GUIDELINES ON THE MANAGEMENT OF ACUTE RESPIRATORY DISTRESS SYNDROME

APPENDIX B
GRADE Evidence Tables

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GRADE Evidence Table: Corticosteroids

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Steroids	Usual care	Relative (95% CI)	Absolute		
Hospital Mortality Tang 2009												
4	randomised trials[1]	serious[2]	serious[3]	no serious indirectness[4]	serious[5]	none[6]	45/191 (23.6%)	53/150 (35.3%)	RR 0.51 (0.24 to 1.09)	173 fewer per 1000 (from 269 fewer to 32 more)	VERY LOW	CRITICAL
Adverse Events Tang 2009 (assessed with: composite of infection; neuromyopathy; diabetes, GI bleeding and other)												
4	randomised trials[1]	serious[7]	no serious inconsistency	no serious indirectness	serious[8]	none	95/260 (36.5%)	82/234 (35%)	RR 0.82 (0.5 to 1.36)	63 fewer per 1000 (from 175 fewer to 126 more)	LOW	CRITICAL
Hospital or 60 day Mortality Ruan 2014												
8[9]	randomised trials	no serious risk of bias[10]	serious[11]	serious[12]	no serious imprecision	none	173/391 (44.2%)	167/334 (50%)	RR 0.91 (0.71 to 1.18)	45 fewer per 1000 (from 145 fewer to 90 more)	LOW	CRITICAL[13]
Hospital Mortality therapeutic steroids Peter 2008												
5	randomised trials	serious[14]	serious[15]	no serious indirectness	serious[16]	none	127/293 (43.3%)	141/268 (52.6%)	RR 0.62 (0.23 to 1.26)	200 fewer per 1000 (from 405 fewer to 137 more)	VERY LOW	CRITICAL
Hospital Length of Stay (measured with: Lamontagne; Better indicated by lower values)												
4	randomised trials	serious[17]	very serious[18]	no serious indirectness	no serious imprecision	none	191	157	-	mean 4.8 lower (9.3 lower to 0.4 higher)	VERY LOW	CRITICAL

[1] Tang 2009 SR of low dose steroids
[2] Tang SR. Quality assessment was fair only with 75% of Cochrane guideline recommendations
[3] point estimates vary widely; confidence intervals overlap; consistent direction of effect; moderate and significant heterogeneity I2= 52%
[4] Most studies preformed before the low TV era. ARDS mortality higher than in current ARDS studies so issue about applicability
[5] confidence interval crosses no effect line; few studies;
[6] not possible to assess from SR
[7] as mortality
[8] very wide 95% CI
[9] Ruan 2014 All doses and durations of steroid use in ARDS included. RCT and cohort studies included but separated in meta-analysis. 3 preventitive studies included in analysis
[10] low risk of bias as judged by cochrane risk of bias tool
[11] Isq=57.2% p=0.022
[12] preventitive studies also included
[13] Ruan 2014
[14] early withdrawel/stopping of some studies
[15] p=0.53
[16] wide CI including significant harm
[17] study quality judged as "fair" with 75% of quality assessment items included
[18] I2=82% p=.001
[19] wide CI includes harm and benefit

GRADE Evidence Table: Extra-corporeal Membrane Oxygenation

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ECMO**	**Usual care**	**Relative (95% CI)**	**Absolute**		
Hospital Mortality - Munshi												
3	Randomised and quasi-randomised trials	Serious	No serious inconsistency	Serious	No serious imprecision	None	78/241 (32.4%)	136/263 (51.7%)	0.64 (0.51-0.79)	186 fewer per 1000 (from 253 fewer to 109 fewer)	VERY LOW	CRITICAL
Bleeding – derived from Munshi												
2	Comparator studies	Serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	None	35/140 (25.0%)	0/210 (0.0%)	11.44 (3.11-42.06)		VERY LOW	IMPORTANT

[1] Non-randomised studies included (case matched)
[2] Two studies just examined patients with H1N1

GRADE Evidence Table: Extra-corporeal Carbon Dioxide Removal

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ECCO2R**	**Usual care**	**Relative (95% CI)**	**Absolute**		
Hospital Mortality Fitzgerald 2014												
13[1]	Observational, uncontrolled studies[2]	serious	serious	serious	serious	Variability in technique for ECCO2R (arterio-venous and veno-venous).	399[3]	58			VERY LOW	CRITICAL
Adverse Events Fitzgerald 2014 (assessed with: composite of infection; neuromyopathy; diabetes, GI bleeding and other)												
13[1]	Observational, uncontrolled studies[2]	serious	serious	serious	serious	Variability in technique for ECCO2R (arterio-venous and veno-venous).	427[4]	58			VERY LOW	CRITICAL

[1] Fitzgerald 2014 SR. Inadequate data to perform MA.
[2] Fitzgerald 2014 SR Quality analysis only occurred with two small RCTs and 12 observational studies, unable to draw meaningful conclusions
[3] Mortality estimates presented as simple descriptions – 27 to 75% (mean 55.5%, standard deviation 47.2 to 60.3)
[4] Complications presented as aggregated simple descriptions – 0-25%

GRADE Evidence Table: Fluid Strategy

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Conservative fluid strategy**	**Liberal fluid strategy**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality - 28 day												
2	randomised trials	not serious	not serious	serious [a,b]	serious [c]	none	10/39 (25.6%)	12/38 (31.6%)	**RR 0.81** (0.41 to 1.60)	**60 fewer per 1,000** (from 186 fewer to 189 more)	LOW	CRITICAL
Mortality - 60 day												
3	randomised trials	not serious	not serious	not serious	serious [c]	none	160/568 (28.2%)	174/561 (31.0%)	**RR 0.91** (0.77 to 1.08)	**28 fewer per 1,000** (from 25 more to 71 fewer)	MODERATE	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Conservative fluid strategy**	**Liberal fluid strategy**	**Relative (95% CI)**	**Absolute (95% CI)**		
Pooled Mortality (up to 60 days)												
5	randomised trials	not serious	not serious	serious [b,d]	serious [c]	none	170/607 (28.0%)	186/599 (31.1%)	**RR 0.91** (0.77 to 1.07)	**28 fewer per 1,000** (from 22 more to 71 fewer)	LOW	CRITICAL
Length of ICU stay												
2	randomised trials	very serious [e]	not serious	very serious [d]	not serious	strong association	65	64	-	MD **3.47 Days fewer** (4.74 fewer to 2.2 fewer)	VERY LOW	IMPORTANT
ICU free days												
1	randomised trials	not serious	not serious	not serious	serious [c]	none	503	497	-	MD **2.2 Days more** (1.09 more to 3.31 more)	MODERATE	IMPORTANT

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Conservative fluid strategy**	**Liberal fluid strategy**	**Relative (95% CI)**	**Absolute (95% CI)**		
Length of Hospital Stay												
1	randomised trials	not serious	not serious	not serious	serious [c]	none	No significant difference in length of hospital stay (median 4.5 days fewer in conservative fluid group, 95% CI -5.8 to 14.8 days)				MODERATE	IMPORTANT
Acute Kidney Injury Incidence												
1	randomised trials	not serious	not serious	not serious	serious [c,f]	none	In the FACTT study, there were a similar number of renal failure free days between conservative and liberal fluid management groups (21.5 +/- 11.2 versus 21.2 +/- 11.15 days, P=0.59). In a post-hoc analysis of this study in which serum creatinine was adjusted for fluid balance and thus volume of distribution, conservative fluid management was associated with lower incidence of AKI than liberal fluid management (290/503, 58% versus 328/497, 66%, P=0.007).				MODERATE	IMPORTANT
Renal Replacement Therapy Requirement												
1	randomised trials	not serious	not serious	not serious	serious [g]	none	50/503 (9.9%)	70/497 (14.1%)	**RR 0.71** (0.50 to 0.99)	**41 fewer per 1,000** (from 1 fewer to 70 fewer)	MODERATE	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Conservative fluid strategy**	**Liberal fluid strategy**	**Relative (95% CI)**	**Absolute (95% CI)**		
Ventilator-free Days (follow up: range 28 days to 30 days)												
2	randomised trials	not serious	not serious	not serious	serious [g]	none	523	517	-	MD **2.49 days more** (1.15 more to 3.82 more)	MODERATE	NOT IMPORTANT
Post-ICU Cognitive Function (assessed with: Cognitive function component of QLQ-C30; Scale from: 0 to 100)												
1	randomised trials	very serious [e]	not serious	serious [h]	not serious	none	50	50	-	MD **10.71 higher** (5.22 higher to 16.2 higher)	VERY LOW	

a. 30-day, rather than 28-day mortality, is reported in these studies [5,6]

b. One study [6] compared the use of hyperoncotic albumin solution versus placebo as an adjunct to furosemide for diuresis, so did not investigate the efficacy of a conservative fluid strategy directly. However, a marked difference in fluid balance was present between study groups.

c. 95% confidence intervals for estimate of effect cross the clinical decision threshold

d. One study [8] compared an EVLW-guided strategy to a PCWP-guided strategy not in widespread clinical use, and fluid balance differences between conservative and liberal groups were clinically insignificant; the details of fluid strategies are largely unclear in the other study [9]

e. High or uncertain risk of bias in the majority of domains

f. Effect is dependent on method of application of diagnostic criteria and adjustment of creatinine values for fluid balance:

g. Optimal information size criteria not met

h. Details of intervention and comparator unavailable, duration of follow-up uncertain [9]

GRADE Evidence Table: High Frequency Oscillation

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**HFOV**	**Usual care**	**Relative (95% CI)**	**Absolute**		
Mortality - 30 day Huang 2014												
5	randomised trials	Low[1]	Moderate[2]	Mild indirectness[3]	low	none	375/800 (46.8%)	53/780 (43.6%)	RR 1.04 (0.83 to 1.31)		MODERATE	CRITICAL
ICU Mortality Gu 2014												
3	randomised trials	low[4]	moderate	Mild indirectness	low	none	303/686 (44.2%)	211/685 (30.8%)	RR 1.218 (0.925 to 1.604)		MODERATE	CRITICAL
Adverse events Gu 2014 (barotrauma)												
4	randomised trials	low[4]	No serious inconsistency	No serious indirectness	serious[5]	none	54/383 (14.1%)	45/369 (12.2%)	RR 1.205 (0.834 to 1.742)		LOW	IMPORTANT

[1] Huang 2014 2 studies stopped early by DMC and 1 incomplete follow-up, otherwise risk of bias consistently low in all domains

[2] Huang 2014 I^2 60%

[3] Huang 2014 changes in conventional ventilation strategy accounted for heterogeneity between studies

[4] Gu 2014 one study >10% crossover

[5] Gu 2014 differences in definition of complications

GRADE Evidence Table: Inhaled Vasodilators

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**iVasoD nitric oxide**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
iVasoD nitric oxide vs placebo/ usual care, effect on morality, Adhikari NK 2014;												
9	RCT	Serious[1]	not serious	Serious[2]	not serious		207/ 615 33.66%	166/ 527 31.50%	**RR 1.10** (0.94 to 1.29)		LOW	CRITICAL
Quality assessment							**№ of patients**		**Effect**		**Quality**	**Importance**
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**iVasoD nitric oxide**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
iVasoD nitric oxide vs placebo, effect on renal dysfunction, Adhikari NK 2007, Ruan SY 2015;												
4	RCT	Serious[3]	not serious	Serious[2]	not serious		93/490 18.98%	53/429 12.35%	RR 1.55 (1.15 to 2.09)		LOW	IMPORTANT

MD – mean difference, RR – relative risk

1 Six out of 9 studies compared iNO with usual care rather than placebo
2 Highly variable dose and duration of iNO and inclusion criteria
3 Variable criteria used to define renal dysfunction

GRADE Evidence Table: Mechanical Ventilation at Lower Tidal Volume with Conventional (Higher) Tidal Volume

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Low tidal volume**	**High tidal volume**	**Relative (95% CI)**	**Absolute**		
Mortality - 60 day												
1[1]	randomised trials	no serious risk of bias	Not applicable (only one study)	no serious indirectness	serious – small sample size & wide CIs	none	27/58 (46.6%)	22/58 (37.9%)	RR 1.23 (0.8 to 1.89)	87 more per 1000 (from 76 fewer to 338 more)	LOW	CRITICAL
								37.9%		87 more per 1000 (from 76 fewer to 337 more)		
Mortality - Hospital												
3[2]	randomised trials	no serious risk of bias	None (CIs do overlap, no statistical heterogeneity evident	serious[3]	no serious imprecision	none	176/518 (34%)	210/515 (40.8%)	RR 0.83 (0.71 to 0.98)	69 fewer per 1000 (from 8 fewer to 118 fewer)	MODERATE	CRITICAL
								46.2%		79 fewer per 1000 (from 9 fewer to 134 fewer)		
								5.3%		9 more per 1000 (from 20 fewer to 63 more)		
ICU Length of Stay (Better indicated by lower values)												

2[4]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious – small sample size & wide CIs	none	118	118	-	MD 4.79 higher (2.06 lower to 11.63 higher)	MODERATE	CRITICAL
Hospital Length of Stay (Better indicated by lower values)												
1[5]	randomised trials	no serious risk of bias	Not applicable (only one study)	no serious indirectness	serious – small sample size & wide CIs	none	60	60	-	MD 6.3 higher (7.53 lower to 20.13 higher)	LOW	
								42.9%		56 fewer per 1000 (from 107 fewer to 4 more)		

[1] Brochard 1998

[2] ARDSNet 2000; Brower 1999; Stewart 1998

[3] ARDSNet study control group had higher TVs (11.5/12) than controls in the other 4 studies

[4] Brochard 1998; Stewart 1998

[5] Stewart 1998

GRADE Evidence Table: Lower Tidal Volume with Higher PEEP and Higher Tidal Volume with Lower PEEP

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Higher PEEP**	**Lower PEEP**	**Relative (95% CI)**	**Absolute**		
Mortality - ICU												
2[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	27/79 (34.2%)	41/69 (59.4%)	RR 0.57 (0.4 to 0.82)	256 fewer per 1000 (from 107 fewer to 357 fewer)	LOW	CRITICAL
								62.1%		267 fewer per 1000 (from 112 fewer to 373 fewer)		
Mortality - 28 day												
1[2]	randomised trials	no serious risk of bias	Not applicable (only one study)	no serious indirectness	no serious imprecision	none	11/29 (37.9%)	17/24 (70.8%)	RR 0.54 (0.31 to 0.91)	326 fewer per 1000 (from 64 fewer to 489 fewer)	LOW	CRITICAL
								70.8%		326 fewer per 1000 (from 64 fewer to 489 fewer)		

Mortality - Hospital												
2[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	30/79 (38%)	42/69 (60.9%)	RR 0.62 (0.44 to 0.87)	231 fewer per 1000 (from 79 fewer to 341 fewer)	LOW	CRITICAL
								63.2%		240 fewer per 1000 (from 82 fewer to 354 fewer)		
								70.8%		290 fewer per 1000 (from 191 fewer to 375 fewer)		

[1] Amato 1998; Villar 2006

[2] Amato 1998

GRADE Evidence Table: Neuromuscular Blocking Agents

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Neuromuscular Blocking Agents (NMBAs)**	**Control**	**Relative (95% CI)**	**Absolute**		
28 Day Mortality - Alhazzani 2013 (assessed with: with a 48 hour infusion of cisatricurim besylate)												
3	randomised trials	serious[1]	no serious inconsistency	serious	no serious imprecision	none[2]	57/223 (25.6%)	81/208 (38.9%)	RR 0.66 (0.50 to 0.87)	132 fewer per 1000 (from 51 fewer to 195 fewer)	MODERATE	CRITICAL
ICU Mortality - Alhazzani 2013 (assessed with: with a 48 hour infusion of cisatricurim besylate)												
3	randomised trials	serious[1]	no serious inconsistency	serious	no serious imprecision	none[2]	70/223 (31.4%)	93/208 (44.7%)	RR 0.70 (0.55 to 0.89)	134 fewer per 1000 (from 49 fewer to 201 fewer)	MODERATE	CRITICAL
Hospital Mortality (truncated at 90 days) - Alhazzani 2013 (assessed with: with 48-hour infusion of cisatracurim besylate**)**												
3	randomised trials	serious[1]	no serious inconsistency	serious	no serious imprecision	none[2]	76/223 (34.1%)	98/208 (47.1%)	RR 0.72 (0.58 to 0.91)	132 fewer per 1000 (from 42 fewer to 198 fewer)	MODERATE	CRITICAL

ICU Acquired Weakness - Alhazzani 2013 (assessed with: with a 48 hour infusion of cisatricurim besyslate)												
3	randomised trials	very serious[4]	serious[5]	serious	no serious imprecision	none[2]	73/223 (32.7%)	62/208 (29.8%)	RR 1.08 (0.83 to 1.41)	24 more per 1000 (from 51 fewer to 122 more)	VERY LOW	IMPORTANT
Quality of Life at 3 or more months (assessed with: Not a primary or secondary outcome in any of three RCTs)												
0	No evidence available					none	-	-	-	-		CRITICAL
ICU Length of Stay (assessed with: Not a primary or secondary outcome in any of three RCTs)												
0	No evidence available					none	-	-	-	-		IMPORTANT
Hospital Length of Stay (assessed with: Not a primary or secondary outcome in any of three RCTs)												
0	No evidence available					none	-	-	-	-		IMPORTANT

[1] Treatment was not blinded in two of the three RCTs included in the meta-analysis (Gainnier 2004 and Forel 2006) - individually rated as "High" overall risk of bias by SR authors. The third (Papazian 2010) was rated "Low" risk of bias, although it is questionable whether patients triggering the ventilator would unmask blinding

[2] All three included RCTs were from same group of researchers, with 431 subjects from total of 20 French centres. Authors of this review included lead authors of the included studies.

[3] Earlier SR with similar findings to Alhazzani 2013 for each of these measures - not reproduced here as Alhazzani is more recent study and had more detailed access to original trial data

[4] Lack of robust screening for weakness in first two RCTs (Gainnier 2004 and Forel 2006). Third RCT (Papazian 2010) only assessed weakness until ICU discharge

[5] Screening methods differed greatly between RCTs (see above)

[6] One of the contributing RCTs (Papaian 2010) included only patients with severe ARDS (P/F ratio <150mmHg) within the first 48 hours

GRADE Evidence Table: Positive End-Expiratory Pressure

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Higher PEEP**	**Control**	**Relative (95% CI)**	**Absolute**		
Hospital Mortality												
3	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	no serious imprecision	none	378/1136 (33.3%)	429/1163 (36.9%)	RR 0.90 (0.81 to 1.01)	37 fewer per 1000 (from 70 fewer to 4 more)	MODERATE	CRITICAL
								0%		-		
28 day mortality												
5	randomised trials	no serious risk of bias	very serious[2]	no serious indirectness	no serious imprecision	none	270/949 (28.5%)	321/972 (33%)	RR 0.83 (0.67 to 1.01)	56 fewer per 1000 (from 109 fewer to 3 more)	LOW	CRITICAL
								0%		-		
ICU Mortality in patients with moderate / severe ARDS (p/f <200) (Subgroup analysis)												
3	randomised trials	no serious risk of bias	very serious[2]	no serious indirectness	no serious imprecision	none	41/109 (37.6%)	54/96 (56.3%)	RR 0.67 (0.48 to 0.95)	186 fewer per 1000 (from 28 fewer to 293 fewer)	LOW	IMPORTANT
								0%		-		
Hospital Mortality in patients with moderate / severe ARDS (P/f <200) (Individual patient data meta-analysis)												
3	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	no serious imprecision	none	324/951 (34.1%)	368/941 (39.1%)	RR 0.90 (0.81 to 1)	39 fewer per 1000 (from 74 fewer to 0 more)	MODERATE	IMPORTANT

								0%		-		
ICU Mortality (up to day 60) in patients with moderate / severe ARDS (P/f <200) (Individual patient data meta-analysis)												
3	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	no serious imprecision	none	288/951 (30.3%)	344/941 (36.6%)	RR 0.85 (0.76 to 0.95)	55 fewer per 1000 (from 18 fewer to 88 fewer)	MODERATE	IMPORTANT
								0%		-		
Adverse event: Barotrauma												
5	randomised trials	no serious risk of bias	very serious[3]	no serious indirectness	serious[3]	none	116/1245 (9.3%)	113/1259 (9%)	RR 0.97 (0.66 to 1.42)	3 fewer per 1000 (from 31 fewer to 38 more)	VERY LOW	IMPORTANT
								0%		-		
ICU free days (Better indicated by lower values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	751	781	-	MD 0.04 higher (1.03 lower to 1.1 higher)	MODERATE	IMPORTANT

[1] different strategies used to set PEEP between trials.
[2] includes studies whose intervention compares high vs low tidal volume
[3] wide confidence interval; 95% CI beyond 25% threshold
[4] I2 = 89.3%; p = 0.002
[5] wide confidence interval, CI beyond 25% threshold

GRADE Evidence Table: Prone Positioning

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Prone Positioning**	**Control**	**Relative (95% CI)**	**Absolute**		
All-cause mortality - Park 2015 (assessed with: PP)												
8	randomised trials	serious[1]	very serious[2]	serious[3]	no serious imprecision	Primary outcome = overall mortality at the longest available follow-up but exact time-frames not reported for individual RCTs. (4) Funnel plot presented would suggest no publication bias	460/1099 (41.9%)	487/1042 (46.7%)	RR 0.90 (0.82 to 0.98)	47 fewer per 1000 (from 9 fewer to 84 fewer)	VERY LOW	CRITICAL
								0%		-		
All-cause mortality - Park 2015 (assessed with: PP+lung protective ventilation (sub-group analysis))												
5	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	a/a	148/458 (32.3%)	202/452 (44.7%)	RR 0.73 (0.62 to 0.86)	121 fewer per 1000 (from 63 fewer to 170 fewer)	MODERATE	CRITICAL
								0%		-		
All-cause mortality - Park 2015 (assessed with: PP+no lung protective ventilation (sub-group analysis))												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	a/a	312/641 (48.7%)	285/590 (48.3%)	RR 1.01 (0.9 to 1.13)	5 more per 1000 (from 48 fewer to 63 more)	MODERATE	CRITICAL
								0%		-		

All-cause mortality - Park 2015 (assessed with: with PP >12h (sub-group analysis))												
5	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	a/a	185/513 (36.1%)	236/493 (47.9%)	RR 0.75 (0.65 to 0.87)	120 fewer per 1000 (from 62 fewer to 168 fewer)	MODERATE	CRITICAL
								0%		-		
All-cause mortality - Park 2015 (assessed with: PP <12h (sub-group analysis))												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	a/a	275/586 (46.9%)	251/549 (45.7%)	RR 1.03 (0.91 to 1.17)	14 more per 1000 (from 41 fewer to 78 more)	MODERATE	CRITICAL
								0%		-		
Adverse events (pooled data) - Park 2015												
7	randomised trials[6]	serious[1]	very serious[4]	no serious indirectness	no serious imprecision	a/a	787/3795 (20.7%)	675/3582 (18.8%)	RR 1.10 (1.01 to 1.2)	19 more per 1000 (from 2 more to 38 more)	VERY LOW	IMPORTANT
								0%		-		
Adverse events : Cardiac events - Park 2015												
3	randomised trials	serious[1]	very serious[5]	no serious indirectness	serious[3]	a/a	224/818 (27.4%)	217/781 (27.8%)	RR 1.01 (0.87 to 1.17)	3 more per 1000 (from 36 fewer to 47 more)	VERY LOW	IMPORTANT
								0%		-		
Adverse events : ETT displacement - Park 2015												
5	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	a/a	111/814 (13.6%)	79/783 (10.1%)	RR 1.33 (1.02 to 1.74)	33 more per 1000 (from 2 more to 75 more)	LOW	IMPORTANT

								0%		-		
Adverse events : VAP - Park 2015												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	a/a	115/531 (21.7%)	118/476 (24.8%)	RR 0.88 (0.71 to 1.09)	30 fewer per 1000 (from 72 fewer to 22 more)	LOW	IMPORTANT
								0%		-		
Adverse events : Pressure sore - Park 2015												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	a/a	262/565 (46.4%)	199/530 (37.5%)	RR 1.23 (1.07 to 1.41)	86 more per 1000 (from 26 more to 154 more)	LOW	IMPORTANT
								0%		-		
Adverse events : Pneumothorax - Park 2015												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	a/a	44/474 (9.3%)	46/686 (6.7%)	RR 0.87 (0.59 to 1.30)	9 fewer per 1000 (from 27 fewer to 20 more)	LOW	IMPORTANT
								0%		-		
Adverse events : Loss of venous access - Park 2015												
2	randomised trials	serious[1]	very serious[6]	no serious indirectness	Serious[7]	a/a	31/320 (9.7%)	16/326 (4.9%)	RR 1.98 (1.11 to 3.55)	48 more per 1000 (from 5 more to 125 more)	VERY LOW	IMPORTANT
								0%		-		

[1] All trials demonstrated detection (failure to blind outcome assessment) bias. In addition Chan, 2007 demonstrated selection bias (failure of allocation concealment), and Fernandez, 2008, Guerin, 2004, Mancebo, 2006 and Taccone, 2009 all demonstrated attrition bias (incomplete outcome data) judged by comparing the protocol and

mortality outcomes

[2] I^2 = 61%, p=0.01

[3] Cohort includes sub-groups receiving additional interventions known to demonstrate a potential mortality benefit e.g. lung-protective ventilation or a longer duration of PP, as well as those not receiving such interventions.

[4] I^2 = 63%, p<0.[4]0001

[5] I^2 = 90%, p<0.0001

[6] I^2 = 88%, p=0.005

[7] See 3. plus wide 95%CI