ORIGINAL ARTICLE

Lower or Higher Oxygenation Targets for Acute Hypoxemic Respiratory Failure

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ABSTRACT

BACKGROUND

Patients with acute hypoxemic respiratory failure in the intensive care unit (ICU) are treated with supplemental oxygen, but the benefits and harms of different oxygenation targets are unclear. We hypothesized that using a lower target for partial pressure of arterial oxygen (Pao_2) would result in lower mortality than using a higher target.

METHODS

In this multicenter trial, we randomly assigned 2928 adult patients who had recently been admitted to the ICU (≤12 hours before randomization) and who were receiving at least 10 liters of oxygen per minute in an open system or had a fraction of inspired oxygen of at least 0.50 in a closed system to receive oxygen therapy targeting a Pao_2 of either 60 mm Hg (lower-oxygenation group) or 90 mm Hg (higher-oxygenation group) for a maximum of 90 days. The primary outcome was death within 90 days.

RESULTS

At 90 days, 618 of 1441 patients (42.9%) in the lower-oxygenation group and 613 of 1447 patients (42.4%) in the higher-oxygenation group had died (adjusted risk ratio, 1.02; 95% confidence interval, 0.94 to 1.11; P=0.64). At 90 days, there was no significant between-group difference in the percentage of days that patients were alive without life support or in the percentage of days they were alive after hospital discharge. The percentages of patients who had new episodes of shock, myocardial ischemia, ischemic stroke, or intestinal ischemia were similar in the two groups (P=0.24).

CONCLUSIONS

Among adult patients with acute hypoxemic respiratory failure in the ICU, a lower oxygenation target did not result in lower mortality than a higher target at 90 days. (Funded by the Innovation Fund Denmark and others; HOT-ICU ClinicalTrials.gov number, NCT03174002.)

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Patients who are admitted to the intensive care unit (ICU) with acute hypoxemic respiratory failure often receive supplemental oxygen with a high fraction of inspired oxygen (Fio_2), which results in a high partial pressure of arterial oxygen (Pao_2). In some clinical trials, such therapy has been associated with increased mortality.[1-3] However, clinical practice guidelines give no recommendation for oxygenation targets in adult patients in the ICU owing to sparse evidence.[4-7]

In a small, multicenter, randomized trial involving patients undergoing mechanical ventilation in the ICU,[8] investigators found that targeting a peripheral oxygen saturation of 88 to 92%, as compared with a value of 96% or above, was feasible without evident harm. In a single-center, randomized trial,[9] patients in the ICU who were treated with a Pao_2 target of 70 to 100 mm Hg had lower mortality than those who were treated with a Pao_2 target of up to 150 mm Hg. In addition, a Pao_2 target of 55 to 80 mm Hg is often referred to as the standard of care in patients with acute respiratory distress syndrome (ARDS), as it was described in several trials performed by the ARDS Network.[10-12] The preference among clinicians for a lower oxygenation target in the ICU has been confirmed in a multinational survey, in which 80% of the respondents would accept a Pao_2 target of 60 mm Hg or lower in clinical trials.[13]

Recently, a systematic review and meta-analysis showed that lower oxygenation targets were preferable in acutely ill adults.[14] However, the Liberal Oxygenation versus Conservative Oxygenation in ARDS ($LOCO_2$) trial was stopped prematurely because of a higher frequency of mesenteric ischemia and a higher 90-day mortality in the lower-oxygenation group than in the higher-oxygenation group.[15] In the large Intensive Care Unit Randomized Trial Comparing Two Approaches to Oxygen Therapy (ICU-ROX), investigators found no between-group differences in the number of ventilator-free days or in mortality within 28 days.[16]

We conducted the Handling Oxygenation Targets in the ICU (HOT-ICU) trial to test the hypothesis that targeting a Pao_2 of 60 mm Hg would reduce 90-day mortality by 5 percentage points as compared with targeting a Pao_2 of 90 mm Hg in patients who were admitted to the ICU with hypoxemic respiratory failure.

Methods

Trial Design and Oversight

HOT-ICU was an investigator-initiated, multicenter, stratified, parallel-group clinical trial with centralized randomization and a computer-generated concealed assignment sequence, with permuted blocks of varying sizes, stratified according to trial site and the presence or absence of chronic obstructive pulmonary disease (COPD) or active hematologic cancer. From June 20, 2017, to August 3, 2020, patients were enrolled at 35 ICUs in Denmark, Switzerland, Finland, the Netherlands, Norway, the United Kingdom, and Iceland. Written informed consent for incapacitated patients without an available surrogate was temporarily obtained (from a doctor independent of the trial) until the patient regained capacity or a surrogate became available. If consent was withdrawn, we asked the patient or surrogate for permission to continue registration of trial data and to include the data in our analyses, in accordance with national regulations. Because of the nature of the trial, clinicians and patients or their surrogates were aware of the trial-group assignments.

The trial was designed and overseen by the steering committee. An independent data and safety monitoring committee, whose members were unaware of trial-group assignments, oversaw the trial and reviewed the planned interim analysis after 1464 patients had completed the 90-day follow-up. Trial data were reviewed at the sites by external monitors, in accordance with the Good Clinical Practice directive of the European Union, and centrally by staff from the coordinating center.

The trial protocol and the statistical analysis plan were published before the enrollment of the last patient in the trial[17,18] and are available in a single document with the full text of this article at NEJM.org. The protocol was approved by the relevant ethics committees, according to national regulations. The members of the steering committee wrote the first draft of the manuscript. All the authors vouch for the adherence of the trial to the protocol, for the accuracy and completeness of the data, and for the reporting of serious adverse events.

Patients

We screened adult patients (≥18 years of age) who were admitted to the ICU with hypoxemic respi-

ratory failure and who were receiving at least 10 liters of oxygen per minute in an open system or who had an F_{IO_2} of at least 0.50 in a closed system; all the patients had placement of an arterial line and were expected to receive supplementary oxygen therapy for at least 24 hours in the ICU. With these thresholds of oxygen supplementation, we assumed that the P_{AO_2}:F_{IO_2} ratio in all the patients would be below 300. We excluded patients who could not undergo randomization within 12 hours after ICU admission. All additional exclusion criteria are provided in the Supplementary Appendix, available at NEJM.org.

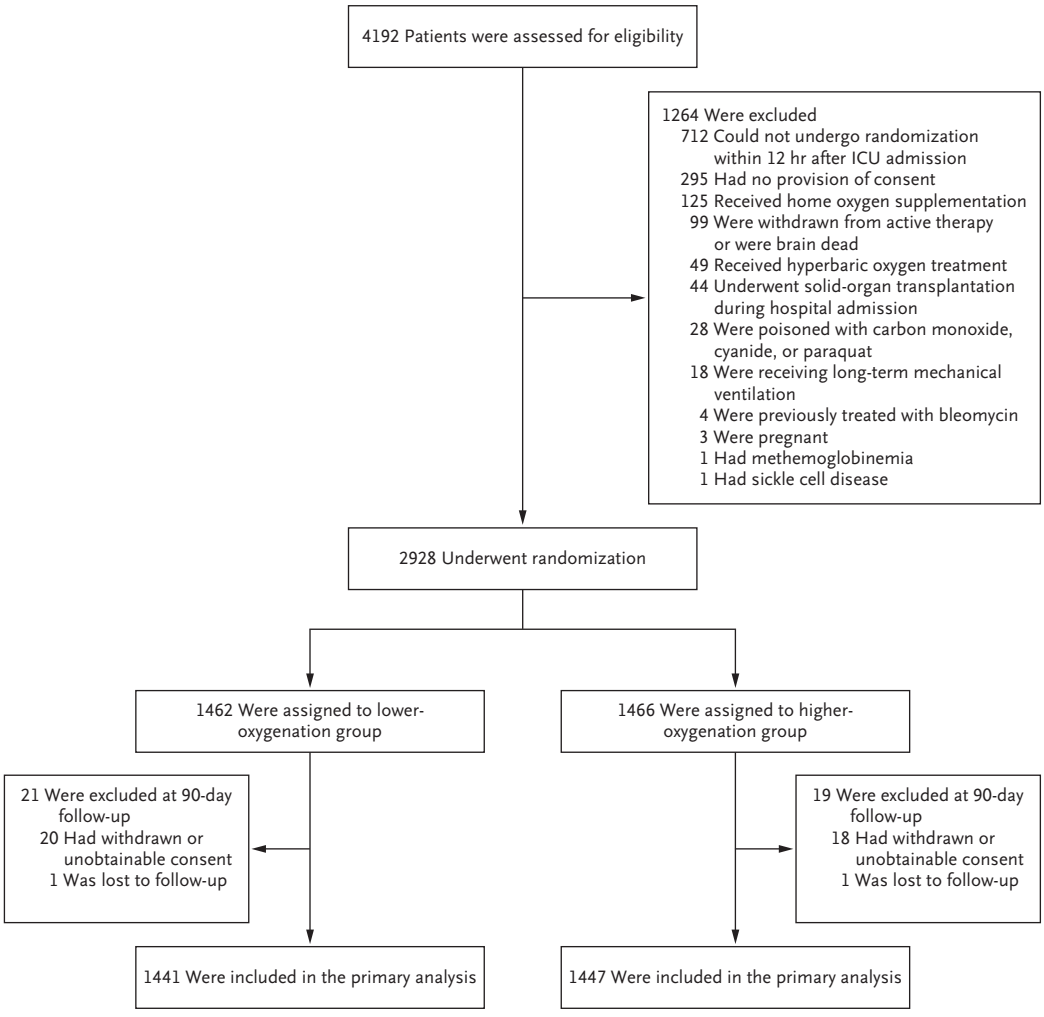


Figure 1. Screening, Randomization, and Follow-up.

Patients could have more than one reason for being excluded from the trial after screening. A total of 40 patients were excluded from the primary analysis after randomization because they or their surrogate did not allow the use of their data (17 in the lower-oxygenation group and 17 in the higher-oxygenation group) or the consent for the use of their data could not be obtained according to national regulations (3 patients and 1 patient, respectively); 1 patient in each group was lost to follow-up. Although 30 patients or surrogates (14 patients and 16 patients, respectively) did not want further data to be registered, mortality data were obtained from national registries, and these patients were included in the primary analysis; however, data regarding some secondary outcomes were missing. One patient in the lower-oxygenation group who had erroneously undergone randomization 5.5 hours after death was excluded from the primary analysis, and an additional patient underwent randomization. A supplemental analysis of the primary outcome that includes the erroneously randomized patient is provided in Table S9. ICU denotes intensive care unit.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Lower-Oxygenation Group (N = 1453)	Higher-Oxygenation Group (N = 1457)
Median age (IQR) — yr	70 (60–77)	70 (60–77)
Male sex — no. (%)	925 (63.7)	946 (64.9)
Median interval between hospital admission and randomization (IQR) — days	1 (0–5)	1 (0–5)
Median interval between ICU admission and randomization (IQR) — hr	4 (2–7)	4 (2–7)
Coexisting illness — no. (%)		
Ischemic heart disease	205 (14.1)	205 (14.1)
Chronic heart failure	140 (9.6)	146 (10.0)
Active metastatic cancer	65 (4.5)	61 (4.2)
Long-term dialysis	19 (1.3)	28 (1.9)
Chronic obstructive pulmonary disease	277 (19.1)	286 (19.6)
Active hematologic cancer	82 (5.6)	86 (5.9)
Type of admission — no. (%)		
Medical	1248 (85.9)	1240 (85.1)
Elective surgery	18 (1.2)	21 (1.4)
Emergency surgery	187 (12.9)	196 (12.9)
Acute illness — no. (%)		
Pneumonia	838 (57.7)	836 (57.4)
Multiple trauma	24 (1.7)	29 (2.0)
Hemorrhagic or ischemic stroke	25 (1.7)	22 (1.5)
Traumatic brain injury	9 (0.6)	15 (1.0)
Myocardial infarction	84 (5.8)	99 (6.8)
Intestinal ischemia	27 (1.9)	41 (2.8)
Cardiac arrest	149 (10.3)	186 (12.8)
ARDS	178 (12.3)	195 (13.4)
Invasive ventilation		
Patients — no. (%)	834 (57.4)	870 (59.7)
Median tidal volume (IQR) — ml	499 (429–582)	499 (426–561)
Median end-expiratory pressure (IQR) — cm of water	9 (7–10)	10 (7–10)
Median peak pressure (IQR) — cm of water	25 (20–29)	25 (21–30)
Noninvasive ventilation or CPAP		
Patients — no. (%)	199 (13.7)	176 (12.1)
Median end-expiratory pressure (IQR) — cm of water	8 (6–9)	7 (5–8)
Open system — no. (%)	420 (28.9)	411 (28.2)
Median Pao_2 (IQR) — mm Hg	77.3 (65.3–93.8)	77.3 (62.3–93.0)
Median Sao_2 (IQR) — %†	94 (91–97)	95 (91–97)
Median Fio_2 (IQR) — fraction‡	0.70 (0.55–0.90)	0.70 (0.56–0.85)
Median Pao_2:Fio_2 ratio (IQR)		
In all systems	118.6 (88.8–157.5)	117.5 (90.0–153.8)
In closed systems	125.7 (91.6–165.0)	125.0 (94.7–163.5)

Table 1. (Continued.)

Characteristic	Lower-Oxygenation Group (N = 1453)	Higher-Oxygenation Group (N = 1457)
Median lactate level (IQR) — mmol/liter	1.8 (1.1–3.2)	1.7 (1.1–3.1)
Median lowest mean arterial pressure (IQR) — mm Hg§	59 (49–68)	58 (48–69)
Use of inotropes — no. (%)	33 (2.3)	37 (2.5)
Use of vasopressors		
Patients — no. (%)	800 (55.1)	791 (54.3)
Median highest dose of norepinephrine (IQR) — μg/kg/min	0.20 (0.10–0.40)	0.21 (0.10–0.40)
Median SOFA score (IQR)¶	8 (5–10)	8 (5–10)

* All baseline variables were missing for 9 patients in each group. ARDS denotes acute respiratory distress syndrome, CPAP continuous positive airway pressure, ICU intensive care unit, IQR interquartile range, and Pao_2 partial pressure of arterial oxygen.
† Values for arterial oxygen saturation (Sao_2) were not available for 191 patients because this measure was not included in blood gas analyses at one trial site.
‡ The fraction of inspired oxygen (Fio_2) in open systems was estimated with the use of standardized conversion tables.
§ Listed is lowest median value of the arterial pressure recorded during the 24 hours before randomization.
¶ Scores on the Sequential Organ Failure Assessment (SOFA) range from 0 to 24, with higher scores indicating more severe organ failure. Data were missing for 48 patients in the lower-oxygenation group and for 50 patients in the higher-oxygenation group.

INTERVENTION

Patients were randomly assigned in a 1:1 ratio to receive oxygen therapy targeting either a Pao_2 of 60 mm Hg (lower-oxygenation group) or a Pao_2 of 90 mm Hg (higher-oxygenation group) until a maximum of 90 days after randomization. The trial period included any readmissions to the ICU. We recorded the lowest and the highest Pao_2 in predefined 12-hour intervals, along with concomitant values of arterial oxygen saturation (Sao_2) and Fio_2. The oxygenation targets were achieved by adjustment of the Fio_2. In the two groups, deviations from the target of more than 7.5 mm Hg were accepted only in patients who had an Fio_2 of 0.21 or in those with an Fio_2 of 1.00. The oxygen-supplementation devices and ventilator settings were chosen by the clinicians. Ventilator settings were registered daily at 8 a.m. if either invasive or noninvasive ventilation or continuous positive airway pressure was being used. A schedule for the sampling of arterial blood gases was not mandated in the protocol, but we assumed that at least four measurements would be performed per day.[3] Since such measures of arterial blood gases were performed at varying times during the day, clinicians and nurses were instructed to monitor all patients with continuous measurement of peripheral oxygen saturation and to identify and maintain the saturation level at which the assigned Pao_2 was measured.

OUTCOME MEASURES

The primary outcome was death from any cause within 90 days after randomization. The secondary outcomes were the number of patients with one or more serious adverse events, which were defined as a new episode of shock, myocardial ischemia, cerebral ischemia, or intestinal ischemia; the percentage of days that patients were alive without life support, as defined by the absence of mechanical ventilation, renal-replacement therapy, or vasopressor or inotrope infusion; and the percentage of days that patients were alive after hospital discharge at the 90-day follow-up. (Additional details about the outcome measures are provided in the Supplementary Appendix.) Data regarding outcome measures were obtained from the patients' files by site investigators, who were aware of the trial-group assignments; data regarding 90-day mortality were also obtained from regional and national registries.

STATISTICAL ANALYSES

We estimated that the enrollment of 2928 patients would provide a power of 90% to detect a between-group difference of 5 percentage points in mortality at 90 days after randomization, which

would correspond to a 20% difference in relative risk at a two-sided alpha level of 5%. In making this determination, we assumed a 90-day mortality of 25% in the higher-oxygenation group on the basis of data from a study involving patients undergoing mechanical ventilation in five Danish ICUs.[3] Analyses of the primary and secondary outcomes were performed in the intention-to-treat population, which included all the patients who had undergone randomization, except those for whom consent was withdrawn or unobtainable.[19]

We compared dichotomous data between the two trial groups using a generalized linear model with a log-link and binomial error distribution with adjustment for stratification variables; results are reported as relative risks and risk differences with 95% confidence intervals for the primary outcome and with 98.75% confidence intervals for the secondary outcomes after adjustment for multiple comparisons.[18] Analysis of the primary outcome was supplemented with crude Kaplan–Meier plots and the calculation of a hazard ratio from a Cox proportional-hazards model with adjustment for stratification variables, as well as a Bayes factor calculation.[20] We used the Van Elteren test after adjustment only for the trial site to compare continuous data, since the assumptions of a Poisson distribution or a negative binomial distribution were not met.[21] Since the trial-group assignments could not be blinded, the analyses of the primary and secondary outcomes were performed with the oxygenation targets masked, and the steering committee wrote two abstracts assuming opposite group assignments before unblinding of the data (see the Supplementary Appendix). These two abstracts document the fully implemented blinding in the statistical analyses and in the main interpretation of the results. Statistical significance was indicated by a two-sided P value below 0.05 for the primary outcome and by a multiplicity-adjusted P value below 0.0125 for the three secondary outcomes.

We conducted a secondary analysis of the primary outcome in the intention-to-treat population using logistic regression (reported as odds ratios and 95% confidence intervals) after adjustment for the stratification variables and predefined risk factors at baseline: age, type of ICU admission, presence or absence of metastatic cancer, and the score on the Sequential Organ Failure Assessment (SOFA). (The SOFA score ranges from 0 to 24, as calculated from subscores ranging from 0 to 4 for each of six organ systems — respiration, coagulation, liver, cardiovascular, central nervous system, and renal — with higher scores indicating more severe organ failure.)[22]

We evaluated the primary outcome in subgroups that were defined according to the presence or absence of shock at the time of randomization, the use of invasive mechanical ventilation, COPD, traumatic brain injury, and cardiac arrest, along with the type of ICU admission (medical, elective surgery, or emergency surgery).[18] Details regarding the subgroup evaluations are provided in the Supplementary Appendix. A per-protocol analysis is also ongoing, so the results are not reported here. No imputations for missing data were performed, since the percentage of missing data was less than 5% for all outcomes.[23] All analyses were performed with the use of Stata statistical software, release 16 (StataNordic).

RESULTS

TRIAL POPULATION

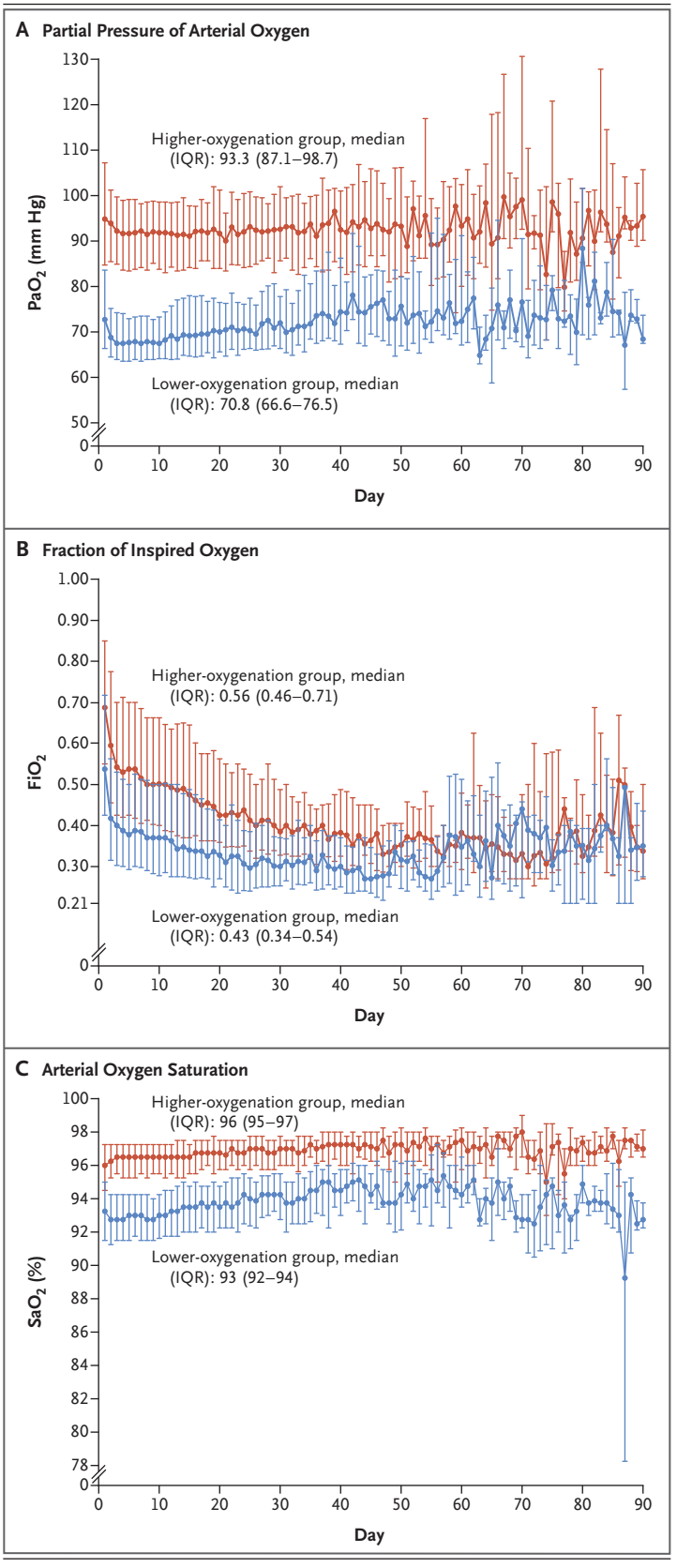
Of the 2928 patients who were enrolled in the trial, 1462 were assigned to the lower-oxygenation group and 1466 to the higher-oxygenation group. We obtained 90-day mortality data regarding 2888 patients (98.6%), which included 1441 patients in the lower-oxygenation group and 1447 patients in the higher-oxygenation group (Fig. 1). The trial groups had similar characteristics at baseline, except for the presence of cardiac arrest (Table 1).

OXYGENATION AND ICU INTERVENTIONS

During the 90-day intervention period, the recorded Pao_2 measurements were lower in the lower-oxygenation group than in the higher-oxygenation group, as were the corresponding Sao_2 and Fio_2 values (Fig. 2). The 12-hour highest and lowest Pao_2 measurements, with corresponding Sao_2 and Fio_2 values, are provided in Figures S1 through S3 in the Supplementary Appendix. The use of mechanical ventilation, prone positioning, inhaled vasodilators, extracorporeal membrane oxygenation, circulatory support, renal-replacement therapy, and blood transfusions were similar in the two groups. Data obtained daily at 8 a.m.

Figure 2. Values for Pao_2, Fio_2, and Sao_2, According to Oxygenation Strategy.

Shown are the median values of daily means of partial pressure of arterial oxygen (Pao_2) (Panel A), fraction of inspired oxygen (Fio_2) (Panel B), and arterial oxygen saturation (Sao_2) (Panel C) of the trial patients until a maximum of 90 days. The daily means were calculated from the 12-hour lowest and highest Pao_2 with concomitant values for Fio_2 and Sao_2. I bars represent interquartile ranges (IQR). Sao_2 values were not available in blood gas analyses from one site and were therefore missing for 191 patients. Data for patients according to day are provided in Table S1.



showed no substantial between-group differences regarding positive end-expiratory pressure, peak inspiratory pressure, or tidal volume among the patients who were undergoing invasive mechanical ventilation or in end-expiratory pressure among those who were undergoing noninvasive ventilation (Table S2).

OUTCOMES

At 90 days after randomization, 618 of 1441 patients (42.9%) in the lower-oxygenation group and 613 of 1447 patients (42.4%) in the higher-oxygenation group had died (risk ratio, 1.02; 95% confidence interval [CI], 0.94 to 1.11; P=0.64) (Table 2). Results were similar in the analysis after adjustment for baseline factors; the hazard ratio was similar as well after adjustment for stratification variables (Fig. 3). A Bayes factor that was substantially higher than 1 supported the finding of no effect of the intervention (see the Supplementary Appendix). The results of the subgroup analyses were similar to those in the primary analysis (Table S3).

At day 90, the percentage of days that patients were alive without life support and the percentage of days that patients were alive after hospital discharge did not differ significantly between the two groups (Table 2; absolute numbers and single components are provided in Tables S4, S5, and S6). Likewise, the number of patients with one or more serious adverse events did not differ significantly between the two groups (Table 2).

DISCUSSION

In this multicenter, randomized trial involving adult patients with acute hypoxemic respiratory failure in the ICU, we found that targeting a Pao_2 of 60 mm Hg rather than a Pao_2 of 90 mm Hg

Table 2. Primary and Secondary Outcomes.

Outcome	Lower-Oxygenation Group	Higher-Oxygenation Group	Risk Ratio (95% CI)*	Risk Difference (95% CI)*	Adjusted Odds Ratio (95% CI)	P Value
Primary outcome†						
Death by day 90 — no./total no. (%)	618/1441 (42.9)	613/1447 (42.4)				
Adjusted for stratification variables‡			1.02 (0.94 to 1.11)	0.63 (−2.92 to 4.17)		0.64
Adjusted for stratification and baseline variables§					1.05 (0.89 to 1.23)	0.58
Secondary outcomes¶						
Median percentage of days alive without life support (IQR)	87.8 (0.0–96.7)	84.4 (0.0–96.0)				0.10
Median percentage of days alive after hospital discharge (IQR)	55.6 (0.0–85.6)	50.0 (0.0–84.4)				0.67
Serious adverse events — no./total no. (%)	525/1453 (36.1)	555/1457 (38.1)	0.95 (0.84 to 1.07)	−1.6 (−6.0 to 2.8)		0.24
Shock	492/1453 (33.9)	521/1457 (35.8)				
Myocardial ischemia	14/1453 (1.0)	8/1457 (0.5)				
Ischemic stroke	19/1453 (1.3)	23/1457 (1.6)				
Intestinal ischemia	32/1453 (2.2)	29/1457 (2.0)				

* For serious adverse events, relative risk and risk difference are reported with 98.75% confidence intervals that have been adjusted for multiple comparisons. Risk differences are reported in percentage points.
† Data regarding the primary outcome were missing for 21 patients in the lower-oxygenation group and for 19 patients in the higher-oxygenation group.
‡ Stratification variables were the trial site and the presence or absence of chronic obstructive pulmonary disease or active hematologic cancer.
§ Baseline variables were age, presence or absence of active metastatic cancer, type of admission (medical, elective surgical, or emergency surgical), and the SOFA score, which ranges from 0 to 24, with higher scores indicating more severe organ failure.
¶ The percentage of days alive without life support was calculated as the number of days without the use of invasive ventilation, noninvasive ventilation, continuous positive airway pressure, vasopressor or inotropic infusion, or renal-replacement therapy, divided by the number of days alive within 90 days. The percentage of days alive after hospital discharge was calculated as the number of days alive and discharged from the hospital divided by the number of days alive within 90 days. Data were missing for 33 patients in each of the oxygenation groups. Absolute numbers and percentages are provided in Tables S6, S7, and S8.

did not result in better values for several key outcomes — including mortality, the percentage of days alive without life support, the percentage of days alive after hospital discharge, and serious adverse events — at 90 days. Our findings lend weight to the utility of conservative oxygen therapy in patients with acute hypoxemic respiratory failure, as compared with the results of the $LOCO_2$ trial.[15] At the same time, the results of our trial do not preclude the possibility of clinically important harm or benefit with a lower-oxygenation strategy in this population or in other types of critically ill patients. In the $LOCO_2$ trial, mesenteric ischemia occurred in five patients who were assigned to a Pao_2 target of 55 to 70 mm Hg and in no patients assigned to a Pao_2 target of 90 to 105 mm Hg. The overall incidence of intestinal ischemia in our trial (2.1%) was similar to that in the $LOCO_2$ trial (2.5%).[15] The $LOCO_2$ trial was stopped early after the inclusion of 201 patients with ARDS; at the time, there was no significant between-group difference in the primary outcome of mortality at day 28, but there was significantly higher 90-day mortality in the lower-oxygenation group. Although we recruited patients with acute hypoxemic respiratory failure regardless of the presence of ARDS, the baseline Pao_2:Fio_2 ratios were remarkably similar to those in the $LOCO_2$ trial.

Notably, we observed a 90-day mortality that was twice as high as had been hypothesized on the basis of data previously obtained in five Danish

ICUs.[3] The higher 90-day mortality in our trial may have been partially due to differences in the types of admissions. Acute medical conditions accounted for 85.5% of the admissions in our trial and for 37.3% of those in the cited cohort study, whereas emergency surgery accounted for 1.3% and 29.8%, respectively, and elective surgery for 13.2% and 32.6%, respectively. Furthermore, although only 12.8% of our patients were recorded as having ARDS at baseline, they had more severe hypoxemic respiratory failure than anticipated, with Pao_2:FIO_2 ratios in the range of those found in patients with moderate-to-severe ARDS. This degree of hypoxemia might also have contributed to the higher mortality observed in our trial. Accordingly, the present results may not be representative of outcomes in a lower-risk population.

In the ICU-ROX trial,[16] not all the patients had acute hypoxemic respiratory failure, as illustrated by a Pao_2:FIO_2 ratio at baseline that was twice as high as that both in our trial and in the $LOCO_2$ trial, as well as a lower FIO_2. The ICU-ROX trial showed no significant between-group differences in the number of ventilator-free days or in mortality at 90 days and 180 days. However, investigators found a potential benefit of a lower oxygenation target in the 164 patients with suspected hypoxic–ischemic encephalopathy (relative risk, 0.73; 95% CI, 0.54 to 0.99). In the 332 patients with cardiac arrest in our trial, there was no clear between-group difference in 90-day mortality according to the randomized oxygenation targets, although firm conclusions cannot be drawn (Table S3).

The strengths of our trial include the variety of ICUs and countries involved and the pragmatic protocol that called for maintaining routine practice except for the oxygenation targets, while obtaining a clear between-group difference in Pao_2, Sao_2, and FIO_2 levels. Limitations must also be considered. The oxygenation targets that we used in our trial may have differed from standard of care in some countries. In a post hoc assessment, we found potential differences in the treatment effects among the individual ICUs (Fig. S4). We tested the two oxygen-therapy strategies by targeting intermittent measurement of the Pao_2; however, to account for the varying sampling schedules, all the patients had continuous monitoring of the peripheral oxygen saturation. Measurement of the Pao_2 may allow for more accurate maintenance of oxygenation targets than other methods, since the peripheral oxygen saturation can substantially differ from the Sao_2 under certain conditions[24,25] and may be less accurate in Black patients than in White patients.[26] However, targeting the Pao_2 is less feasible without placement of an arterial line and without the availability of point-of-care blood gas analysis. The use of standardized conversion tables for FIO_2 in open systems is another limitation, since the oxygen content in the lung varies with the patient's breathing patterns among other factors. Our evaluation of the between-group difference in values for Pao_2, FIO_2, and Sao_2 was limited by a diminishing number of patients in the ICU after the initial 14 to 21 days.

In a meta-analysis,[14] investigators reported the possibility that more liberal oxygen therapy in acutely ill adults may result in increased mortality.[14] However, an updated systematic review and meta-analysis with trial sequential analysis, including the ICU-ROX trial[16] among others, showed neither beneficial nor harmful effects of higher versus lower oxygenation strategies.[27] Although we found no differences in clinical outcomes between the two oxygenation groups in adults with

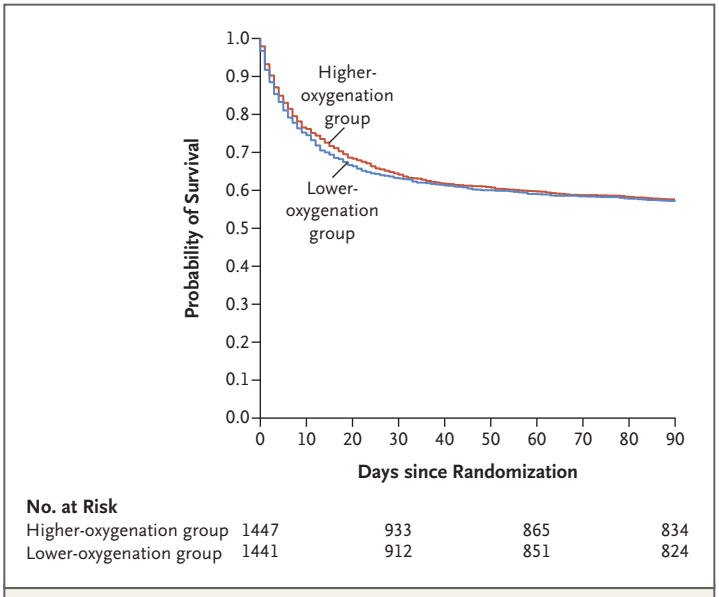


Figure 3. Kaplan–Meier Estimates of Survival.

Shown are the results of Kaplan–Meier analysis of data regarding survival, which were administratively censored at 90 days (adjusted hazard ratio, 1.04; 95% confidence interval, 0.93 to 1.16). The Cox proportional-hazards model was adjusted for the trial site and for the presence or absence of chronic obstructive pulmonary disease or active hematologic cancer.

acute hypoxemic respiratory failure, the results do not preclude the possibility of clinically important harm or benefit with the lower oxygenation strategy.

Thus, a lower oxygenation target did not result in lower mortality at 90 days than a higher-oxygenation target among patients in the ICU with acute hypoxemic respiratory failure.

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APPENDIX

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