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Higher versus lower oxygenation strategies in acutely ill adults. A systematic review with meta-analysis and Trial Sequential Analysis

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Higher versus lower oxygenation strategies in acutely ill adults. A systematic review with meta-analysis and Trial Sequential Analysis

Running head: systematic review of oxygenation strategies in acutely ill adults

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ABBREVIATIONS LIST

CI	confidence interval
F_IO_2	fraction of inspired oxygen
GRADE	Grading of Recommendations Assessment, Development and Evaluation
I^2	inconsistency statistics
ICU	intensive care unit
PaO_2	partial pressure of arterial oxygen
RCTs	randomised clinical trials
RR	relative risk
SAEs	serious adverse events
SaO_2	arterial oxygen saturation
SpO_2	peripheral oxygen saturation
TSA	Trial Sequential Analysis

ABSTRACT

OBJECTIVES: Liberal oxygen supplementation is often used in acute illness but has, in some studies, been associated with harm. We aimed to assess the benefits and harms of higher versus lower oxygenation strategies in acutely ill adults.

METHODS: We conducted an updated systematic review with meta-analysis and Trial Sequential Analysis (TSA) of randomised clinical trials (RCTs), having a clear differentiation (separation) between a higher (liberal) oxygenation and a lower (conservative) oxygenation strategy, on all-cause mortality, serious adverse events (SAEs), quality of life, lung injury, sepsis, and cardiovascular events, at timepoint closest to three months in acutely ill adults.

RESULTS: We included 50 RCTs of 21,014 participants; 36 trials with a total of 20,166 participants contributed data to the analyses. Meta-analysis and TSAs showed no difference between higher and lower oxygenation strategies in trials at overall low risk of bias except for blinding: mortality relative risk (RR) 0.98, 95% confidence interval (CI) 0.89-1.09, TSA-adjusted CI 0.86-1.12 (low certainty evidence); SAEs RR 0.99, 95% CI 0.89-1.12, TSA-adjusted CI 0.83-1.19 (low certainty evidence). The corresponding summary estimates including trials with overall low and high risk of bias showed similar results. We did not find a difference between higher and lower oxygenation strategies in meta-analyses and TSAs regarding quality of life, lung injury, sepsis, and cardiovascular events (very low certainty evidence).

CONCLUSION: We did not find evidence of beneficial or harmful effects of higher versus lower oxygenation strategies in acutely ill adults (low to very low certainty evidence).

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INTRODUCTION

The mainstay treatment and prevention strategy for hypoxaemia is supplemental oxygen, which is frequently used in acute care settings. Despite lack of robust evidence regarding the balance between benefit and harm, oxygen therapy is widely recommended in international practice guidelines [1-5]. Accordingly, clinical practice of oxygen use is often liberal and often results in hyperoxaemia or high fraction of inspired oxygen (F_IO_2), which has been associated with harms [6-12].

Adverse outcomes may be caused by pulmonary complications due to atelectasis formation [13-15] or pulmonary formation of reactive oxygen species [16-18]. However, they may also be related to decreased local blood flow on normal and non-diseased vasculature induced by hyperoxaemic vasoconstriction [19, 20]. Although the possible adverse effects of hyperoxia are known, prevention of hypoxia through hyperoxia seems to have been prioritized - if a little of something is good then lots must be better. It therefore seems as historically held beliefs and practices rather than treatment based on evidence has led the way of predominating liberal oxygenation strategies [7, 9-11, 21-23].

Two meta-analyses of observational studies found an association between hyperoxaemia and mortality in critically ill adults [17, 24] and recently a systematic review of randomised clinical trials (RCTs) found an increase in mortality [25] resulting in a recent clinical practice guideline recommending a more restrictive use of oxygen in acutely ill adults [26].

As new trial data have been published [27], we performed a systematic review comparing the effects of higher versus lower oxygenation strategies in acutely ill adults. We hypothesised that higher oxygenation strategies were associated with increased mortality and serious adverse events (SAEs).

METHODS

This systematic review was conducted according to the pre-planned statistical analysis plan of the published protocol [28]. We registered the protocol in the international prospective register of systematic reviews database (PROSPERO) (CRD42017058011), used the methodology of the Cochrane Collaboration supplemented with worst-best case and best-worse case scenarios for participants lost to follow-up, Trial Sequential Analysis (TSA), Bayes factor, and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (e-Appendix) [29, 30].

Eligibility criteria

We included RCTs having a clear differentiation (separation) between a higher (liberal) oxygenation and a lower (conservative) oxygenationation strategy using arterial partial pressure of oxygen (PaO_2), arterial oxygen saturation (SaO_2), peripheral oxygen saturation (SpO_2)) or F_IO_2 applied by any device in acutely ill adults. Both mechanically ventilated and non-mechanically ventilated adults were eligible for inclusion. We included RCTs irrespective of durations of interventions. Quasi randomised trials were excluded.

Outcomes

Predefined co-primary outcomes were all-cause mortality and the proportion of participants with one or more SAEs (composite outcome reported by trialists).

Co-secondary outcomes were: quality of life; severe lung injury (composite outcome) defined as either ARDS, pulmonary fibrosis or pneumonia, or as defined by trialists; sepsis; and cardiovascular events (composite outcome) defined as either myocardial infarction, stroke, peripheral arterial

thrombosis, deep vein thrombosis, pulmonary embolism, or as defined by trialists. Each predefined component of the composite outcome of severe lung injury and cardiovascular events were analysed separately.

For the composite outcomes, we estimated the reported proportion of participants with one or more SAEs (in addition to the primary analysis on SAEs), lung injuries and cardiovascular events in two ways:

1. by choosing the one specific event with the highest proportion reported in each trial that addresses the lowest possible proportion of participants with one or more events (this analysis may exclude patients with events not included in the group of patients having the type of SAE with the highest frequency).
2. by cumulating all reported events, assuming that participants only experience one event (the number of participants in each group will constitute a maximum), address the highest possible reported proportion of participants with one or more events (this analysis may include double counting).

For all outcomes, we used the trial results reported at time-points closest to 90 days [28].

Search methods

We searched the following electronic databases: Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library; Ovid MEDLINE; Ovid Embase; Science Citation Index Expanded (Web of Science); Biosis Previews (Web of Science); and PubMed. Search strategies are presented in the e-Appendix.

The literature search was last updated on 17 October 2019. We manually identified additional potential eligible trials by screening the reference lists of the included studies, other relevant systematic reviews, and searched trial registries.

Trial selection and data extraction

Three review authors (MB, OLS, SRK) independently and in pairs screened titles and abstracts. Reports deemed potentially relevant were obtained in full-text and assessed for inclusion. Disagreements were resolved by consensus and JW was consulted when agreement could not be met.

Three review authors (MB, OLS, SRK) independently and in pairs extracted predefined data of the included trials using a predefined data collection form (e-Appendix).

Risk of bias assessment

MB, OLS and SRK independently and in pairs assessed the risk of systematic errors (bias) of the included trials using the Cochrane Collaboration's risk of bias tool [29]. We planned to present trials at 'overall low risk of bias' when all bias domains were adjudicated at low risk of bias except for blinding of participants and personnel as we did not expect to identify any trials using adequate blinding of participants and personnel due to the practice of administration of oxygen [28]. We post-hoc decided to also accommodate the possible challenges of blinding of outcome assessors in this setting and presented trials at overall low risk of bias when any blinding was not maintained or not reported adequately – but the other bias domains were adjudicated at low risk of bias. Conversely, trials were adjudicated at 'overall high risk of bias' when unclear or high risk of bias was adjudicated in domains other than blinding.

We assessed publication bias by inspecting funnel plots for signs of asymmetry when ten or more trials were included in an analysis [29, 31]. We tested asymmetry with the Harbord test [32].

Data synthesis

Summary measures

Risk ratios (RRs) with 95% confidence intervals (CIs) and CIs adjusted for sparse data, multiple outcomes and testing (TSA adjusted CIs) were calculated for dichotomous outcomes. For continuous outcomes, mean-scores were used and mean difference (MD) with CIs and TSA adjusted CIs were calculated.

Meta-analysis

We calculated pooled effect estimates using Review Manager 5 [33]. We used the Mantel-Haenszel statistical method when using a fixed effect model and the DerSimonian and Laird inverse variance methods when using a random effects model. We used a family wise error rate of 5% and considered a p-value of 0.05/[(2+1)/2] = 0.033 or less as statistically significant in the analyses of each co-primary outcome, and we considered a p-value of 0.05/[(4+1)/2] = 0.02 or less as statistically significant in the analyses of each co-secondary outcome to account for statistical multiplicity due to multiple outcomes [31]. We calculated Bayes factor to assess if the summary effect estimates fitted better with the null hypothesis than alternative hypotheses of the anticipated intervention effects [31].

Dealing with missing data

Corresponding authors were contacted to clarify important missing data related to the methods, data reporting, or if further trial details were needed (e-Appendix).

We conducted a predefined sensitivity analysis by imputing missing outcome data in a best-worst case scenario and a worst-best case scenario to assess the potential impact of loss to follow-up [28, 31].

Assessment of heterogeneity

We assessed heterogeneity by visual inspection of the forest plots and calculated the inconsistency statistics (I^2) and the diversity statistics (D^2) [34]. We assessed intervention effects with both random-effects model meta-analyses and fixed-effect model meta-analyses. We used the more conservative point estimate of the two, which is the point estimate closest to no effect. If the estimates from the two models were approximately equal, we used the estimate with the widest CI [28, 31].

Subgroup analyses and sensitivity analyses

We conducted the following predefined subgroup analyses: trials with overall low risk of bias except for blinding versus overall high risk of bias; oxygen level defined by F_IO_2 versus oxygen level defined by targets of PaO_2, SaO_2 or SpO_2; low versus high oxygen strategy in control group (lower strategies defined as F_IO_2 below/at 0.30 or PaO_2 below/at 8 kPa or SaO_2/SpO_2 below/at 90% versus higher strategies defined as F_IO_2 above 0.30 or PaO_2 above 8 kPa or SaO_2/SpO_2 above 90%); subpopulations of acutely ill adults; and duration of oxygen administration according to administration of oxygen below median of duration of supplemental oxygen versus administration of oxygen above median of duration of supplemental oxygen. We conducted a post-hoc subgroup analysis of the effect of supplemental oxygen versus no supplemental oxygen.

Trial Sequential Analysis

We used TSA adjusted CI to assess the uncertainty (risk of random errors) due to sparse data, multiple outcomes, and multiple testing of accumulating data [35-44], and we calculated the required information size [34].

We used a power of 90% (beta 10%) and a diversity as suggested by the trials in the meta-analysis [31, 34, 44]. As anticipated intervention effects for the primary and secondary outcomes in the TSA, we used a realistic a priori relative risk reduction (RRR) or relative risk increase (RRI) of 20%, and a ½ SD in Quality of life. We post hoc chose to report 10% difference in mortality, 15% difference in SAEs, and ¼ standard deviation (4 points) in quality of life as we had information enough (participants) included to be able to reject such a difference.

We present 95% CI and TSA adjusted CI. For a more detailed description of the statistical analysis plan and TSA, we refer to the published review protocol [28].

Grading certainty of evidence

We used The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the overall certainty of evidence for all pre-defined outcomes [45]. We appraised the certainty of the evidence and our confidence in the effect estimates based on risk of bias, inconsistency, indirectness, imprecision and publication bias. Thus, we rated the overall certainty of evidence as high, moderate, low or very low.

RESULTS

Results of the search and selection of trials

We identified 61,852 titles and assessed 327 full text for eligibility (e-Appendix). We included 50 RCTs (of which one was a three-arm trial constituting two trials in this paper) randomising a total of 21,014 participants to higher versus lower oxygenation strategies.

Characteristics of included trials

Fifteen RCTs did not report on any of our outcomes; 35 RCTs contributed with data to the meta-analyses. The number of participants in the trials ranged from 9 to 8003 and all included acutely ill adults in different clinical settings (Table 1).

All trials assessed a higher versus a lower oxygenation strategy using either F_IO_2 or arterial oxygenation targets or a combination. However, the definitions of higher and lower oxygenation strategies differed to a great extent between the trials. In the higher groups, F_IO_2 ranged from 0.28 to 1.00. In the control groups, 23 trials did not use an F_IO_2 or oxygenation target corresponding to our definition of 'low' (F_IO_2 below/at 0.30 or PaO_2 below/at 8 kPa or SaO_2/SpO_2 below/at 90%), whilst 17 trials did not apply supplemental oxygen by default. Duration of oxygen administration ranged from 15 minutes to 6 days.

Risk of bias

Nine trials were at overall low risk of bias except for blinding [27, 46-53]. The remaining trials were at overall high risk of bias (e-Appendix). Funnel plots indicated asymmetry but Harbord tests indicated no small-study effect (e-Appendix).

Effect of interventions

All-cause mortality

Thirty-four trials including 19,439 participants reported on all-cause mortality, 8 of these trials (16,156 participants) were at overall low risk of bias except for blinding. At follow-up, 1102 of 11,037 (10.0%) participants in the higher oxygenation strategy group had died versus 812/8402 (9.7%) in the lower group (follow-up ranged from 1 day to 1 year). Meta-analysis of 8 trials at overall low risk of bias except for blinding showed no evidence of a difference of higher versus lower oxygenation groups (RR 0.98; 95% CI 0.89-1.09; I^2= 0%; TSA-adjusted CI 0.86-1.12; Figure 1-2). The certainty of the evidence, using the GRADE approach, was low (Table 2). The corresponding summary estimate of all 34 trials regardless of risk of bias showed similar results (RR 1.04; 95% CI 0.96-1.13; I^2=2%; TSA-adjusted CI 0.96-1.13; Bayes factor for a 20% RRI=135; Bayes factor for a 20% RRR=37,517,301; Figure 1, e-Appendix). The certainty of evidence was very low (Table 2). Results of the subgroup analyses and sensitivity analyses are reported in the e-Appendix.

Serious adverse events

Six trials including 8874 participants reported data on the proportion of participants with at least one SAE, 3 of these trials (8056 participants) were at overall low risk of bias except for blinding. A total of 924 of 5727 participants (16.1%) in the higher oxygenation strategy group had at least one SAE versus 578 of 3147 (18.4%) in the lower group (follow-up ranged from 1 day to 1 year). Meta-analysis of 3 trials at overall low risk of bias except for blinding showed no evidence of a difference of higher versus lower oxygenation groups (RR 0.99; 95% CI 0.89-1.12, I^2=0%; TSA-adjusted 0.83-1.19; Figure 4-5). The certainty of the evidence was low (Table 2). The corresponding summary estimate of all 6 trials regardless of risk of bias showed similar results (RR 1.03; 95% CI 0.95-1.13; I^2=17%, TSA-adjusted CI 0.91-1.18; Bayes factor for a 20% RRI=127; Bayes factor for a 20%

RRR=785767; e-Appendix). The certainty of the evidence was low (Table 2). Results of the subgroup analyses and sensitivity analyses are reported in the e-Appendix.

Thirty-five trials including 19,502 participants reported on single SAEs; 8 of these trials (16,156 participants) were at overall low risk of bias except for blinding. Results of the estimated reported proportion of participants with one or more SAEs are reported in the e-Appendix.

Quality of life

Six trials including 7445 participants reported on quality of life using the EuroQoL visual analogue scale (EQ-VAS). Mean scores were 66.1 in the higher oxygenation strategy group versus 64.6 in the lower group (follow-up ranged from 90 to 180 days). Meta-analysis regardless of risk of bias showed no evidence of a difference of higher versus lower oxygenation groups (MD 0.37; 95% CI -1.55-2.29; I^2= 57%; TSA-adjusted CI -2.41-3.16; e-Appendix). The certainty of evidence was very low (Table 2).

Lung injury

Ten trials including 9279 participants reported on lung injury. A total of 248 of 5934 participants (4.2%) in the higher oxygenation strategy group developed lung injury versus 227 of 3293 (6.9%) in the lower group (follow-up ranged from 4 to 90 days). Meta-analysis regardless of risk of bias showed no evidence of a difference of higher versus lower oxygenation groups when assessing the estimated highest reported proportion of specific lung injury events in each trial (RR 0.93; 95% CI 0.76-1.12; I^2= 0%; TSA-adjusted CI 0.64-1.32; e-Appendix). The certainty of evidence was very low (Table 2). Meta-analysis of the estimated cumulated number of lung injuries showed similar results (RR 0.92; 95% CI 0.78-1.10; I^2=0%; e-Appendix). Meta-analysis showed no evidence of a difference of higher versus lower oxygenation groups when assessing ARDS and pneumonia individually (e-Appendix).

Sepsis

Four trials including 1307 participants reported on new onset of sepsis after randomisation. A total of 33 of 649 participaents (5.1%) in the higher oxygenation strategy group developed sepsis versus 20 of 658 (3.0%) in the lower group (follow-up ranged from 6 days to 6 months). Meta-analysis regardless of risk of bias did not show a statistically significant difference of higher versus lower oxygenation groups (RR 1.64; 95% CI 0.96-2.80; I^2= 0%; e-Appendix). As only 2.89% of the required information size (n=45,241) had been reached, TSA-adjusted CI could not be calculated. The certainty of evidence was very low (Table 2).

Cardiovascular events

Sixteen trials including 16,615 participants reported on cardiovascular events. A total of 277 of 9580 participants (2.9%) in the higher oxygenation strategy group had a cardiovascular event versus 225 of 7027 (3.2%) in the lower group (follow-up ranged from 1 day to 1 year). Meta-analysis regardless of risk of bias showed no evidence of a difference of higher versus lower oxygenation groups when assessing the estimated highest reported proportion of specific cardiovascular events in each trial (RR 1.06; 95% CI 0.86-1.31; I^2= 11%; TSA-adjusted CI 0.45-2.51; e-Appendix). The certainty of evidence was very low (Table 2). Meta-analysis of the estimated cumulated number of cardiovascular events showed similar results (RR 1.10; 95% CI 0.98-1.23; I^2=8%; e-Appendix). Meta-analysis showed no evidence of a difference in myocardial infarction, stroke, deep vein thrombosis, pulmonary embolism individually between the higher versus lower oxygenation groups (e-Appendix).

DISCUSSION

In this systematic review we found no evidence of a difference in mortality or SAEs with the use of higher versus lower oxygenation strategies. TSA considering multiple outcomes, sparse data, and repetitive testing, revealed that we obtained the information to reject a 15% relative change in mortality and a 20% relative change in SAEs.

There was no evidence of a 4-point difference in quality of life as measured with EQ-VAS with higher versus lower oxygenation strategy group, and TSA revealed that we obtained the information size required to reject such difference.

There was no evidence of a 20% relative change in lung injury, sepsis and cardiovascular events with higher versus lower oxygenation strategies, but the TSA revealed that more data are required. Furthermore, duration of supplemental oxygen for 12 hours or more was not associated with harm as compared to duration of supplemental oxygen of less than 12 hours. And we found no association between the use of a predifined true low level of supplemental oxygen in the control group and the effect of supplemental oxygen.

Strengths and limitations

Our review has several strengths. We included trials regardless of publication type, publication status, language, and choice of outcomes and we contacted relevant trial investigators if additional information was needed. We used predefined, up-to-date systematic review methodology, and the few differences between protocol and review are transparently reported. We used GRADE to assess the certainty of the evidence and TSA with adjusted CI to control the risk of random errors due to multiple outcomes, sparse data, and multiple testing on accumulating data. We assessed the risk of bias of each trial to evaluate the risk of systematic errors (bias) and we used an eight-step procedure

to assess if the thresholds for statistical and clinical significance were crossed [31]. We also tested the robustness of our results in sensitivity analyses.

Our review also has several limitations. The primary limitation was that trials did not use the same definition of a higher versus a lower oxygenation strategy. Some trials used a fixed F_IO_2, whilst others used a targeted oxygenation interval, resulting in a large span of oxygenation levels achieved in the trials, in both intervention groups. Patients randomised to a high saturation does not imply that they eventually get more oxygen supplementation, as patients with "good" lung-function do not need as much oxygen to reach the same saturation as patients with "bad" lung-function. We have therefore conducted subgroup analyses separating trials in those using F_IO_2, PaO2 and SaO_2/SpO_2 and we found no clear difference in effect between these subgroups. Targeting specific PaO_2, SaO_2 or SpO_2 may be the right way to discern and compare interventions of oxygen supplementation and a standardized delivery of different F_IO_2 levels may be a too simplistic way to apply different levels of oxygen supplementation, as many patients will not need high F_IO_2 levels to reach an acceptable PaO_2, SaO_2 or SpO_2 target and some patients will need higher F_IO_2 levels to reach even a low PaO_2, SaO_2 or SpO_2 target. To summarise all available evidence however, we believe it is correct to meta-analyse trials randomising participants to a higher or lower oxygenation strategy to be able to explore an eventual signal of a difference in outcomes of the benefits and harms of the two strategies. Furthermore, the oxygenation targets used in some trials can be considered to be overlapping, meaning that these trials might not be categorised as comparing truly high to truly low targets [27, 54-57]. Clinical heterogeneity also included differences in diagnoses and settings. Nonetheless, statistical heterogeneity appeared to be low.

None of the included trials had overall low risk of bias and only two trials were fully blinded [58, 59]; this was not unexpected due to the complexity and difficulties of blinding interventions of oxygen

supplementation for participants and personnel, and possibly for outcome assessors. Inadequate blinding is therefore a limitation in the included trials, as it is associated with exaggeration of beneficial intervention effects and underestimation of harmful effects [60, 61]. We thus cannot rule out a biased effect estimate of the included trials.

To estimate the effects on SAEs, lung injuries and cardiovascular events reported in the included trials, we conducted two supplementary analyses to estimate the effect on the proportion of participants having one or more SAEs, lung injuries and cardiovascular events, which may be expected to lie between the effect estimates of the estimated highest reported proportion and the estimated cumulated number.

Our results in relation to previous reviews

Our systematic review includes twice as many trials as the review by Chu and colleagues, which indicated increased mortality with higher oxygenation strategies (RR 1.14, 95% CI 1.01-1.28) and rated the evidence as high quality [25]. Our results conflict with those of Chu. First, we found no evidence of a difference on mortality. Second, we do not agree on the certainty of evidence, which we believe should be downgraded for risk of bias when analysing all trials and inconsistency, especially the risk of outcome reporting bias seems substantial as 15 trials did not report any of our patient related outcomes measures. We performed TSA in order to control the risk of random errors in a cumulative meta-analysis and to prevent premature statements regarding the inferiority of higher versus lower oxygenation strategies. TSA was also used by Chu and colleagues, but they did not adjust for multiple outcomes and may have used an inadequate power of 80% [25, 62]. Including more information, we did not find a difference in mortality and were able to exclude a 15% relative change. Recently, we published a systematic review finding an increase in mortality with higher oxygenation strategies in patients admitted to the ICU in the traditional meta-analysis; however, TSA showed that the required information to detect or reject a 20% RRI was not reached and the

evidence was very low [63]. The findings of the current review, including results from two recently reported trials conducted in the ICU setting, could not demonstrate evidence of a difference in mortality. This highlights that care should be taken when concluding based on meta-analyses with insufficient information size.

Definitions of acute illness in systematic reviews often differs, and data are analysed and presented in different subgroups; therefore, it may be difficult to consider our assessed subpopulations in relation to other reviews. Our results regarding the lack of a 20% relative change in mortality in patients with acute myocardial infarction support the results of previous systematic reviews [64, 65]. We found no effect on mortality in patients randomised prior to hospital admission, in patients admitted to the ICU, in patients with any cerebral disease, in patients with any cardiac disease, in patients with trauma, and in patients with out-of-hospital-cardiac arrest.

Clinical implications and perspectives

We found no evidence supporting the use of either higher or lower oxygenation strategies in acutely ill adults. Despite a lack of robust evidence of effectiveness, oxygen administration is widely recommended in international clinical practice guidelines [1-3, 66]. However, a change towards a more restrictive approach is under way. Based on the results from the systematic reviews by Chu and colleagues [25], clinical practice guidelines are now being updated and revised and now recommend a restrictive oxygenation strategy [26].

We did not find evidence supporting a specific F_IO_2 or target of PaO_2, SaO_2 or SpO_2, particularly due to the very high clinical heterogeneity in the types of interventions in the trials included in this review [26, 62]. However, it may be worth noticing that almost all the point estimates in our meta-analyses favored a lower oxygenation strategy.

With our findings, we cannot reject that higher versus lower oxygenation strategies impact mortality, but any such effect appears to be below a relative change of 15%. We therefore need more patients randomised into trials with the lowest possible risk of bias to be able to show smaller, but still relevant differences in patient important outcomes with the use of higher versus lower oxygenation strategies.

CONCLUSIONS

The evidence for the use of higher versus lower oxygenation strategies in acutely ill adults is of low or very low certainty. Our analyses refuted a relative change of 15% in mortality and 20% in SAEs. The evidence is inconclusive regarding smaller effects of higher versus lower oxygenation strategies on mortality, SAEs, quality of life, lung injury, sepsis and cardiovascular events because too few participants have been randomised. Thus, more patients should be randomised in trials with the lowest possible risk of bias.

TABLES

Table 1. Characteristics of included trials

					Interventions						
	Trial/ comparison	**Country**	**Setting**	**Sample size**	**Duration, h**	**Higher group**			**Lower group**			**Maximum follow-up**
						F_IO_2/O_2 flow*	**PaO_2**	**SaO_2/SpO_2**	**F_IO_2/O_2 flow***	**PaO_2**	**SaO_2/SpO_2**	
1	Ali 2013 [50]	UK	Stroke	301	72	2 L/min by nasal cannula if baseline SpO_2 > 93% and 3 L/min if baseline SpO_2 ≤ 93%			No supplemental oxygen			6 months
2	Asfar 2017 [67]	France	Septic shock, invasively mechanically ventilated	442	24	1.00					88-95%	90 days
3	Austin 2010 [68]	Australia	AECOPD	405	Pre-hospital transport (mean 47	8-10 L/min by non-rebreather					88-92%	In-hospital

					min)	facemask						
4	Baekgaard 2019 [69]	Denmark	Trauma	41	24	15 L/min by non-rebreather facemask and F_IO_2 of 1.00 (or 0.80 if $SpO_2 \geq 98\%$) when mechanically ventilated					94%	30 days
5	Bardsley 2018 [70]	New Zealand	AECOPD	90	0.25	8 L/min by nebulisation mask			No supplemental oxygen (air 8 L/min by nebulisation mask)			-
6	Bickel 2011 [71]	Israel	Acute appendicitis	210	2	0.80 peroperatively, postoperatively 10 L/min by non-rebreather facemask			0.30 peroperatively, postoperatively 4 L/min by nasal cannula			14 days
7	Bray 2018 [72]	Australia	Cardiac arrest	62	Pre-hospital transport (mean 50 min)	1.00			2-4 L/min via bag-valve mask		≥ 94% (≥ 90% in amended protocol)	In-hospital
8	Butler 1987A *Skin oxygen study* [73]	UK	Limb ischaemia /amputation	20	48	0.28			No supplemental oxygen			14 days
9	Butler 1987B *Healing*	UK	Limb ischaemia /amputation	39	48	0.28			No supplemental oxygen			1 year

	study [73]											
10	Girardis 2016 [54]	Italy	Critical care	480	ICU stay (median 144)	≥ 0.40	≤ 20 kPa (150 mmHg)	97%-100%		9.3-13.3 kPa (70-100 mmHg)	94%-98%	60 days
11	Gomersall 2002 [55]	Hong Kong	AECOPD	36	Length of hospital stay (median 144)		> 9.0 kPa (67.5 mmHg)			> 6.6 kPa (50 mm Hg)		In-hospital
12	Heidari 2017 [74]	Iran	Acute coronary syndrome	79	6	4-6 L/min by nasal cannula			No supplemental oxygen			In-hospital
13	Hofmann 2017 [47, 75]	Sweden	Myocardial infarction	6629	6-12 (IQR 11.64)	6 L/min by open facemask			No supplemental oxygen (unless SpO_2 < 90%)			1 year
14	Huynh Ky 2017 [76]	Canada	Acute coronary syndrome	39	Maximum 24 (mean 12)			97%			92%	Not specified
15	ICU-ROX investigators 2019 [27]	New Zealand	Critical care, mechanically ventilated	1000	ICU admission, maximum 672 (median 120)	Conventional oxygen administration (F_IO_2 < 0.30 discouraged during mechanical ventilation)					91-96%	180 days
16	Ishii 2018 [77]	Japan	Critical care, invasively mechanically ventilated	51	Until first analysis of arterial blood sampling	1.00				100 mmHg (13.3 kPa)		3 days

17	Jakkula 2018 [49]	Finland	Cardiac arrest	123	36		20-25 kPa (150-187.5 mmHg)			10–15 kPa (75-112.5 mmHg)	95%-98%	6 months
18	Jun 2019 [56]	-	AECOPD and myocardial infarction, invasively mechanically ventilated	58	-	0.50-0.70 for the first 48 hours, hereafter 0.40-0.50			0.30-0.50			-
19	Khoshnood 2018 [78, 79]	Sweden	Myocardial infarction	160	Pre-hospital transport and PCI (mean 1.4)	10 L/min by open facemask			No supplemental oxygen (unless SpO_2 < 94%)			6 months
20	Kuisma 2006 [80]	Finland	Cardiac arrest	32	1	1.00			0.30		≥ 95%	In-hospital
21	Lång 2018 [81]	Finland	Traumatic brain injury	70	Mechanical ventilation, maximum 336 (mean 136)	0.70			0.40			6 months
22	Mazdeh 2015 [82]	Iran	Stroke	52	12	0.50			No supplemental oxygen			6 months
23	Meyhoff 2009 [46]	Denmark	Acute abdominal surgery	385	2 (postop)	0.80 peroperatively, postoperatively 0.80 by non-rebreather facemask			0.30 peroperatively, postoperatively 0.30 by non-rebreather facemask			3 months

24	NCT02378545 [83]	UK	Sepsis	50	ED stay	15 L/min by non-re-breather facemask					94%	90 days
25	NCT02687217 [57]	India	Acute appendicitis	60	2	≥ 0.50 peroperatively, 0.31 postoperatively			0.21 peroperatively, 0.28 postoperatively			-
26	Padma 2010 [84]	India	Stroke		12	10 L/min by open facemask			No supplemental oxygen or up to 2 L/min by open facemask		≥ 95%	3 months
27	Panwar 2016 [51]	Australia, New Zealand, France	Critical care, invasively mechanically ventilated	104	Mechanical ventilation (median 114)			≥ 96%			88-92%	90 days
28	Perrin 2011 [52]	New Zealand	Acute exacerbation of asthma	106	1	8 L/min by open facemask					93-95%	1 h
29	Ranchord 2012 [85]	New Zealand, UK	Myocardial infarction	148	6	6 L/min by open facemask. Concentrations were delivered		≥ 92%			93-96%	30 days
30	Rawles 1976 [58]	UK	Myocardial infarction	200	24	6 L/min by open facemask			No supplemental oxygen (air 6 L/min by open facemask)			In-hospital
31	Rodrigo 2003 [86]	Uruguay	Acute exacerbatio	77	0.33	1.00 oxygen by non-			0.28 by open facemask			20 min

			ns of asthma			rebreather facemask						
32	Rodrigues de Freitas Vianna 2017 [87]	Brazil	Critical care, invasively mechanically ventilated		Endotracheal suctioning procedure	1.00			0.20 above baseline F_IO_2			30 min
33	Roffe 2010 [88]	UK	Stroke	63	12 (nocturnally)	2 L/min via nasal cannula			No supplemental oxygen			14 days
34	Roffe 2017A *Continuous oxygen* [48]	UK	Stroke	4002	72	3 L/min by nasal cannula if baseline $SpO_2 \leq 93\%$ and 2 L/min if baseline $SpO_2 > 93\%$			No supplemental oxygen			90 days
35	Roffe 2017B *Nocturnal oxygen* [48]	UK	Stroke	4001	10 x 3 (nocturnally)	3 L/min if baseline $SpO_2 \leq 93\%$ or less and 2 L/min if baseline > 93%			No supplemental oxygen			90 days
36	Sepehrvand 2019 [89]	Canada	Acute heart failure	50	72			≥ 96%			90-92%	30 days
37	Shi 2017 [90]	China	Stroke	18	4	10 L/min by open facemask			No supplemental oxygen			7 days
38	Sills 2003 [91]	UK	Stroke	25	8 (nocturnally)	2 L/min by nasal cannula			No supplemental oxygen			3 days
39	Singhal 2005 [92]	US	Stroke	16	8	45 L/min by open facemask			0-3 L/min by nasal cannula		≥ 96%	3 months

40	Singhal 2013 [93]	US	Stroke	85	8	30-45 L/min by open facemask			No supplemental oxygen (air 30-45 L/min by open facemask)			3 months
41	Stewart 2019 [94]	New Zealand	Acute coronary syndrome		-			≥ 95%			90-94%	1 year
42	Stub 2015 [95]	Australia	Myocardial infarction	638	Pre-hospital transport and PCI (mean 1.09)	8 L/min by open facemask					94%	6 months
43	Taher 2016 [96]	Iran	Traumatic brain injury		6	0.80			0.50			6 months
44	Thomas 2019 [97]	UK	Cardiac arrest	35	1	1.00					94-98%	90 days
45	Ukholkina 2005 [98]	Russia	Myocardial infarction		3.5	0.40-0.60			No supplemental oxygen			-
46	Wijesinghe 2012 [53]	New Zealand	Pneumonia	150	1	8 L/min by open facemask					93-95%	1 hour
47	Wilson 1997 [99]	UK	Myocardial infarction	50	24	4L/min by open facemask			No supplemental oxygen			-
48	Wu 2014 [100]	China	AECOPD	9	0.25	group B: 6–7 L/min by nebulisation mask, group C: 8–9 L/min by nebulisation mask			group A: 4–5 L/min by nebulisation mask			30 minutes
49	Young 2014 [101]	New Zealand	Cardiac arrest	18	72	1.00 prehospitally, conventional		> 95% (suggested in ED			90-94%	72 h

						oxygen administration in ED and ICU		and ICU)				
50	Zughaft 2013 [59]	Sweden	Stable angina or acute coronary syndrome	304	PCI	3 L/min by nasal cannula			No supplemental oxygen (air 3 L/min by nasal cannula)			1 year

*The specific F_IO_2 is stated when delivered by mechanical ventilation, bag-valve mask (with flow ≥ 10 L/min), or venturi masks, unless otherwise specified

Table 2. Summary of findings

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher	Lower	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality - overall low risk of bias except for blinding												
8	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	798/9362 (8.5%)	562/6794 (8.3%)	**RR 0.98** (0.89 to 1.09)	**2 fewer per 1,000** (from 9 fewer to 7 more)	⨁⨁◯◯ LOW	CRITICAL
All-cause mortality - All trials												
34	randomised trials	serious [d]	not serious	serious [b]	serious [c]	publication bias strongly suspected [e]	1102/11037 (10.0%)	812/8402 (9.7%)	**RR 1.04** (0.96 to 1.13)	**4 more per 1,000** (from 4 fewer to 13 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher	Lower	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events - overall low risk of bias except for blinding												
3	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	705/5313 (13.3%)	387/2743 (14.1%)	**RR 0.99** (0.89 to 1.12)	**1 fewer per 1,000** (from 16 fewer to 17 more)	⨁⨁◯◯ LOW	CRITICAL
Serious adverse events - All trials												
6	randomised trials	serious [f]	not serious	serious [b]	serious [c]	none	924/5727 (16.1%)	578/3147 (18.4%)	**RR 1.03** (0.95 to 1.13)	**6 more per 1,000** (from 9 fewer to 24 more)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life - All trials												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher	Lower	Relative (95% CI)	Absolute (95% CI)		
6	randomised trials	serious [g]	serious [h]	serious [b]	serious [c]	none	4851	2594	-	MD **0.37 higher** (1.55 lower to 2.29 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Lung injury - All trials												
10	randomised trials	serious [i]	not serious	serious [b]	serious [c]	publication bias strongly suspected [e]	248/5934 (4.2%)	172/3293 (5.2%)	**RR 0.92** (0.76 to 1.11)	**4 fewer per 1,000** (from 13 fewer to 6 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Sepsis - All trials												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher	Lower	Relative (95% CI)	Absolute (95% CI)		
4	randomised trials	serious [j]	not serious	serious [b]	serious [c]	none	33/649 (5.1%)	20/658 (3.0%)	**RR 1.64** (0.96 to 2.80)	**19 more per 1,000** (from 1 fewer to 55 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Cardiovascular events - All trials												
16	randomised trials	serious [k]	not serious	serious [b]	serious [c]	publication bias strongly suspected [e]	277/9580 (2.9%)	225/7027 (3.2%)	**RR 1.06** (0.86 to 1.31)	**2 more per 1,000** (from 4 fewer to 10 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Participants and personnel and/or outcome assessors were not blinded; b. Differences in inspiratory oxygen fraction and target of arterial oxygenation in the experimental and control groups between trials; c. Wide confidence intervals; d. 26/34 trials were overall at high risk of bias; e. Funnel plot indicated asymmetry; however, Harbord test indicated no small-study effects; f. 27/35 trials were at overall high risk of bias; g. 2/6 trials were overall high risk of bias; h. I^2=57% (P=0.04), Signs of heterogeneity in forest plot; i. 5/10 trials were at overall high risk of bias; j. 3/4 trials were at overall high risk of bias; k. 5/16 trials were at overall high risk of bias.

FIGURE LEGENDS

Figure 1. Forest plot on mortality in trials with overall low risk of bias except for blinding versus trials with overall high risk of bias. Size of squares for risk ratio reflects weight of trial in pooled analysis. Horizontal bars represent 95% confidence interval.

Figure 2. Trial sequential analysis of overall low risk of bias except for blinding trials of the effect of higher versus lower oxygenation strategies on mortality using an alpha of 3.3%, a power of 90%, control event proportion of 8.27% (from the included trials), a diversity (D2) of 0%, and a relative risk increase of 15%. The relative risk was 0.98 with a TSA-adjusted CI 0.86-1.12. Futility was reached, suggesting that a relative change of 15% can be excluded.

Figure 3. Forest plot on mortality stratified by population group. Size of squares for risk ratio reflects weight of trial in pooled analysis. Horizontal bars represent 95% confidence interval.

Figure 4. Forest plot on the proportion of participants with at least one serious adverse event, as reported by trialists, in trials with overall low risk of bias except for blinding versus trials with overall high risk of bias. Size of squares for risk ratio reflects weight of trial in pooled analysis. Horizontal bars represent 95% confidence interval.

Figure 5. Trial sequential analysis of overall low risk of bias except for blinding trials of the effect of higher versus lower oxygenation strategies on the proportion of participants with at least one serious adverse event, as reported by trialists using an alpha of 3.3%, a power of 90%, control event proportion of 14.11% (from the included trials), a diversity (D2) of 0%, and a relative risk increase of 20%. The relative risk was 0.99 with a TSA-adjusted CI 0.83-1.19. Required information size was reached, suggesting that a relative change of 20% can be excluded.

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Author contributions

All authors contributed to the study protocol. Search strategy was built by MB who also performed the literature search. MB, OLS and SRK performed the literature screening, data extraction and risk of bias evaluation. MB conducted the analyses. The first draft of the manuscript was written by MB and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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ADDITIONAL INFORMATION

The e-Appendix can be found in the Supplemental Materials section of the online article.

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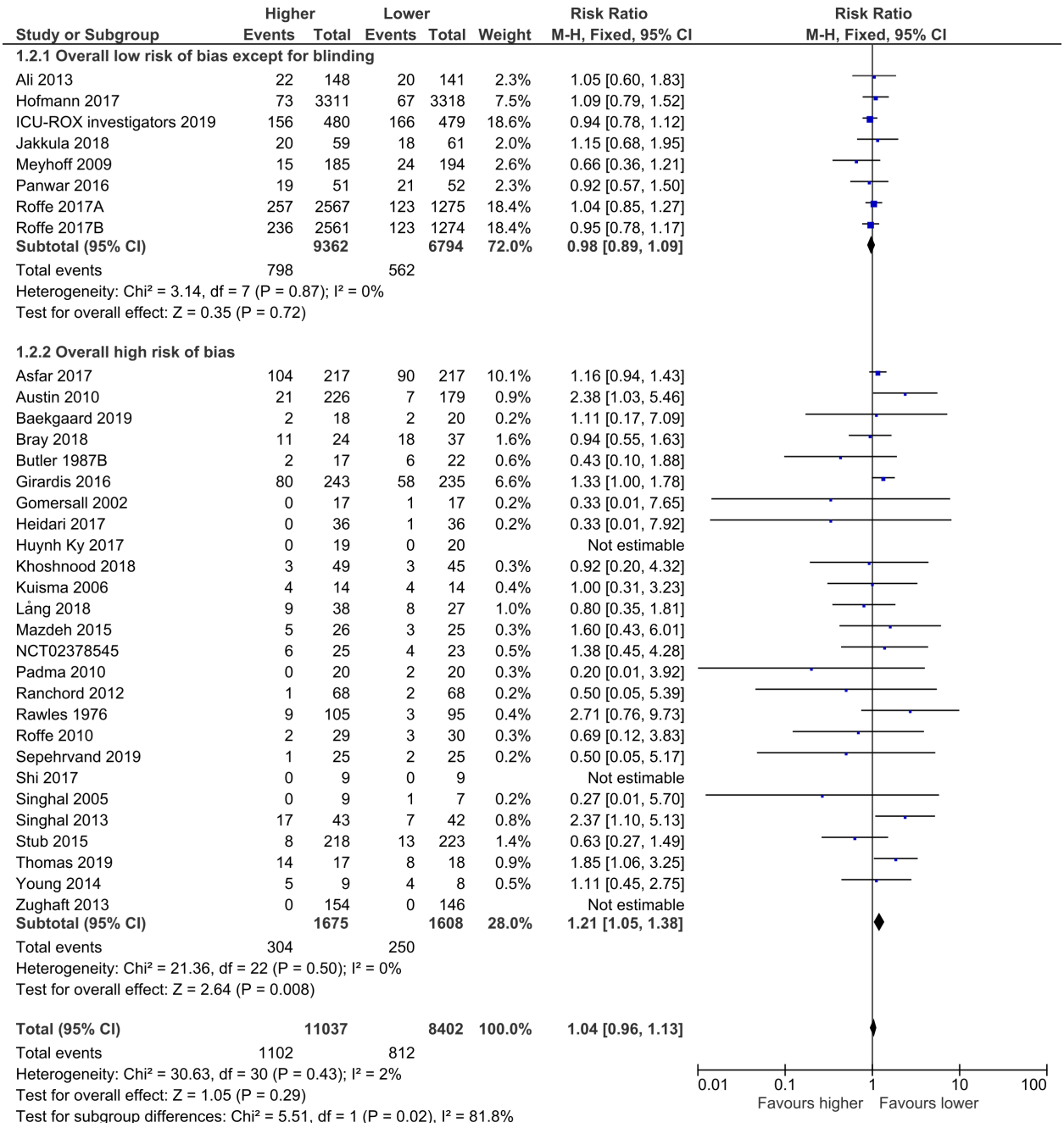
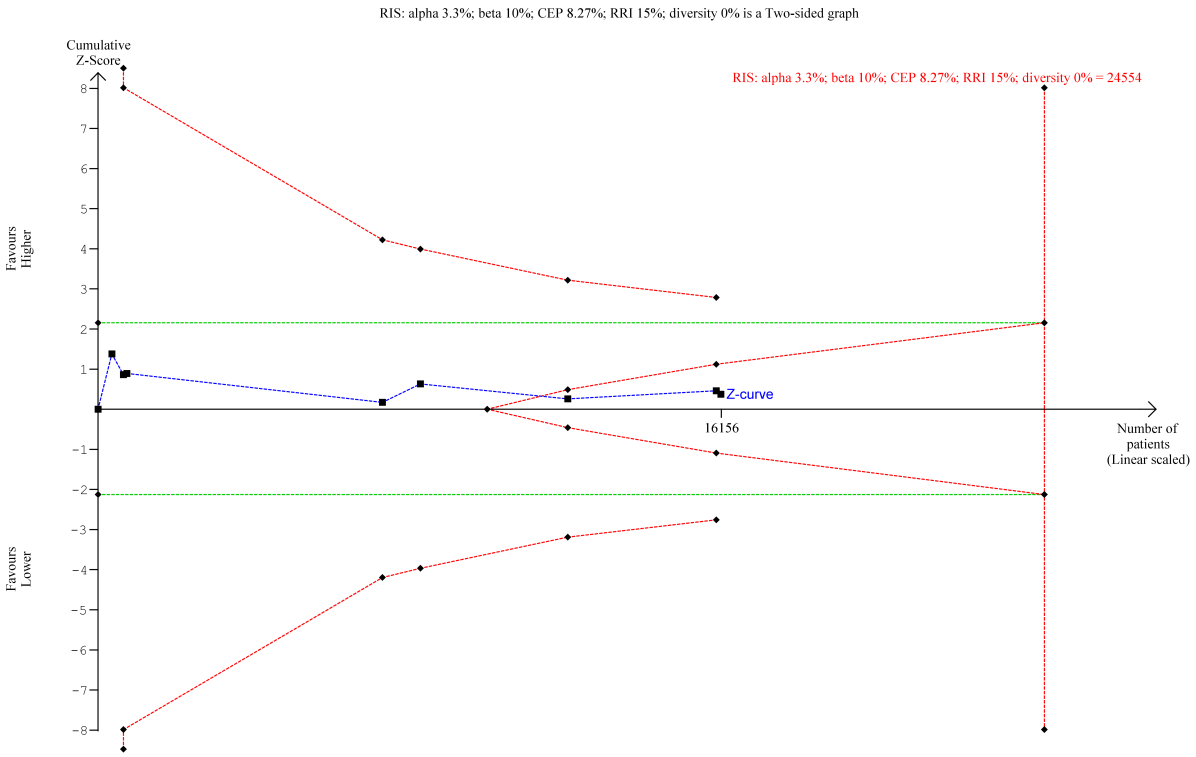
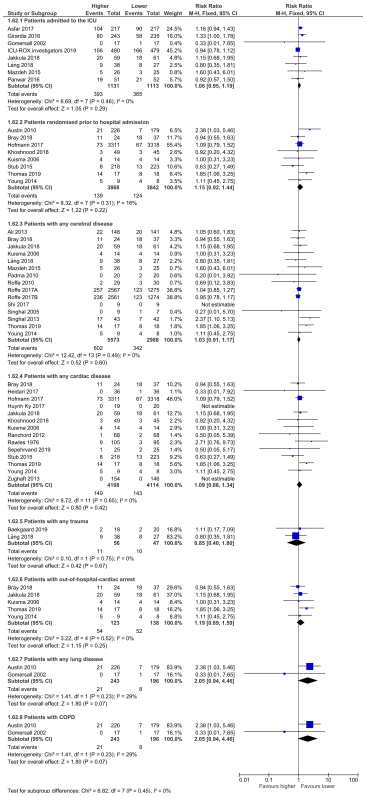

Higher
Lower
Risk Ratio
Risk Ratio
Study or Subgroup
Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
1.2.1 Overall low risk of bias except for blinding
Ali 2013 22 148 20 141 2.3% 1.05 [0.60, 1.83]
Hofmann 2017 73 3311 67 3318 7.5% 1.09 [0.79, 1.52]
ICU-ROX investigators 2019 156 480 166 479 18.6% 0.94 [0.78, 1.12]
Jakkula 2018 20 59 18 61 2.0% 1.15 [0.68, 1.95]
Meyhoff 2009 15 185 24 194 2.6% 0.66 [0.36, 1.21]
Panwar 2016 19 51 21 52 2.3% 0.92 [0.57, 1.50]
Roffe 2017A 257 2567 123 1275 18.4% 1.04 [0.85, 1.27]
Roffe 2017B 236 2561 123 1274 18.4% 0.95 [0.78, 1.17]
Subtotal (95% CI) 9362 6794 72.0% 0.98 [0.89, 1.09]
Total events 798 562
Heterogeneity: Chi² = 3.14, df = 7 (P = 0.87); I² = 0%
Test for overall effect: Z = 0.35 (P = 0.72)
1.2.2 Overall high risk of bias
Asfar 2017 104 217 90 217 10.1% 1.16 [0.94, 1.43]
Austin 2010 21 226 7 179 0.9% 2.38 [1.03, 5.46]
Baekgaard 2019 2 18 2 20 0.2% 1.11 [0.17, 7.09]
Bray 2018 11 24 18 37 1.6% 0.94 [0.55, 1.63]
Butler 1987B 2 17 6 22 0.6% 0.43 [0.10, 1.88]
Girardis 2016 80 243 58 235 6.6% 1.33 [1.00, 1.78]
Gomersall 2002 0 17 1 17 0.2% 0.33 [0.01, 7.65]
Heidari 2017 0 36 1 36 0.2% 0.33 [0.01, 7.92]
Huynh Ky 2017 0 19 0 20 Not estimable
Khoshnood 2018 3 49 3 45 0.3% 0.92 [0.20, 4.32]
Kuisma 2006 4 14 4 14 0.4% 1.00 [0.31, 3.23]
Lång 2018 9 38 8 27 1.0% 0.80 [0.35, 1.81]
Mazdeh 2015 5 26 3 25 0.3% 1.60 [0.43, 6.01]
NCT02378545 6 25 4 23 0.5% 1.38 [0.45, 4.28]
Padma 2010 0 20 2 20 0.3% 0.20 [0.01, 3.92]
Ranchord 2012 1 68 2 68 0.2% 0.50 [0.05, 5.39]
Rawles 1976 9 105 3 95 0.4% 2.71 [0.76, 9.73]
Roffe 2010 2 29 3 30 0.3% 0.69 [0.12, 3.83]
Sepehrvand 2019 1 25 2 25 0.2% 0.50 [0.05, 5.17]
Shi 2017 0 9 0 9 Not estimable
Singhal 2005 0 9 1 7 0.2% 0.27 [0.01, 5.70]
Singhal 2013 17 43 7 42 0.8% 2.37 [1.10, 5.13]
Stub 2015 8 218 13 223 1.4% 0.63 [0.27, 1.49]
Thomas 2019 14 17 8 18 0.9% 1.85 [1.06, 3.25]
Young 2014 5 9 4 8 0.5% 1.11 [0.45, 2.75]
Zughaft 2013 0 154 0 146 Not estimable
Subtotal (95% CI) 1675 1608 28.0% 1.21 [1.05, 1.38]
Total events 304 250
Heterogeneity: Chi² = 21.36, df = 22 (P = 0.50); I² = 0%
Test for overall effect: Z = 2.64 (P = 0.008)
Total (95% CI) 11037 8402 100.0% 1.04 [0.96, 1.13]
Total events 1102 812
Heterogeneity: Chi² = 30.63, df = 30 (P = 0.43); I² = 2%
Test for overall effect: Z = 1.05 (P = 0.29)
Test for subgroup differences: Chi² = 5.51, df = 1 (P = 0.02), I² = 81.8%
0.01 0.1 1 10 100
Favours higher Favours lower





Study or Subgroup	Higher Events	Higher Total	Lower Events	Lower Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.18.1 Overall low risk of bias except for blinding						
Meyhoff 2009	63	185	65	194	9.3%	1.02 [0.77, 1.35]
Roffe 2017A	348	2567	161	1275	31.4%	1.07 [0.90, 1.28]
Roffe 2017B	294	2561	161	1274	31.4%	0.91 [0.76, 1.09]
Subtotal (95% CI)		**5313**		**2743**	**72.0%**	**0.99 [0.89, 1.12]**
Total events	705		387			
Heterogeneity: Chi² = 1.73, df = 2 (P = 0.42); I² = 0%						
Test for overall effect: Z = 0.10 (P = 0.92)						
1.18.2 Overall high risk of bias						
Asfar 2017	185	217	165	217	24.1%	1.12 [1.02, 1.23]
Singhal 2013	24	43	20	41	3.0%	1.14 [0.76, 1.73]
Zughaft 2013	10	154	6	146	0.9%	1.58 [0.59, 4.24]
Subtotal (95% CI)		**414**		**404**	**28.0%**	**1.14 [1.03, 1.26]**
Total events	219		191			
Heterogeneity: Chi² = 0.53, df = 2 (P = 0.77); I² = 0%						
Test for overall effect: Z = 2.59 (P = 0.010)						
Total (95% CI)		**5727**		**3147**	**100.0%**	**1.03 [0.95, 1.13]**
Total events	924		578			
Heterogeneity: Chi² = 6.01, df = 5 (P = 0.31); I² = 17%						
Test for overall effect: Z = 0.77 (P = 0.44)						
Test for subgroup differences: Chi² = 3.08, df = 1 (P = 0.08), I² = 67.6%