Targeted interventions in mechanically ventilated patients

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PART I

OXYGEN

Higher versus lower oxygenation strategies in the general intensive care unit population:

a systematic review, meta-analysis and meta-regression of randomized controlled trials

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ABSTRACT

Purpose

Oxygen therapy is vital in adult intensive care unit (ICU) patients, but it is indistinct whether higher or lower oxygen targets are favorable. Our aim was to update the findings of randomized controlled trials (RTCs) comparing higher and lower oxygen strategies.

Materials and Methods

MEDLINE, EMBASE, and Web of Science were searched. RCTs comparing higher (liberal, hyperoxia) and lower (conservative, normoxia) oxygen in adult mechanically ventilated ICU patients were included. The main outcome was 90-day mortality; other outcomes include serious adverse events (SAE), support free days and length of stay (LOS).

Results

No significant difference was observed for 90-day mortality. A lower incidence was found for SAEs, favoring lower oxygenation (OR, 0.86; 95%CI, 0.77-0.96; I^2 13%). No differences were observed in either support free days at day 28 or ICU and hospital LOS.

Conclusions

No difference was found for 90-day mortality, support free days and ICU and hospital LOS. However, a lower incidence of SAEs was found for lower oxygenation. These findings may have clinical implications for practice guidelines, yet it remains of paramount importance to continue conducting clinical trials, comparing groups with a clinically relevant contrast and focusing on the impact of important side effects.

INTRODUCTION

Oxygen therapy has been successfully used in the acute care setting for over a century (1). Most critically ill patients are at risk for hypoxemia which may cause tissue damage, organ failure or even death. Owing to these risks, the professional norm among health care specialists is to attentively avoid and sometimes even overcompensate hypoxemic events by liberally administering oxygen or deliberately inducing supranormal arterial oxygen levels (2, 3). Oxygen has proven to be very effective in the treatment of hypoxemic patients, but may not be beneficial in all patients. The deleterious properties of oxygen are increasingly acknowledged. Harmful effects can include cerebral and coronary vasoconstriction, reduction of cardiac output, absorption atelectasis, acute lung injury and central nervous system toxicity (4). In addition, studies repeatedly showed a negative correlation between hyperoxia and patient centered outcomes (5-7). Accordingly, newer guidelines on oxygen therapy generally recommend a more conservative approach (8). However, not all cautions with regards to hyperoxia have been conclusively justified as observational studies and randomized controlled trials (RCTs) comparing higher versus lower oxygen targets show heterogeneous results.

Few systematic reviews have been conducted in order to provide guidance for administering oxygen in a safe and efficient manner to intensive care unit (ICU) patients. The results were unequivocal (5, 9-12), but new studies have recently been published (13, 14). Furthermore, important data concerning vital secondary outcomes, such as ischemic events and shock, have not been aggregated in detail before. By systematically combining all available evidence from RCTs comparing higher and lower targeted oxygen strategies in mechanically ventilated patients, we aimed to provide conclusive insights into favorable oxygen therapy.

MATERIALS AND METHODS

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews and meta-analyses (supplemental table 1) (15). The protocol of this study was registered on PROSPERO (CRD42021286372). Inclusion criteria were as follows: RCTs comparing higher (liberal) and lower (conservative) oxygen therapy strategies in the general adult ICU population of which the majority is mechanically ventilated.

Information sources and search

After consulting a librarian, electronic databases of Medline (1962-2021), EMBASE (1970-2021) and Web of Science (1970-2021) were searched. This search was supplemented

by manually screening reference lists of included studies and other relevant articles. Full search terms and search strategies can be found in supplemental file 1. Main MeSH headings and key words were "oxygen inhalation therapy", "hyperoxia", "hypoxia", "oxygen" and "respiration, artificial". The literature search was last updated August 9th 2022.

Study selection and Data collection process

Two authors (L.I.W, H.J.F.H) independently and in pairs screened articles on title and abstract. Reports considered potential for inclusion were screened in full text. Differences in this process were resolved by consensus. When no consensus was reached, a third co-author would resolve the issue. No language or timeline restrictions were applied. Studies were excluded using the following criteria: patients younger than 18 years, animal studies, extracorporeal life support and perioperative settings. Studies that solely focused on one specific patient group (e.g. myocardial or cerebral infarction) were excluded to improve the comparability of the study population. Duplicates were removed using the method of Bramer et al (9).

Data analysis and outcomes

Data abstraction was done by two content area experts (L.I.W., H.J.F.H) using an a priori created electronical standardized data abstraction sheet. Extractions were reviewed by two review authors independently. Disagreements were resolved by consensus. If no consensus could be reached, a third co-author would resolve the issue. The main outcome of interest was mortality at day 90. Mortality at day 28, day 180 and ICU and hospital mortality were also analyzed. Other outcomes were adverse events, support-free days at day 28 and length of stay (LOS).

Corresponding authors were contacted to clarify important missing data, for further trial details and when outcome data was not available in mean and standard deviation (SD). When no mean and SD could be provided the data was omitted from the analysis. The Grading Of Recommendation, Assessment, Development and Evaluation (GRADE) approach was used to grade the certainty of evidence (supplemental table 3) (16). Heterogeneity between studies and between subgroups was assessed by visual inspection of the forest plots by checking the point estimates and the confidence interval (CI) overlap. Additionally, Chi^2 and I^2 statistics were used and presented as p-values and percentages. A low p-value ($p<0.1$) was considered as evidence of heterogeneity of intervention effects. An I^2 of 0 to 40% was considered not important, 30 to 60% was considered moderate, 50 to 90% was considered substantial and 75 to 100% considerable (17). Interventions effects were assessed using a random effects model.

Odd ratios (ORs) with 95% CIs were calculated for dichotomous data, mean difference with CIs for continuous outcomes. Dichotomous data was analyzed using a Mantel and Haenszel (M-H) model; continuous data using an inverse variance model. Pooled estimates are displayed in forest plots. The effects of hyperoxia by achieved oxygenation in the randomized groups were analyzed using a meta-regression framework (16). For this meta-regression analyses we calculated a combined score in order to assess the effects of the achieved difference in PaO_2 (contrast) between the oxygenation groups in combination with the degree of hyperoxia that was achieved in the higher oxygenation group. Hence, the combined score was calculated as: between group difference in achieved PaO_2 plus the achieved PaO_2 in the highest group. The ORs were based on the 90-day mortality. Our hypothesis was that a higher between-group difference and a more severe hyperoxic target in the higher group, increase the effect size for 90-day mortality. All analyses were conducted using RevMan 5.3 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark) and R version 4.0.3. (R Foundation for Statistical Computing, Vienna, Austria) with RStudio (RStudio, Boston, MA).

In order to assess bias, the Cochrane risk of bias tool for randomized trials was used (18). Reporting bias was displayed in a funnel plot, using standard errors of the intervention effect estimate. Asymmetry was tested by visual inspection.

RESULTS

Study selection and study characteristics

Figure 1 depicts the study flowchart. Our search strategy resulted in 1551 studies considered for inclusion after deleting duplicates. In total, 68 full-text articles were assessed for eligibility after title and abstract screening. The most important exclusion reasons were study types other than RCTs, post hoc analyses or lack of comparison between higher and lower oxygenation. For the final analysis nine studies with 5807 patients were included (table 1) (13, 14, 19-25). Data collection took place between 2010 and 2020; study reports were published between 2015 and 2021. All included studies were RCTs comparing a higher versus a lower oxygenation in mechanically ventilated patients focusing on the general ICU population. Either PaO_2, SpO_2, FiO_2 or a combination of these parameters were used to pursue oxygenation targets. The duration of the interventions ranged from 24 hours to 90 days.

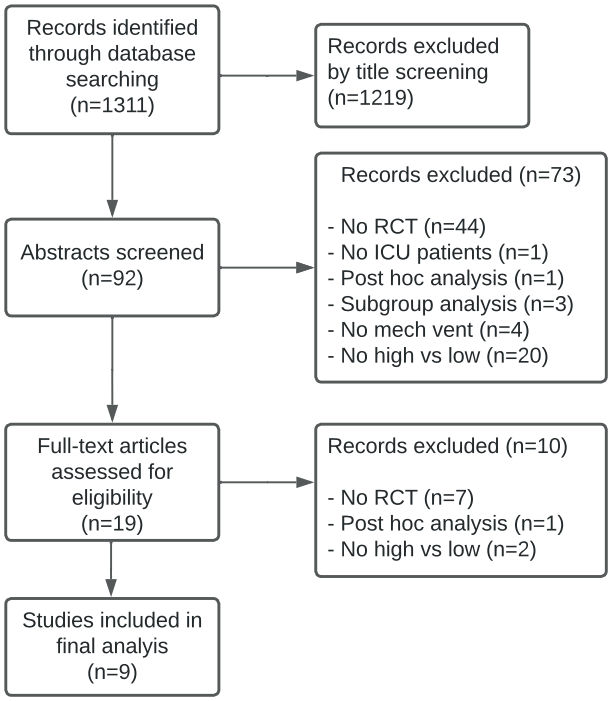

Figure 1. Flowchart of study selection

Risk of bias in studies

Overall, the risk of bias was moderate to low, except for blinding and early stopping bias (supplemental table 2, supplemental figure 1,2). Due to the design of the trials, it was essentially unfeasible to blind clinicians for the assigned treatment group. If clinicians were not blinded but outcome assessors were, the trial was graded low risk of bias for blinding. Visual inspection of the funnel plot suggested no funnel plot asymmetry (supplemental figures 3, 4).

Main outcome

Mortality at day 28, day 90, day 180, in the ICU and in the hospital were assessed separately (figure 2). No effect of different oxygenation strategies was found for mortality at day 90 (OR, 1.01; 95% CI, 0.85-1.20; I^2, 38%). The certainty of evidence, using the GRADE approach, was rated low (supplemental table 3). Also no difference was seen at day 28 (OR, 0.94; 95% CI, 0.63-1.40; I^2, 43%; very low certainty), day 180 (OR, 1.05; 95% CI, 0.81-1.38; low certainty), ICU mortality (OR, 0.90; 95% CI, 0.63-1.28; I^2, 43%; low certainty) or hospital mortality (OR, 0.86; 95% CI, 0.54-1.38; I^2, 50%; very low certainty).

Table 1. Characteristics of included studies

Study	Journal	Year	Country	Sample size	Population	Intervention		Primary endpoint	Duration intervention
						Lower oxygenation	Higher oxygenation		
Asfar (20)	Lancet	2017	France	442	Sepsis	SpO_2 88%-95%	FiO_2 1.0	28 day mortality	24h
Barrot (21)	NEJM	2020	France	205	ARDS	PaO_2 55-70 mm Hg or SpO_2 88-92%	PaO_2 90-105 mm Hg or SpO_2 at least 96%	28 day mortality	7 days
Gelissen (14)	JAMA	2021	Netherlands	400	Total ICU population	PaO_2 8-12 kPa	PaO_2 14-18 kPa	Cumulative daily delta SOFA score from day 1 to day 14	14 days or ICU discharge
Girardis (22)	JAMA	2016	Italy	480	Total ICU population	PaO_2 70-100 mm Hg or SpO_2 94-98%	PaO_2 up to 150 mm Hg or SpO_2 97-100%	ICU mortality	ICU discharge
Mackle (19)	NEJM	2019	New Zealand, Australia	1000	Total ICU population	SpO_2 91-97%, FiO_2 as low as possible	≥ 91% without upper limit	Number of ventilator free days	ICU discharge or day 28
Martin (25)	JICS	2021	England	34	Total ICU population	SpO_2 88-92%	SpO_2 ≥ 96%	Feasibility	Until extubation, tracheostomy, transfer or death
Panwar (23)	AJRCCM	2015	Australia, New Zealand, France	104	Total ICU population	SpO_2 of 88-92%	SpO_2 ≥ 96%	Mean AUC for SpO_2, SaO_2, PaO_2 and FiO_2. % spent off target	Entire duration of mechanical ventilation
Schjørring (13)	NEJM	2021	Denmark, Switzerland, Finland, The Netherlands, Norway, the United Kingdom, Iceland	2928	Total ICU population	PaO_2 60 mm Hg	PaO_2 90 mm Hg	90 day mortality	ICU discharge or day 90
Yang (24)	J Thorac Dis	2019	China	214	Total ICU population	SpO_2 of 90-95%	SpO_2 of 96-100%	28 day mortality	14 days or ICU discharge

Study or Subgroup	Lower targets Events	Total	Higher targets Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.1.1 Day 28						
Asfar Lancet 2017	77	217	93	217	44.6%	0.73 [0.50, 1.08]
Barrot NEJM 2020	34	99	27	102	27.7%	1.45 [0.79, 2.66]
Yang JTD 2019	26	100	32	114	27.7%	0.90 [0.49, 1.65]
Subtotal (95% CI)		**416**		**433**	**100.0%**	**0.94 [0.63, 1.40]**
Total events	137		152			
Heterogeneity: Tau² = 0.05; Chi² = 3.49, df = 2 (P = 0.17); I² = 43%						
Test for overall effect: Z = 0.31 (P = 0.75)						
1.1.2 Day 90						
Asfar Lancet 2017	90	217	104	217	13.3%	0.77 [0.53, 1.13]
Barrot NEJM 2020	44	99	31	102	7.2%	1.83 [1.03, 3.27]
Gelissen JAMA 2021	72	205	67	205	12.1%	1.12 [0.74, 1.68]
Girardis JAMA 2016	58	235	80	243	12.5%	0.67 [0.45, 1.00]
Mackle NEJM 2019	166	479	156	480	19.7%	1.10 [0.84, 1.44]
Martin JICS 2021	8	17	6	17	1.5%	1.63 [0.41, 6.46]
Panwar AJRCCM 2015	21	52	19	51	4.2%	1.14 [0.52, 2.52]
Schjørring NEJM 2021	618	1441	613	1447	29.5%	1.02 [0.88, 1.18]
Subtotal (95% CI)		**2745**		**2762**	**100.0%**	**1.01 [0.85, 1.20]**
Total events	1077		1076			
Heterogeneity: Tau² = 0.02; Chi² = 11.36, df = 7 (P = 0.12); I² = 38%						
Test for overall effect: Z = 0.11 (P = 0.91)						
1.1.3 Day 180						
Mackle NEJM 2019	170	476	164	475	100.0%	1.05 [0.81, 1.38]
Subtotal (95% CI)		**476**		**475**	**100.0%**	**1.05 [0.81, 1.38]**
Total events	170		164			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.38 (P = 0.70)						
1.1.4 ICU						
Barrot NEJM 2020	36	99	27	102	19.0%	1.59 [0.87, 2.90]
Gelissen JAMA 2021	50	205	49	195	24.7%	0.96 [0.61, 1.51]
Girardis JAMA 2016	25	216	44	218	21.5%	0.52 [0.30, 0.88]
Martin JICS 2021	6	17	5	17	5.4%	1.31 [0.31, 5.53]
Panwar AJRCCM 2015	13	52	12	51	11.4%	1.08 [0.44, 2.67]
Yang JTD 2019	21	100	32	114	18.0%	0.68 [0.36, 1.28]
Subtotal (95% CI)		**689**		**697**	**100.0%**	**0.90 [0.63, 1.28]**
Total events	151		169			
Heterogeneity: Tau² = 0.08; Chi² = 8.80, df = 5 (P = 0.12); I² = 43%						
Test for overall effect: Z = 0.60 (P = 0.55)						
1.1.5 Hospital						
Gelissen JAMA 2021	66	205	61	195	45.2%	1.04 [0.68, 1.59]
Girardis JAMA 2016	52	216	74	218	45.3%	0.62 [0.41, 0.94]
Martin JICS 2021	7	17	5	17	9.5%	1.68 [0.41, 6.96]
Subtotal (95% CI)		**438**		**430**	**100.0%**	**0.86 [0.54, 1.38]**
Total events	125		140			
Heterogeneity: Tau² = 0.08; Chi² = 3.99, df = 2 (P = 0.14); I² = 50%						
Test for overall effect: Z = 0.63 (P = 0.53)						

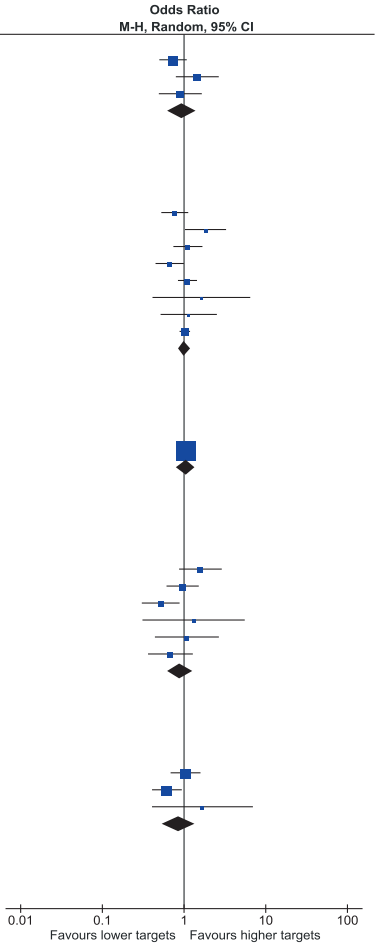

Figure 2. Forest plot mortality

Other outcomes

Adverse events were categorized in the following subgroups: myocardial ischemia, intestinal ischemia, ischemic stroke, respiratory infection, systemic infection, shock, organ failure, renal replacement therapy and arrythmias (figure 3). Regarding the adverse infectious events, respiratory infection (OR, 0.88; 95% CI, 0.63 -1.22; I^2, 0%) showed no significant difference between groups, although lower targets were favorable in cases of systemic infection (OR, 0.51; 95% CI, 0.29-0.88; I^2, 0%). The evidence was graded very low for both outcomes. For ischemia, including myocardial ischemia (OR, 1.29; 95% CI, 0.61-2.73; I^2, 14%; very low certainty), intestinal ischemia (OR, 1.12; 95% CI, 0.43-2.93; I^2, 47%; very low certainty) and ischemic stroke (OR, 0.94; 95% CI, 0.44-2.04; I^2, 12%; very low certainty), an uncertain effect was found considering the wide confidence intervals. Overall, the incidence of adverse events showed a significant OR of 0.86 (95% CI, 0.77-0.96; I^2, 13%) in favor of lower targets. The certainty of evidence was graded very low.

Support-free days were analyzed as ventilator- and vasopressor-free days at day 28 (figure 4). In general, the support-free days did not show a significant difference (mean difference (MD), 0.19; 95% CI, -0.40-0.78; I^2, 24%). The evidence was graded very low.

The analysis of LOS was categorized according to two subgroups (figure 5): hospital LOS (MD, -0.19; 95% CI, -8.43-8.04; I^2, 42%; very low certainty) and ICU LOS (MD, -0.64; 95% CI, -1.75-0.47; I^2, 0%; very low certainty). No significant differences were observed in the different subgroups.

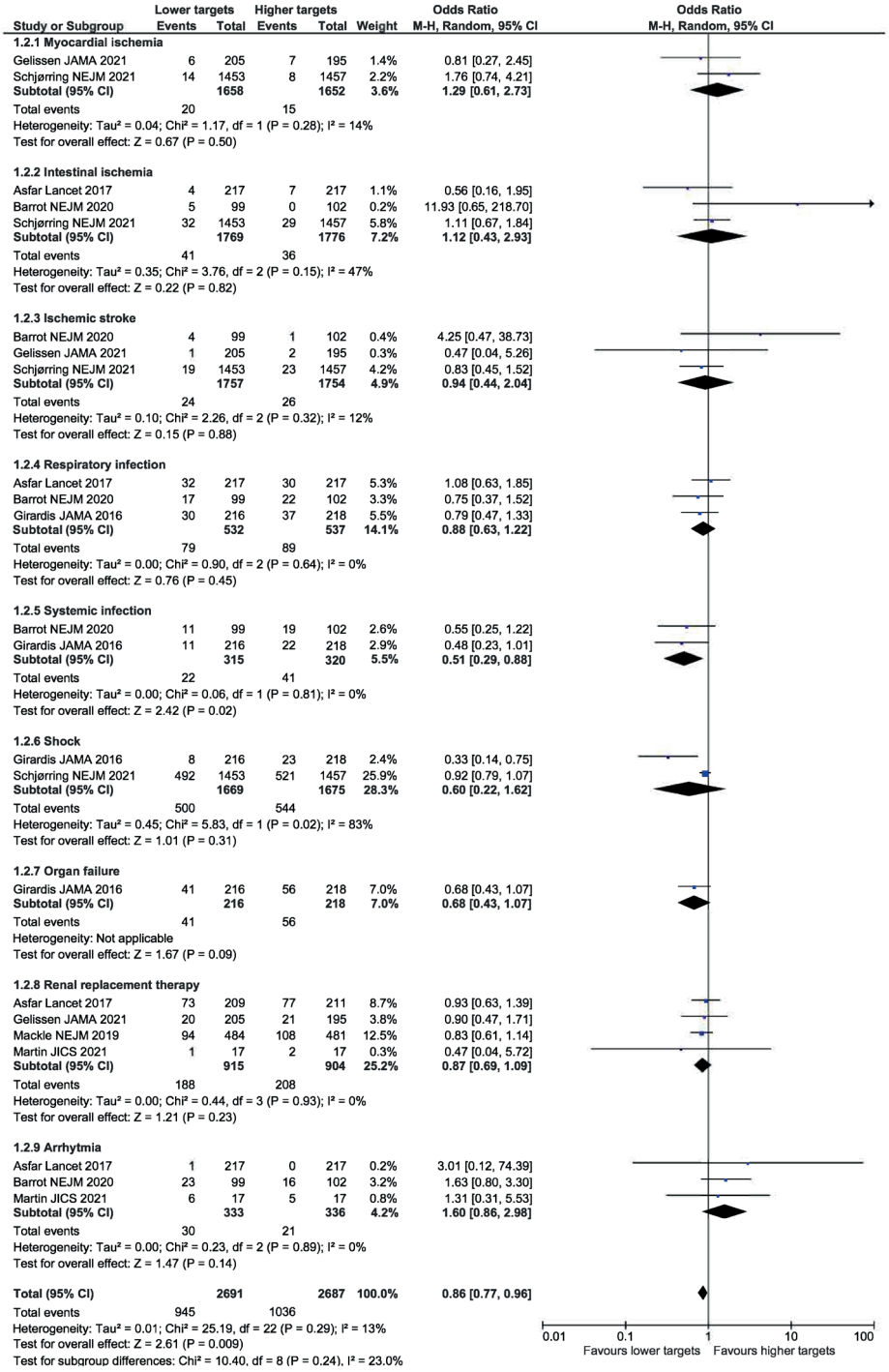

Figure 3. Forest plot serious adverse events. Patients from each study are counted once in the test for overall effect.

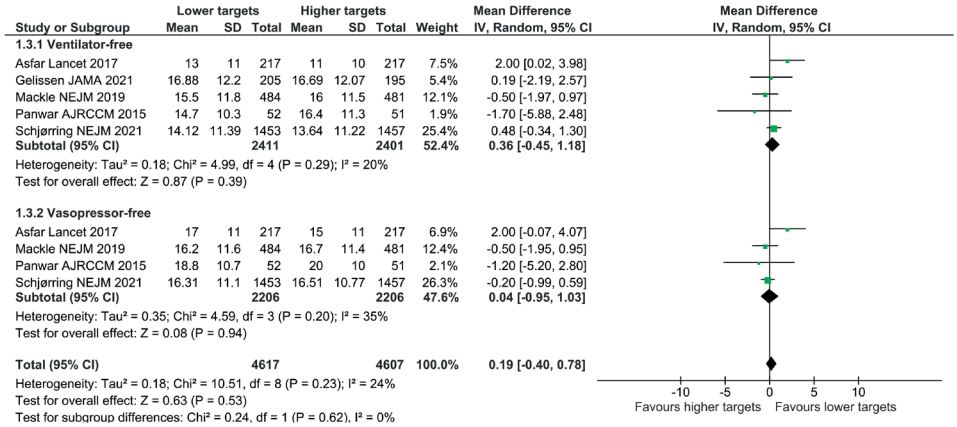

Figure 4. Forest plot support free days at day 28

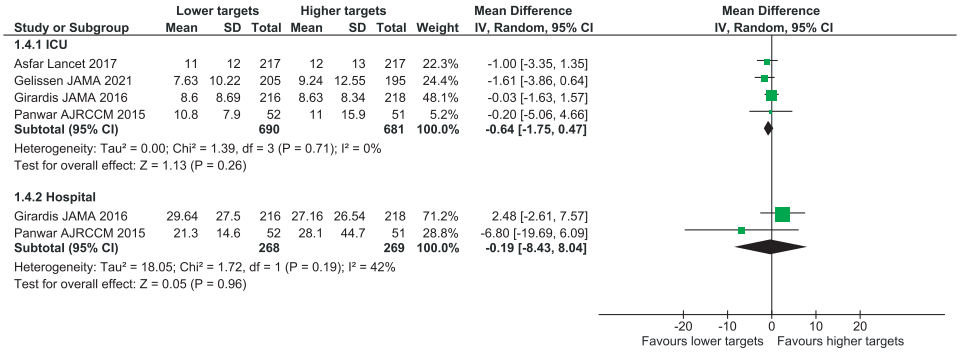

Figure 5. Forest plot hospital and ICU length of stay.

Meta-regression

All included studies in this meta-analysis were assessed using the GRADE approach (16). In most cases, the certainty of evidence was very low to low (supplemental table 3). Due to a variety in the chosen targets of the studies, we performed a meta-regression analysis that compared the odds for lower oxygenation on 90-day mortality for different achieved oxygenation targets. The regression was performed for both the achieved high and low oxygenation groups (supplemental Figures 5, 6) and for the combined score (Figure 6). The combined score is calculated by combining the achieved difference between the high and low oxygenation targets and the achieved higher oxygenation targets (Table 4, supplemental digital content). Figure 6 shows that this combined score is in the same order of magnitude for the majority of the trials (13, 14, 19, 21-23, 25) and the OR of mortality in the lower group approximates 1. One

trial (20) showed a combined score of 260 mm Hg in combination with a lower OR for mortality in the lower group. Taken together, the risk of mortality after 90 days in the lower group may be dependent on the combined score, i.e. the combination of the difference of achieved oxygenation and the severity of achieved hyperoxia in the higher group. However, the beta associated with this meta-regression analysis did not reach statistical significance.

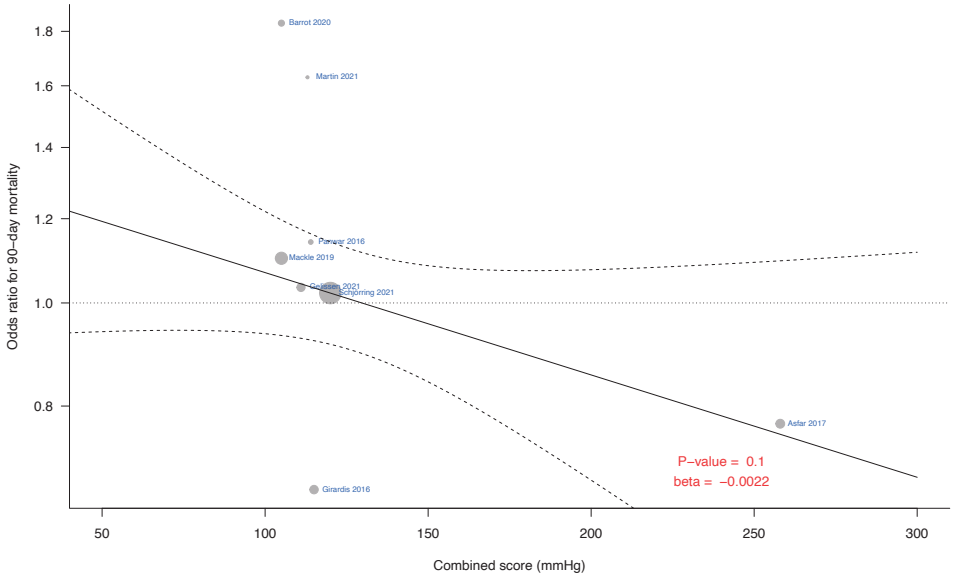

Figure 6. Meta regression analysis for the crude effects of lower oxygenation on 90-day mortality by combined score. Scatters indicate odds ratios for 90-day mortality for lower oxygenation on a logarithmic scale, according to the combined score in the indicated studies. The combined score is calculated as the difference between achieved oxygenation (PaO_2) of lower and higher group plus the achieved oxygenation (PaO_2) of the higher group. The point sizes are inversely proportional to the standard error of the mean of the individual studies (i.e., larger/more precise studies are shown as larger *circles*). The predicted effect sizes are modeled in a linear mixed-effects model with corresponding 95% CI boundaries and a β-coefficient with *p* value for the meta-regression line. An OR <1 is beneficial to the lower oxygenation group.

DISCUSSION

This systematic review and meta-analysis showed no difference in mortality at day 90 when aggregating data from RCTs comparing lower and higher oxygenation targets. For secondary outcomes, a significant effect favoring lower oxygenation targets was identified with regards to serious adverse events.

The following study strengths should be considered. First, this meta-analysis is the most recent update on RCT's, including the four most recently published high impact trials (13, 14, 19, 21), a unique novel meta-regression analysis and a meta-analysis on important secondary outcomes (e.g. serious adverse events), unlike other recently published data aggregations on this subject (9-12). Second, in order to ensure comprehensiveness of the data, corresponding authors were contacted for additional data. Also, established guidelines, such as the PRISMA and GRADE approach, were used to ensure the quality of our methodology and certainty of evidence, of which especially the GRADE approach is lacking in earlier published meta-analyses (10-12).

A key limitation is that all trials on oxygenation used varying thresholds for PaO_2 targets and study durations. For example, a patient randomised in the high oxygenation group can be assigned to a target of 90-105 mmHg for 7 days, whereas a patient included in the higher group of another trial may follow a target of 105-135 mmHg for 14 days (14, 21). Moreover, some trials used SpO_2 targets rather than PaO_2 targets and one study managed liberal oxygenation by applying an FiO_2 of 1.0 (irrespective of SpO_2) during the first 24 hours while not using different SpO_2 or PaO_2 targets afterwards. A PaO_2 of 90 mmHg can correspond with a SpO_2 of 100% but also 93%, partially depending on the underlying disease. Therefore, a higher PaO_2 cannot be consistently translated into a fixed SpO_2 (26). As thresholds differ, a patient could be categorized in the higher oxygenation group in one trial, whereas this could be the lower oxygenation group in the other trial. Moreover, in some studies chosen oxygenation targets can overlap (19, 22), suggesting there may not be a true comparison between a 'high' and a 'low' group. In order to address this issue of contrast but also of heterogeneity in targets we implemented a meta-regression framework for both the *achieved* high and low groups (supplemental figures 5&6) and for the combined score (figure 6), thereby providing a useful visual understanding of targets and its impact on the outcome effects. We also re-analyzed the data excluding the Hyper2S trial since the higher group (normobaric hyperoxia) was considered the intervention group in this study, whereas conservative oxygenation was the intervention group in the other studies (20). Also, the chosen targets differ from the other included trials. In this sensitivity analysis, the results were virtually unchanged (data not shown).

Another limitation is the heterogeneity of the ICU population in combination with the heterogenous treatment effect that can be expected from oxygen therapy in certain subgroups. For example, in vasodilatory septic shock, arterial hyperoxia may be beneficial due to antibacterial properties and the counteraction of vasodilation (27, 28), while in ischemia and reperfusion injuries, such as myocardial infarction, hyperoxia may have detrimental effects (29). Recent reviews explored the optimal oxygen targets per subgroup by underlying disease (30, 31) and no optimal oxygen target per subgroup

could be identified, though it seems justifiable to avoid both hypoxemia and excess hyperoxemia. Hence, the key question remains whether we should settle for a one-strategy-that-fits all (optimal) oxygen therapy approach, or whether optimal oxygen strategies can be applied per subgroup.

None of the included trials were blinded, which can be considered a limitation since the latest literature could have imposed bias towards the beneficial effect of lower oxygenation targets (32, 33). Therefore, clinicians may be more prone to adhere to the lower targets, making it more difficult to create contrast in oxygenation between two different groups. However, owing to the design of the trial, it was essentially unfeasible to blind clinicians for the assigned treatment group. Also, our main outcome mortality is not subjective and probably unlikely to be influenced by blinding. Though, the 95% CI's around the mortality treatment effect estimates remain wide, therefore we cannot exclude the possibility of important increases (or decreases) in mortality attributable to the oxygen regimens evaluated.

Our findings are in line with recent systematic reviews showing that different oxygenation strategies did not have a significant impact on mortality (9-12). However, the findings are in contrast to previously published reviews (5, 34, 35), that support a conservative oxygen strategy. A simple explanation for these contradictions might be that patients either simply do not benefit from a lower oxygenation strategy or that the achieved lower and higher PaO_2 in both groups lack sufficient contrast to be able to detect a difference. In the included trials it has proven to be difficult to accomplish a clinical contrast between the intervention and the control group. The majority of the trials that reported on the achieved oxygenation show a difference of 10 to 20 mmHg (14, 19, 21-23). Our sensitivity analysis using a meta-regression framework (figure 6, supplemental figures 5, 6) shows that trials with a smaller achieved difference (10-20 mm Hg) (14, 19, 21-23) and studies with a larger achieved difference (25-70 mm Hg) (13, 20, 25) both show heterogenous results. It should be noted that achieved differences are in the same order of magnitude for most studies (10-30 mm Hg) despite one outlier (70 mm Hg). When a large difference is achieved there is a sign that patients may benefit from a lower oxygenation target. Though, due to lack of significant results, this may also be originated by chance. Furthermore, when specifically targeting a very high or low target a significant clinical difference may be achieved but neither the intervention nor the control group may then represent usual care. Accordingly, the present study may demonstrate that a broad range of less extreme achieved oxygenation falls within a fairly safe category.

The different results amongst included trials can also be explained by secondary factors such as early stopping bias, subgroup analysis and not choosing a truly hyperoxic

target. Taking all included trials that reported on achieved targets together, an average higher oxygenation around 110 mm Hg was achieved, with an individual maximum of 185 mm Hg (20). The hypothesis that 110 mm Hg is not a truly hyperoxic target is supported by earlier literature that showed a significant increase in mortality in the hyperoxic group, where hyperoxia was defined as PaO_2 > 300 mmHg (29). Our meta-regression analysis (figure 5) shows that when a hyperoxic target of 185 mm Hg is achieved (20), patients may have a lower risk of mortality in the lower oxygenation group. In line, these results are not significant and the more severe the higher target, the less it represents usual care and the higher the chances of mortality.

Three recent meta-analyses reported on serious adverse events (10-12). However, other study designs than RCTs were included (12), no forest plots or only a small selection of serious adverse events were included (10-12) or important high impact trials were missing (10-12). Our updated meta-analysis including only RCTs confirms that serious adverse events are more likely to occur in the higher oxygenation groups. As in previous studies, serious adverse events should be critically reviewed to evaluate whether the event is consistent with the natural history of the critical illness (36). If a large difference is observed, similar to the difference found in our meta-analysis, it might be attributable to the different interventions. As serious adverse events can highly impair patient health and quality of life, the potential negative impact of higher targets may also be a compelling argument to adhere to a lower oxygenation strategy. However, the results on adverse events are dominated by one study (22) and a low number of studies reported on the individual adverse events groups. To add, the evidence was graded low to very low. Even though this finding may be an important signal for clinical practice guidelines, more robust data is needed for a compelling conclusion.

CONCLUSION

In the present meta-analysis comparing higher and lower oxygenation targets we found no difference in 90-day mortality for the adult ICU population. Importantly, we did find a significant difference in serious adverse events favoring lower oxygenation targets. Differences in methodology, oxygenation targets and primary and secondary endpoints may hamper a comparison of studies. Robust future clinical trials remain of paramount importance, ideally adequately separating the intervention groups based on achieved oxygenation and focusing on the impact of important side effects.

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