Targeted interventions in mechanically ventilated patients

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Conservative versus Liberal Oxygenation Targets in Intensive Care Unit Patients:

a randomized clinical trial

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American Journal of Respiratory and Critical Care. 2023 Oct 1; 208(7): 770–779. doi: 10.1164/rccm.202303-0560OC

Supplemental digital content of this article is available online

ABSTRACT

Rationale
Supplemental oxygen is widely administered to intensive care unit (ICU) patients, but appropriate oxygenation targets remain unclear.

Objective
This study aims to determine whether a low-oxygenation strategy would lower 28-day mortality compared to a high-oxygenation strategy.

Methods
This randomized multicentre trial included mechanically ventilated ICU patients with an expected ventilation duration of at least 24 hours. Patients were randomized 1:1 to a low-oxygenation (PaO_2 55-80 mmHg or SpO_2 91-94%) or high-oxygenation (PaO_2 110-150 mmHg or SpO_2 96-100%) target until ICU discharge or 28 days after randomization, whichever came first. The primary outcome was 28-day mortality. The study was stopped prematurely due to the COVID-19 pandemic when 664 of the planned 1512 patients were included.

Measurements and main results
Between November 2018 and November 2021, a total of 664 patients were included in the trial: 335 in the low-oxygenation group and 329 in the high-oxygenation group. The median achieved PaO_2 was 75 mmHg (IQR, 70-84) and 115 mmHg (IQR 100-129), in the low- and high-oxygenation groups, respectively. At day 28, 129 (38.5%) and 114 (34.7%) patients had died in the low- and high-oxygenation group, respectively (Risk Ratio 1.11, 95% Confidence Interval 0.9-1.4, P=0.30). At least one Serious Adverse Event was reported in 12 (3.6%) and 17 (5.2%) patients in the low- and high-oxygenation group, respectively.

Conclusion
Among mechanically ventilated ICU patients with an expected mechanical ventilation duration of at least 24 hours, using a low-oxygenation strategy did not result in a reduction of 28-day mortality compared to a high-oxygenation strategy.

Trial registration
This trial was registered in the National Trial Register (NTR) and the International Clinical Trials Registry Platform (ICTPR) under number NTR7376.

INTRODUCTION

Arterial oxygen levels are fundamental in maintaining a physiological balance and ensuring proper function of various organ systems. Hypoxic patients are at risk for cell injury, tissue damage, and organ failure. In this context, oxygen therapy is a lifesaving intervention and is therefore widely and liberally applied to acutely ill patients. The administration of high oxygen concentration has also been associated with beneficial effects due to antibacterial properties and counteraction of vasodilation (1,2). However, several studies have shown that liberal oxygen therapy with supranormal arterial oxygen levels is not without risks (3,4). Excessive oxygen administration may cause atelectasis, vasoconstriction, inflammation, and toxicity due to an imbalance in reactive oxygen species (ROS) (5,6).

Several randomized clinical trials (RCTs) have been conducted to identify the optimal oxygenation targets in mechanically ventilated intensive care unit (ICU) patients (7-13). One trial showed a lower mortality rate with lower oxygenation targets (9), while six other trials reported no difference in mortality between the higher and lower targets (7, 8, 10-13). Results from individual or aggregated data analyses have been inconclusive so far, which may be influenced by differences in the study population (subgroups), different targets (either SpO_2 or PaO_2), lack of power, or insufficient contrast between groups (14, 15). Goals for arterial oxygenation are increasingly implemented but clinical practice guidelines and clinician behaviour do not consistently rely on directive data from robust interventional studies (16).

Our aim was to provide additional data regarding the general adult ICU population using PaO_2 targets that are widely used in clinical practice. Accordingly, we conducted a multicentre, binational trial to test whether the use of conservative oxygen therapy results in reduced 28-day mortality compared to liberal oxygen therapy in mechanically ventilated ICU patients. Some of the results of this study have been previously reported in the form of an abstract (17,18).

METHODS

Study design

This investigator-initiated parallel group RCT was conducted in eight ICUs in the Netherlands and one in Italy. Ethical approval was granted for all centres by the Medical Ethical Committee of Leiden, The Hague and Delft (P18.109). The protocol was prospectively registered in the National Trial Register (NTR) and the International Clinical Trials Registry Platform (ICTPR) under number NTR7376 and published (19).

The study was funded by the Dutch Research Council (NWO) (Project number 401.16.009). An independent Data and Safety Monitoring (DSMB) committee periodically reviewed blinded efficacy and safety data, with the option to request unblinded data if required.

Participants

All patients aged 18 or older with an expected mechanical ventilation time of 24 hours or longer were screened for eligibility. The main exclusion criteria included a decision to withhold life-sustaining treatment, acute respiratory distress syndrome (ARDS) with a PaO_2/FiO_2 ratio of less than 150 mmHg, acute decompensation of chronic obstructive pulmonary disease (COPD), severe not rapidly reversible low cardiac output shock (cardiac index $\leq$ 2L/min/m^2), veno-arterial extracorporeal membrane oxygenation (VA-ECMO), underlying diseases with an indication for hyperoxygenation, severe anaemia (haemoglobin < 4.0 mmol/l) that is not rapidly reversible and uncontrollable intracranial hypertension (19). Patients with ARDS who had a PaO_2/FiO_2 ratio less than 150 mmHg were excluded from the study because they were likely to require very high FiO_2 for prolonged periods if assigned to the high PaO_2 target group. Patients with COPD were excluded from the study because they commonly have chronically low PaO_2 values. The full list of in- and exclusion criteria can be found in the online data supplements 1 and 2.

Randomization and blinding

Patients were assessed for eligibility by clinicians and, when appropriate, randomized within 2 hours after intubation to either the low- (conservative) or the high- (liberal) oxygenation group with secure web-based randomization software developed by Castor EDC/CDMS (20) using computer-generated variable block randomization with a 1:1 ratio and stratification based on study site. Clinicians and outcome assessors were not blinded for the intervention, while data analysts remained blinded. Informed consent was obtained according to national regulations and if possible, prior to randomization. Given the emergency setting of this trial, deferred consent from a proxy was permitted. If a patient died before delayed informed consent could be obtained, their data was still included in the analysis. Patients were excluded from the study if informed consent was not obtained within 5 days after randomization.

Trial procedures

Oxygenation was targeted at maintaining a PaO_2 level between 55-80 mmHg for patients in the low-oxygenation group and between 110-150 mmHg for patients in the high-oxygenation group. In addition to blood gas measurements, oxygen could also be adjusted based on peripheral saturation (SpO_2). The target SpO_2 range was 91-94% for the low-oxygenation group and 96-100% for the high-oxygenation group.

Oxygenation targets were pursued until ICU discharge or 28 days after randomization, whichever came first. At least one arterial blood sample per shift was collected while patients were mechanically ventilated (three per 24 hours). If PaO_2 values fell outside the specified ranges, the FiO_2 or positive end-expiratory pressure (PEEP) could be adjusted accordingly at the discretion of the treating physician. To guide this process, the protocol specified a recommended PEEP and FiO_2 table (Table E1 in the online data supplements). To prevent prolonged exposure to high inspiratory oxygen concentrations used solely to achieve the high oxygenation target, the protocol allowed clinicians to temporarily decrease FiO_2 to 0.8 and limit the PEEP to a maximum of 15 cm H_2O, if the FiO_2 was higher than 0.8 or the PEEP was higher than 14 cm H_2O for more than 2 hours. In those cases, the achievability of the PaO_2 targets was reassessed every two hours. When the patient was extubated, oxygenation targets were still pursued. For patients randomized to the low-oxygenation group, supplemental oxygen was generally avoided, unless PaO_2 fell below 55 mmHg. Patients in the high-oxygenation group received a nasal cannula of 5L oxygen, unless the PaO_2 exceeded 150 mmHg.

Rescue therapy, e.g. prone position, recruitment manoeuvres or Extracorporeal Membrane Oxygenation (ECMO) were only applied on clinical indications and not solely to achieve the study PaO_2 targets. The use of a high FiO_2 during planned interventions involving upper airways (e.g. bronchoscopy) was permitted but restricted to the shortest possible duration. Further details of the study protocol have been previously published (19).

Data collection

Data from the patient data management system and from the Dutch National Intensive Care Evaluation (NICE) registry database were collected and recorded in an electronic case report form (eCRF) designed with Castor EDC (20,21). The APACHE IV score (22) was used to assess disease severity upon admission, while Sequential Organ Failure Assessment (SOFA) scores (23)nwere used to evaluate daily disease severity. Acute and chronic diagnosis were registered based on the data definitions provided by the NICE registry (21). Further details regarding the data collected in the eCRF can be found in the published study protocol (19).

Outcomes

Primary outcome measure was all-cause mortality at day 28 after randomization. Secondary outcomes included the number of ventilator-free days and alive at day 28 (VFDs), ICU and hospital length of stay (LOS), ICU, hospital and 90-day mortality, and ischemic events. Ventilator free days were defined as the number of days that a patient was alive and free from invasive ventilation, calculated from the time of randomization, provided that the period of unassisted breathing lasted at least 24 consecutive hours

(24). Serious adverse events (SAE) were categorised as follows: PaO_2 of < 37.5 mm Hg, SpO_2 <80% for longer than ten minutes, cardiac arrest, or intestinal, cerebral, cardiac, or peripheral limb ischemia.

Statistical analysis

Based on an expected mortality of 24% in the control group (25), the original sample size was determined to be 1512 patients in order to detect an absolute difference of 6% between the two study groups, with a two-sided α of 0.05 and a power of 80%.

After careful consideration and in concordance with the DSMB we decided to stop the study prematurely after inclusion of 664 patients. The main reason for the early termination of the study was the corona pandemic, which significantly increased the workload for all participating ICUs and resulted in a substantial decrease in patient enrolment. An estimation was made that continuing at the current pace of enrolment would require an additional 5 years to reach the intended inclusion range. As a result, recruitment was stopped on November 21, 2021.

For the primary endpoint of 28-day mortality, rates were calculated according to a modified intention-to-treat principle, including all patients, except those who did not provide signed informed consent or were excluded after randomization on the basis of exclusion criteria. Differences were assessed using a chi-squared test. A two-sided hypothesis test was performed with a significance level of 0.05, and presented as relative risk with two-sided 95% confidence intervals. In addition, a per-protocol analysis was performed that only considered patients in the low-oxygenation group if 50% or more of the PaO_2 values in the arterial blood gas (ABG) analysis were equal to or below 80 mmHg, and patients in the high-oxygenation group if 50% or more of the PaO_2 values in the ABG analysis were equal to or above 110 mmHg.

For the secondary endpoints, continuous variables with a normal distribution were presented as means and standard deviations (SDs), while variables with a non-normal distribution were presented as medians and interquartile ranges (IQRs). Differences between groups were assessed using a Mann-Whitney U test. Categorical variables were presented as frequencies and percentages, and a chi-squared test was used to analyse differences. Survival curves were calculated using the Kaplan Meier methods and compared using the log-rank test. Statistical significance was defined as a P-value of <0.05 in a two-sided test. When appropriate, 95% confidence intervals were used to express statistical uncertainty. In addition, an exploratory post-hoc subgroup analysis was conducted to assess the heterogeneity of treatment effects. Patients were divided into subgroups based on the diagnosis criteria of the NICE APACHE IV admission diagnosis model (21). Solely the largest subgroups were included in the analysis,

including patients with sepsis, pneumonia, cardiac arrest, abdominal causes and stroke. Additionally, predefined subgroups defined as patients with ARDS (PaO_2/FiO_2 < 200 mmHg) or elevated lactate level (>2mmol/l) at ICU admission, were included in the analysis. Statistics for both primary and secondary endpoints were calculated as described above.

As randomization was stratified by site, we conducted an additional analysis that involved including the study site in the analysis of both primary and secondary endpoints. For binary endpoints, we performed a logistic regression analysis while for continuous endpoints, we conducted a linear regression analysis. In both cases, we included the randomization group and study site as categorical variables.

Interim analyses were not planned beforehand, but after the study started, the DSMB deemed it necessary to conduct interim analyses of mortality. These analyses were planned after the inclusion of 500, 750, and 1000 patients to ensure the safety of both treatment targets. As per request of the DSMB, an interim analysis was performed after 500 patients. The interim analysis indicated no significant difference in in-hospital mortality between the two groups. Stopping rules were defined beforehand and can be found in the protocol (19).

All statistical analyses were performed using the R language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria, version 4.0.3).

RESULTS

From 19th of November 2018 until 21st of November 2021, 972 patients were screened for eligibility. In total, 882 patients met the inclusion criteria and were randomized to either the low or the high-oxygenation group. Deferred written informed consent was available for 664 patients (Figure 1). Baseline characteristics were comparable between the groups (Table 1). No patients were lost to follow up, and end-point data was available for all patients.

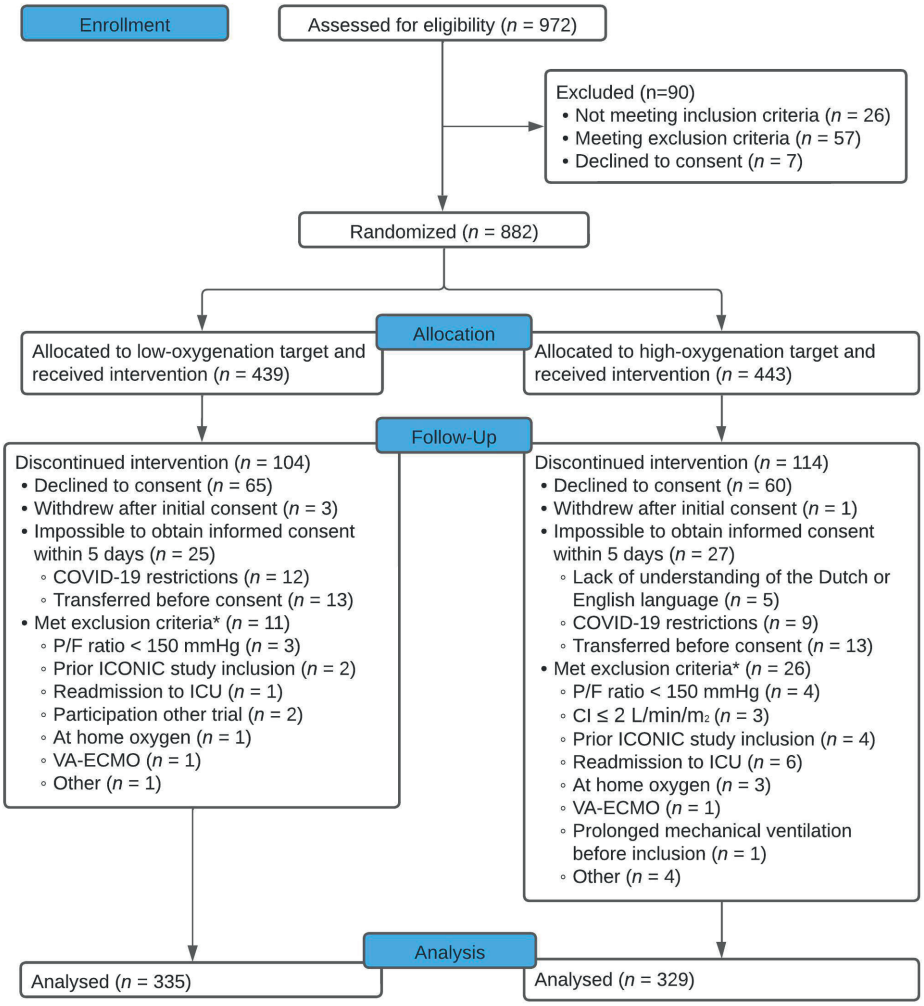


Figure 1. Consort flow diagram. The full list of in- and exclusion criteria can be found in Appendix 1-2 in the online data supplement. Data was available on primary and secondary outcomes for all patients. *Patients were only withdrawn from the study if exclusion criteria were present at the time of inclusion. This was checked within 24 hours after randomization. CI=cardiac index; P/F=Pa_{O2}/FI_{O2} ratio; VA-ECMO=venoarterial extracorporeal membrane oxygenation

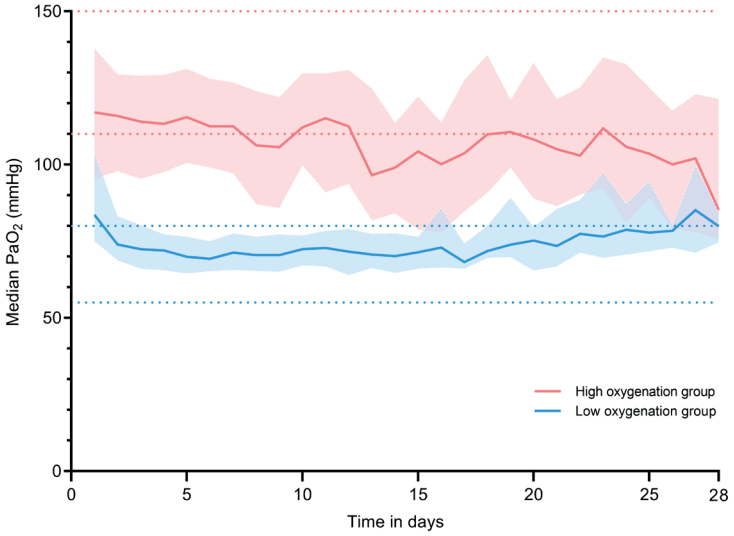
Table 1. Baseline characteristics of included patients.

	Low- oxygenation targets (55-80 mmHg) (N=335)	High-oxygenation target (110-150 mmHg) (N=329)
Sex = female, No. (%)	111 (33.1)	118 (35.9)
Age (median (IQR))	67 (59, 74)	67 (56, 73)
SOFA admission score (median (IQR))	9 (7, 11)	9 (7, 11)
Apache IV score on admission (median (IQR))	87 (66, 107)	86 (65, 113)
Mechanical ventilation in the first 24h of admission, No. (%) *	289 (87.3)	296 (92.2)
Duration mechanical ventilation prior to enrolment (minutes) (median (IQR))	0 (0, 58)	2 (0, 61)
Type of admission, No. (%) †		
Medical	258 (77.2)	251 (76.3)
Emergency surgery	61 (18.3)	56 (17)
Elective surgery	15 (4.5)	22 (6.7)
Acute diagnosis, No. (%) ‡		
Sepsis	53 (15.8)	42 (12.8)
Pneumonia **	54 (16.1)	43 (13.1)
Cardiac arrest	89 (26.6)	96 (29.2)
Abdominal	29 (8.7)	37 (11.2)
Neurologic	32 (9.6)	32 (9.7)
Trauma	12 (3.6)	12 (3.6)
Other	66 (19.7)	67 (20.4)
Chronic diagnosis on admission, No. (%) §		
Chronic kidney failure	20 (6)	22 (6.7)
Chronic dialysis	6 (1.8)	3 (0.9)
COPD (drug dependent)	39 (11.6)	37 (11.2)
Chronic respiratory insufficiency	6 (1.8)	1 (0.3)
Cardiovascular insufficiency (NYHA IV)	2 (0.6)	9 (2.7)
Liver cirrhosis	14 (4.2)	14 (4.3)
Diabetes	52 (15.5)	52 (15.8)
Metastasized neoplasm	8 (2.4)	5 (1.5)
Haematological malignancy	14 (4.2)	19 (5.8)
Immunological insufficiency	33 (9.9)	43 (13.1)

Abbreviations: SOFA, sequential organ failure assessment; RRT, renal replacement therapy; COPD, chronic obstructive pulmonary disease, NYHA,, New York Heart Association.
* Information on mechanical ventilation in the first 24 hours of admission was missing for four patients in the low-oxygenation group and eight patients in the high-oxygenation group.
† Information on type of admission is missing for one patient in the low-oxygenation group
‡ Acute diagnosis is classified according to the APACHE IV model
** In the low and high oxygenation groups, 11 and 8 patients admitted with pneumonia had COVID-19 disease. Information on whether patients were admitted with a COVID-19 infection was only available for patients included in the Netherlands.
§ More than one chronic diagnosis can be present in the same patient

Oxygenation

The first PaO2 measured after inclusion in the study was 92.3 mmHg (IQR, 76.5, 123.2) and 106.5 mmHg (IQR, 83.3, 147) in the low- and high-oxygenation group, respectively. More information about the first blood gas analysis can be found in Table E2 in the online data supplement. During the whole period of mechanical ventilation, the median PaO_2 was 75 mmHg (IQR, 69.8-83.5) in the low-oxygenation group and 115 mmHg (IQR, 100.3 - 129.0) in the high-oxygenation group (P<0.001) (Table 2, Figure 2). Corresponding median SpO_2 values were 95% (IQR, 94-97) and 99% (IQR, 98-100), respectively (P<0.001) (Table 2, Figure E1 in online data supplement). While spontaneously breathing without mechanical ventilation, the median PaO_2 was 75 mmHg (IQR, 68.3-82.9) in the low-oxygenation group and 85.5 (IQR, 73.8-102.8) in the high-oxygenation group. The corresponding median SpO_2 values were 95 (IQR, 94-97) and 99 (IQR, 98-100), respectively (P<0.001) (Table 2, Figure E2 and E3 in the online data supplements). Additional data on ventilation is displayed in Table E2 and Figure E4 in the online data supplement.



No. of patients

High oxygenation group	328	186	80	40	28	20	12
Low oxygenation group	328	192	82	46	24	19	10

Median no. of arterial blood gasses per day

High oxygenation group	4	4	4	4	4	3	4
Low oxygenation group	4	4	4	4	4	4	3

Figure 2. Median PaO_2 per day during mechanical ventilation. The PaO_2 values were calculated based on the median PaO_2 values per day by study group, where median values were taken per patient per day before aggregating the data. Lines represent the achieved median PaO_2 per oxygenation group. Faded areas around the lines represent the interquartile ranges. The dotted horizontal lines represent the boundaries of the higher and lower target. Blood gas data was not available for seven patients in the low-oxygenation group and one patient in the high-oxygenation group.

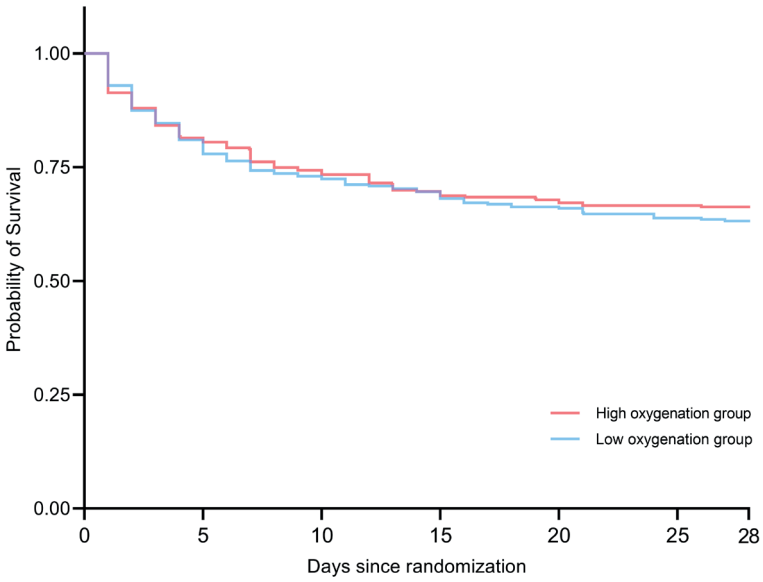
Table 2. Ventilation data and outcomes

	Low-oxygenation target (55-80 mmHg) (N=335)	High-oxygenation target (110-150 mmHg) (N=329)	P-value
Ventilation data			
No. of arterial blood gasses (mean (SD)) *	30.8 (30.8)	33.1 (37.6)	0.38
Duration mechanical ventilation - days (median (IQR))	3 (1.4, 6.5)	2.8 (1.4, 6.1)	0.6
Mechanical ventilation			
PaO_2 (mmHg) (median (IQR))	75 (69.8, 83.5)	115 (100.3, 129)	<0.001
SpO_2 (%) (median (IQR))	95 (94, 97)	99 (98, 100)	<0.001
$PaCO_2$ (mmHg) (median (IQR))	39.8 (36, 44.3)	41.3 (36.8, 45)	0.054
Off mechanical ventilation			
PaO_2 (mmHg) (median (IQR))	75 (68.3, 82.9)	85.5 (73.8, 102.8)	<0.001
SpO_2 (%) (median (IQR))	95 (94, 97)	99 (98, 100)	<0.001
$PaCO_2$ (mmHg) (median (IQR))	37.2 (34.5, 40.6)	39.8 (36, 43.5)	0.001
Primary endpoint			
28 day mortality, No. (%)	129 (38.5)	114 (34.7)	0.34
Secondary endpoints			
ICU mortality, No. (%)	109 (32.5)	94 (28.6)	0.29
Hospital mortality, No. (%)	127 (37.9)	111 (33.7)	0.3
90 day mortality, No. (%)	144 (43)	133 (40.4)	0.56
ICU length of stay - days (median (IQR))	4.9 (2.3, 10.8)	4.7 (2.5, 9.9)	0.89
Hospital length of stay - days (median (IQR))	14 (5, 26)	12 (5, 23)	0.65
Ventilator free days at day 28 - days (median (IQR))	18.3 (0, 25.4)	20.2 (0, 25.7)	0.36
Serious adverse events, No. (%) †			
Serious adverse events	13	22	
Patients with at least one SAE	12 (3.6)	17 (5.2)	
Patients with more than one SAE	1 (0.3)	3 (0.9)	
PaO_2 <37.5 mm Hg	0 (0)	0 (0)	
Ischemia	10 (3)	15 (4.6)	
Cerebral	4 (1.2)	4 (1.2)	
Cardiac	0 (0)	3 (0.9)	
Intestinal	4 (1.2)	7 (2.1)	
Extremities	2 (0.6)	1 (0.3)	
SpO_2 < 80% longer than 10 minutes	1 (0.3)	2 (0.6)	
Cardiac arrest	2 (0.6)	4 (1.2)	
Other	0 (0)	1 § (0.3)	

Abbreviations: ICU, intensive care unit; SAE, serious adverse event.
* During the whole study period
† As reported in the case report form in Castor
§ Severe refractory hypotension most likely due to tamponade

Outcomes

The modified intention-to-treat analysis showed no significant difference in the primary outcome between the two oxygenation groups (P=0.34). In total, mortality at day 28 occurred in 129 (38.5%) patients in the low-oxygenation group and 114 (34.7%) patients in the high-oxygenation group (Risk Ratio 1.11, 95% Confidence Interval 0.9-1.4, P=0.30). The Kaplan Meier survival curve (Figure 3) showed no difference in the probability of survival between the two groups (log rank test P=0.4). Similar results on 28-day mortality were observed when applying a per protocol analysis, namely, 82/229 (35.8%) patients died in the low-oxygenation versus 67/171 (39.2%) patients in the high-oxygenation group (Table E3 in the online data supplement).



No. at risk

High oxygenation group	329	263	240	225	219	215	215
Low oxygenation group	335	264	238	227	216	208	206

Figure 3. Kaplan Meier survival curve of survival until day 28. On day 28 129 (38.5%) patients had died within the low-oxygenation group and 114 (34.7%) in the high-oxygenation group. Statistical analysis of the Kaplan Meier curve showed no significant difference (P=0.4, P-value adjusted for study site P=0.4).

No significant differences were observed between the two groups with respect to ICU, hospital, and 90-day mortality (Table 2, Figure E5 in the online data supplement). In addition, the analyses of ICU LOS, hospital LOS and number of VFDs at day 28 yielded no significant differences (Table 2). The median LOS in the ICU was 4.9 (IQR,

2.3-10.8) days in the low-oxygenation group versus 4.7 (IQR, 2.5-9.9) days in the high-oxygenation group. Adjusted analysis for study site for both primary and secondary endpoints can be found in Table E4 in the online data supplement.

A total number of 13 versus 22 SAEs occurred in the low- and high-oxygenation group, respectively (Table 2). Ischemic events were the most frequently reported SAE, 10 (3.0%) and 15 (4.6%) occurred in the low- and high-oxygenation group, respectively. Most common ischemic events were cerebral and intestinal (Table 2).

During the ICU admission, maximal and daily SOFA scores were comparable in both groups (Figure E6 in the online data supplement). No differences were found for predefined primary and secondary endpoints within the subgroups. Details of this analysis can be found in Table E5 of the online data supplement.

DISCUSSION

In this multicentre randomized trial, which included mechanically ventilated adult ICU patients, no significant difference was found in 28-day mortality between patients treated with a low- or a high-oxygenation strategy. Additionally, we did not find evidence of a between group difference in ICU-, in-hospital or 90-day mortality, ventilator-free days, length of stay, or ischemic events.

Our findings are in line with recent studies showing similar outcomes of ICU patients irrespective of oxygenation targets (8, 10-12) but are in contrast with earlier studies suggesting better survival with less oxygen (9) or a benefit for high-oxygenation targets regarding serious adverse events (7). The first publication reporting higher mortality after adjustment for severity of illness in ICU patients with high PaO_2 values, originated from an ICU registry in the Netherlands in 2008 (6). Since then, many observational studies were performed in various subsets of ICU patients. A meta-analysis of these studies showed that hyperoxia was associated with higher mortality, but the heterogeneity of studied populations and the observational nature of studies warranted cautious interpretation of these findings (4). Results from the first RCT on oxygenation in ICU patients were published in 2016 and demonstrated that a conservative protocol for oxygen therapy versus conventional therapy resulted in lower ICU mortality (9) (9). This RCT appeared to confirm the results from earlier observational studies. However, since then four additional RCTs have been published all showing no differences in mortality between patients treated with conservative versus liberal oxygen targets (7, 8, 10, 11). In addition, the very recent cluster-randomized PILOT-trial, which compared three SpO_2 targets (90%, 94% and 98%), also showed no differences in outcome (12). It should

be noted that in every previous trial other definitions of low- and high-oxygenation targets were used.

The fact that several large RCTs performed in different countries do not show an effect of oxygen targets on outcomes of ICU patients can be considered as evidence that different oxygenation strategies don't have an impact on mortality. However, it can't be ruled out that the absence of an effect from these strategies may be caused by a lack of contrast between the studied targets**.** In previous studies contrast between study groups were at times small, from as low as a difference of 7.5 mmHg to 15 mmHg (7-10) or 22 mmHg in arterial oxygen levels (11). Such differences may be to be too small to demonstrate effects of a certain oxygenation target. The findings of our study add important contributions to the existing literature, as the tested intervention resulted in more contrast between achieved oxygen levels, as high as 40 mmHg. However, we still did not observe an effect on mortality. Thus, we don't consider a lack of contrast to be the main explanation for the absence of a benefit. It is worth nothing that a larger contrast in oxygenation between intervention groups doesn't necessarily mean that a PaO_2 related mortality difference can be detected. It is also possible that the lowest mortality risk falls in between the studied targets. However, considering that previous RCTs (7, 8, 10, 11) examining slightly different target ranges also showed no difference in outcomes, it is less likely that in all of these studies the optimal PaO_2 target would have fallen between the studied targets.

One would expect that adhering to higher PaO_2 targets would result in increased reliance on invasive mechanical ventilation and a higher need for sedative drugs, potentially leading to a prolonged mechanical ventilation time. However, our results demonstrated that mechanical ventilation time was similar for both groups. This finding is consistent with the ICU-ROX and the PILOT-trial, which also reporting similar numbers of ventilator free days (10, 12). When considering length of stay, ICU-, hospital- and 90-day mortality, ischemic events, and other SAEs, no differences were found between the groups. These findings are in line with earlier studies (8, 10-12). Notably, in one of the previous RCTs a trend towards a higher incidence of intestinal ischemic events in the low-oxygenation group was reported (7). However, in our trial, we did not find any difference in intestinal or other ischemic events for the two study groups.

The latest literature indicates that the general ICU population does not derive benefits from a low- or a high-oxygenation strategy. Yet, there are thoughts that specific subgroups of ICU patients, such as those following cardiac arrest, could benefit from specific targets. The ICU-ROX investigators reported improved outcomes in patients with hypoxic-ischemic encephalopathy when treated with a conservative oxygen strategy (10). Similarly, Kilgannon and colleagues found a higher mortality when

cardiac arrest patients were treated with high levels of oxygen (26). However, it should be noted that high oxygenation in the latter study was defined as a PaO_2 > 300 mmHg, which is twice as high as the upper limit of our high target. This disparity may explain why our results did not show a difference in outcome for cardiac arrest patients. In addition, two recent RCTs comparing oxygenation strategies (SpO_2 of 90%-94% and 98%-100% or PaO_2 68-75 mmHg or 98-105 mmHg) in cardiac arrest patients also found no difference in outcomes (27, 28).

The absence of a difference in mortality related to lower or higher oxygenation targets could also be caused by a lack statistical of power. Interestingly, both the present study and previous RCTs have shown non-significant trends towards lower mortality in patients treated with higher oxygenation targets (8, 10, 11). The absolute differences in 90-day mortality ranged from 0.5 to 1.2 % in the previously published trials and 2.6% in the present study. However, none of these RCTs did have the power to rule out small mortality effects. Interestingly, two very large trials are ongoing at the moment (UK-ROX and MEGA-ROX) including 16.500 and 40.000 patients, respectively (29). The results of these trials will provide important insights in the possible smaller effects on survival, potentially in favour of higher oxygenation targets.

Some relevant limitations of this study must be considered. First, due to early termination, we were only able to include 664 of the planned 1512 patients which resulted in lack of statistical power to detect clinically important differences. However, with 664 patients the ICONIC trial remains one of the larger RCTs in this field. Second, because inclusion in the study was allowed before consent was obtained (deferred consent), a substantial number of patients were withdrawn from the study after initial inclusion and randomization if written informed consent could not be obtained. Excluding patients after inclusion raises concerns about potential selection bias. According to Dutch legislation, we are not allowed to provide data about this population and we therefore can't compare characteristics of excluded patients with patients that were included in our study. To minimize the risk of selection bias, the protocol had strict criteria for patient withdrawal, which was only permitted if patients declined consent or if consent was not given within 5 days after inclusion. In addition, patients could be withdrawn within 24 hours after inclusion if exclusion criteria became apparent at the time of inclusion. Patients who died within 5 days before consent could be obtained remained in the study. Third, some patients randomized to the high PaO_2 group were unable to reach this target. If, for example, a patient needed 100% oxygen to reach the high-oxygenation goal for prolonged periods, the protocol allowed lowering the FiO_2 to 0.8 to decrease the risk of pulmonary toxicity. This may have diminished the contrast in oxygenation between groups. Nevertheless, the difference between median PaO_2 values was still 40 mmHg. Furthermore, this is representative for real life

treatment in the ICU: high-oxygenation targets are not feasible in patients with very severe pulmonary dysfunction. Fourth, due to the nature of the intervention it was not possible to blind clinicians to the study intervention. However, the chosen endpoints such as 28-days mortality and ventilator-free days are objective and are less likely to be influenced by bias. Moreover, data analysts of this study were blinded for the study intervention. Finally, the findings of our study cannot be generalized to patients with severe ARDS or COPD, as these patients were excluded from participation in this study. Both the present study and previous RCTs showed no differences between the intervention groups. This is in contrast with popular believes and common practices, as over the last years there appeared to be a strong opinion among health care professionals that low-oxygen targets are better than high-oxygen targets (30, 31). While it is still possible that marked hyperoxia with PaO_2 much higher than studied in the RCTs may increase mortality, it is unlikely that new RCTs comparing conservative oxygenation with marked hyperoxia will ever be conducted in ICU patients.

In conclusion, among adult mechanically ventilated ICU patients with an expected mechanical ventilation duration of at least 24 hours, using a low-oxygenation strategy did not result in a reduction in 28-day mortality when comparing to a high-oxygenation strategy. It is noteworthy that the trend towards lower mortality in patients treated with higher oxygen targets, as also found in previous studies, precludes definite conclusions regarding what the best oxygen targets are and urges for additional studies.

REFERENCES

1. Hafner S, Beloncle F, Koch A, Radermacher P, Asfar P. Hyperoxia in intensive care, emergency, and peri-operative medicine: Dr. Jekyll or Mr. Hyde? A 2015 update. Ann Intensive Care. 2015;5(1):42.
2. Knighton DR, Halliday B, Hunt TK. Oxygen as an antibiotic. The effect of inspired oxygen on infection. Arch Surg. 1984;119(2):199-204.
3. Helmerhorst HJ, Arts DL, Schultz MJ, van der Voort PH, Abu-Hanna A, de Jonge E, et al. Metrics of Arterial Hyperoxia and Associated Outcomes in Critical Care. Crit Care Med. 2017;45(2):187-95.
4. Helmerhorst HJ, Roos-Blom MJ, van Westerloo DJ, de Jonge E. Association Between Arterial Hyperoxia and Outcome in Subsets of Critical Illness: A Systematic Review, Meta-Analysis, and Meta-Regression of Cohort Studies. Crit Care Med. 2015;43(7):1508-19.
5. Asfar P, Singer M, Radermacher P. Understanding the benefits and harms of oxygen therapy. Intensive Care Med. 2015;41(6):1118-21.
6. de Jonge E, Peelen L, Keijzers PJ, Joore H, de Lange D, van der Voort PH, et al. Association between administered oxygen, arterial partial oxygen pressure and mortality in mechanically ventilated intensive care unit patients. Crit Care. 2008;12(6):R156.
7. Barrot L, Asfar P, Mauny F, Winiszewski H, Montini F, Badie J, et al. Liberal or Conservative Oxygen Therapy for Acute Respiratory Distress Syndrome. N Engl J Med. 2020;382(11):999-1008.
8. Gelissen H, De Grooth H-J, Smulders Y, Wils E-J, De Ruijter W, Vink R, et al. Effect of Low-Normal vs High-Normal Oxygenation Targets on Organ Dysfunction in Critically Ill Patients. JAMA. 2021;326(10):940.
9. Girardis M, Busani S, Damiani E, Donati A, Rinaldi L, Marudi A, et al. Effect of Conservative vs Conventional Oxygen Therapy on Mortality Among Patients in an Intensive Care Unit. JAMA. 2016;316(15):1583.
10. ICU-ROX. Conservative Oxygen Therapy during Mechanical Ventilation in the ICU. N Engl J Med. 2020;382(11):989-98.
11. Schjørring OL, Klitgaard TL, Perner A, Wetterslev J, Lange T, Siegemund M, et al. Lower or Higher Oxygenation Targets for Acute Hypoxemic Respiratory Failure. N Engl J Med. 2021;384(14):1301-11.
12. Semler MW, Casey JD, Lloyd BD, Hastings PG, Hays MA, Stollings JL, et al. Oxygen-Saturation Targets for Critically Ill Adults Receiving Mechanical Ventilation. N Engl J Med. 2022.
13. Panwar R, Hardie M, Bellomo R, Barrot L, Eastwood GM, Young PJ, et al. Conservative versus Liberal Oxygenation Targets for Mechanically Ventilated Patients. A Pilot Multicenter Randomized Controlled Trial. American Journal of Respiratory and Critical Care Medicine. 2016;193(1):43-51.
14. Barbateskovic M, Schjørring OL, Krauss SR, Meyhoff CS, Jakobsen JC, Rasmussen BS, et al. Higher vs Lower Oxygenation Strategies in Acutely Ill Adults. Chest. 2021;159(1):154-73.
15. van der Wal LI, Grim CCA, van Westerloo DJ, Schultz MJ, de Jonge E, Helmerhorst HJF. Higher versus lower oxygenation strategies in the general intensive care unit population: A systematic review, meta-analysis and meta-regression of randomized controlled trials. J Crit Care. 2022;72:154151.
16. Siemieniuk RAC, Chu DK, Kim LH, Guell-Rous MR, Alhazzani W, Soccal PM, et al. Oxygen therapy for acutely ill medical patients: a clinical practice guideline. BMJ. 2018;363:k4169.
17. Van Der Wal LI, Grim CCA, Helmerhorst HJF, Van Westerloo DJ, Pelosi P, Schultz MJ, et al. Conservative versus Liberal Oxygenation Targets in Intensive Care Unit Patients: A Multicentre Randomised Clinical Trial. Neth J Crit Care. 2023;31(1):45-6.
18. Van Der Wal LI, Grim CCA, Helmerhorst HJF, Van Westerloo DJ, Pelosi P, Schultz MJ, et al. Conservative versus Liberal Oxygenation Targets in Intensive Care Unit Patients: A Multicentre Randomised Clinical Trial. Abstract presented at the Smart Congress May 2023; Milan, Italy. Available from: https://www.smartonweb.org/poster/posterhome.php?year=2023 (Accessed 31 May 2023).
19. Grim CCA, Van Der Wal LI, Helmerhorst HJF, Van Westerloo DJ, Pelosi P, Schultz MJ, et al. ICONIC study—conservative versus conventional oxygenation targets in intensive care patients: study protocol for a randomized clinical trial. Trials. 2022;23(1).
20. Castor EDC. Castor Electronic Data Capture 2019 (27 Aug. 2019). Available from: https://castoredc.com.
21. Arts D, De Keizer N, Scheffer G-J, De Jonge E. Quality of data collected for severity of illness scores in the Dutch National Intensive Care Evaluation (NICE) registry. Intensive Care Med. 2002;28(5):656-9.

22. Zimmerman JE, Kramer AA, McNair DS, Malila FM. Acute Physiology and Chronic Health Evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. Crit Care Med. 2006;34(5):1297-310.
23. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Medicine. 1996;22(7):707-10.
24. Yehya N, Harhay MO, Curley MAQ, Schoenfeld DA, Reeder RW. Reappraisal of Ventilator-Free Days in Critical Care Research. Am J Respir Crit Care Med. 2019;200(7):828-36.
25. Van De Klundert N, Holman R, Dongelmans DA, De Keizer NF. Data Resource Profile: the Dutch National Intensive Care Evaluation (NICE) Registry of Admissions to Adult Intensive Care Units. Int J Epidemiol. 2015;44(6):1850-h.
26. Kilgannon JH. Association Between Arterial Hyperoxia Following Resuscitation From Cardiac Arrest and In-Hospital Mortality. JAMA. 2010;303(21):2165.
27. Schmidt H, Kjaergaard J, Hassager C, Mølstrøm S, Grand J, Borregaard B, et al. Oxygen Targets in Comatose Survivors of Cardiac Arrest. N Engl J Med. 2022;387(16):1467-76.
28. Bernard SA, Bray JE, Smith K, Stephenson M, Finn J, Grantham H, et al. Effect of Lower vs Higher Oxygen Saturation Targets on Survival to Hospital Discharge Among Patients Resuscitated After Out-of-Hospital Cardiac Arrest. JAMA. 2022;328(18):1818.
29. Paul J Young YMA, Sean M Bagshaw, Rinaldo Bellomo, Tomoko Fujii, Rashan Haniffa, Carol L Hodgson, Bharath Kumar Tirupakuzhi Vijayaraghavan, Edward Litton, Diane Mackle, Alistair D Nichol, Jessica Kasza. Protocol and statistical analysis plan for the mega randomised registry trial research program comparing conservative versus liberal oxygenation targets in adults receiving unplanned invasive mechanical ventilation in the ICU (Mega-ROX). Crit Care Resusc. 2022;24(2):137-49.
30. Grim CC, Helmerhorst HJ, Schultz MJ, Winters T, Van Der Voort PH, Van Westerloo DJ, et al. Changes in Attitudes and Actual Practice of Oxygen Therapy in ICUs after Implementation of a Conservative Oxygenation Guideline. Respiratory Care. 2020;65(10):1502-10.
31. Schjørring OL, Toft-Petersen AP, Kusk KH, Mouncey P, Sørensen EE, Berezowicz P, et al. Intensive care doctors' preferences for arterial oxygen tension levels in mechanically ventilated patients. Acta Anaesthesiologica Scandinavica. 2018;62(10):1443-51.