

Why develop Nordic guidelines for intensive care medicine? Intensive care medicine, and particularly mechanical ventilation, has a long-standing tradition in Nordic anaesthesiology, and much of the early pioneering work was done by anaesthetists in the Nordic countries.[32–34] It is therefore only natural that SSAI develops guidelines and standards that emphasise the role of anaesthesiology in intensive care medicine. Also, across the Nordic societies, there is considerable professional, cultural, and economic homogeneity. This is important because there are many shared values, preferences, and resource considerations, which are important elements in the GRADE system throughout our societies.

The guideline process serves to inform us that, despite advances, there are many areas of our practice that are characterised by a paucity of hard evidence. Ideally, guideline developers work in concert with trialists to make informed choices when allocating resources for costly investigations. Close collaboration with the SCCTG is therefore essential for further progress.

A limitation of this work is that we have restricted our recommendations to those that can be deduced from randomised trials only. There are limited data available from randomised trials for several treatment options (e.g. various ventilator modes with spontaneous breathing, FiO2). This leaves the clinician who cares for ARDS patients and who applies our guideline with the choice between a conservative approach based on available evidence from randomised trials, and careful use of new treatment options and physiological targets. We cannot exclude that available observational studies could have provided valuable evidence to inform some of our recommendations. Indeed observational studies may result in moderate to high-quality evidence according to the GRADE system although such cases are few and far between.[35]

Although the rationale for many treatment options have been that the intervention has been shown to improve physiological parameters (e.g. oxygenation), the history of critical care research has often shown that such a strategy may be faulty. Indeed, a recent before and after study in mechanically ventilated patients (mixed ICU population) indicates that a conservative oxygenation strategy was not harmful and may be beneficial.[36] Also, we have learned that it is not obvious which part of our pathophysiological insight will provide therapeutic strategies that benefit patients; the practice of gentle ventilation derives from the 'baby lung' concept that was developed from experimental and clinical studies of lung mechanics in ARDS.[37] In clinical practice, gentle ventilation will often challenge us to accept blood gases that are far from 'normal', yet the benefit to patients has been clearly demonstrated.[38] Conversely, recruitment manoeuvres may significantly improve oxygenation and lung aeration, particularly in the acute stage of ARDS,[39] but clinical benefit has yet to be clearly demonstrated in randomised trials. Whether due to study design or harms that outweigh benefit, the

available literature does not dictate a strong recommendation.[26] We believe that it is correct to avoid giving recommendations based on physiological data only, and hope that gaps in our list of recommendations may stimulate Scandinavian multi-centre trials.

Conclusion

This and the accompanying paper represent the first attempt by SSAI to develop a clinical guideline that adheres to the principles developed by the GRADE working group. We invite readers of this guideline to carefully review the recommendations that have been derived from the evidence presented herein and apply them in clinical practice to the benefit of their patients.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. (A) Forest plot of comparison: pressure and volume limitation (protective ventilation) vs. control, outcome: mortality at end of each study period. (B) Forest plot of comparison: pressure and volume limitation (protective ventilation) vs. control, outcome: 28-day mortality. (C) Forest plot of comparison: pressure and volume limitation (protective ventilation) vs. control, outcome: hospital mortality. (D) Forest plot of comparison: pressure and volume limitation (protective ventilation) vs. control, outcome: mortality at different plateau pressure in control groups. (E) Forest plot of comparison: Pressure and volume limitation (protective ventilation) vs. control, outcome: Duration of mechanical ventilation (Days). (F) Forest plot of comparison: pressure and volume limitation (protective ventilation) vs. control, outcome: barotrauma.

Fig. S2. (A) Forest plot of comparison: high PEEP vs. low PEEP, outcome: hospital mortality (death before discharge). (B) Forest plot of comparison: high PEEP vs. low PEEP, outcome: oxygenation efficiency (PO2/FiO2). (C) Forest plot of comparison: high PEEP vs. low PEEP, outcome: barotrauma.

Fig. S3. (A) Forest plot of comparison: pressure control vs. volume control, outcome: ICU mortality. (B) Forest plot of comparison: pressure control vs. volume control, outcome: hospital mortality. (C) Forest plot of comparison: pressure control vs. volume control, outcome: barotrauma. (D) Forest plot of comparison: pressure control vs. volume control, outcome: ventilator-free days. (E) Forest plot of comparison: pressure control vs. volume control, outcome: ICU days.

Fig. S4. (A) Forest plot of comparison: prone positioning vs. control, outcome: mortality at 28 days. (B) Forest plot of comparison: prone positioning vs. control, outcome: mortality at 90 days. (C) Forest plot of comparison: prone positioning vs. control, outcome: ventilator-free days [Days]. (D) Forest plot of comparison: prone positioning vs. control, outcome: ICU days survivors (Days). (E) Forest plot of comparison: prone positioning vs. control, outcome: barotrauma.

Fig. S5. (A) Forest plot of comparison: prone positioning vs. control, outcome: barotrauma. (B) Forest plot of comparison: lung recruitment manoeuvres vs. no recruitment, outcome: ICU mortality. (C) Forest plot of comparison: lung recruitment manoeuvres vs. no recruitment, outcome: barotrauma.

Fig. S6. (A) Forest plot of comparison: high-frequency oscillatory ventilation (HFOV) vs. conventional ventilation (control), outcome: hospital or 30-day mortality. All included trials. (B) Forest plot of comparison: HFOV vs. conventional ventilation (control), outcome: hospital or 30-day mortality. All included trials. (C) Forest plot of comparison: HFOV vs. conventional ventilation

(control), outcome: barotrauma. (D) Forest plot of comparison: HFOV vs. conventional ventilation (control), outcome: duration of mechanical ventilation.

Table S1. Summary of evidence for mortality at different times of follow up for pressure and volume limited ventilation (PVL) in ARDS.

Table S2. Summary of evidence for utilisation of PEEP in ARDS patients. Stratified for severity of illness.

Table S3. Summary of evidence for modes of ventilation in ARDS.

Table S4. Summary of evidence for prone ventilation in ARDS.

Table S5. Summary of evidence for recruitment manoeuvres in ARDS.

Table S6. Summary of evidence for high-frequency oscillatory ventilation in ARDS.

Table S7. Search method for identification of studies.