ORIGINAL ARTICLE

Oxygen Saturation and Outcomes in Preterm Infants

The BOOST II United Kingdom, Australia, and New Zealand Collaborative Groups

ABSTRACT

BACKGROUND

The optimum oxygen saturation for preterm infants is unknown. Previous studies have shown that infants had reduced rates of retinopathy of prematurity when lower targets of oxygen saturation were used.

METHODS

In three international randomized, controlled trials, we evaluated the effects of targeting an oxygen saturation of 85 to 89%, as compared with a range of 91 to 95%, on disability-free survival at 2 years in infants born before 28 weeks' gestation. Halfway through the trials, the oximeter-calibration algorithm was revised. Recruitment was stopped early when an interim analysis showed an increased rate of death at 36 weeks in the group with a lower oxygen saturation. We analyzed pooled data from patients and now report hospital-discharge outcomes.

RESULTS

A total of 2448 infants were recruited. Among the 1187 infants whose treatment used the revised oximeter-calibration algorithm, the rate of death was significantly higher in the lower-target group than in the higher-target group (23.1% vs. 15.9%; relative risk in the lower-target group, 1.45; 95% confidence interval [CI], 1.15 to 1.84; P=0.002). There was heterogeneity for mortality between the original algorithm and the revised algorithm (P=0.006) but not for other outcomes. In all 2448 infants, those in the lower-target group for oxygen saturation had a reduced rate of retinopathy of prematurity (10.6% vs. 13.5%; relative risk, 0.79; 95% CI, 0.63 to 1.00; P=0.045) and an increased rate of necrotizing enterocolitis (10.4% vs. 8.0%; relative risk, 1.31; 95% CI, 1.02 to 1.68; P=0.04). There were no significant between-group differences in rates of other outcomes or adverse events.

CONCLUSIONS

Targeting an oxygen saturation below 90% with the use of current oximeters in extremely preterm infants was associated with an increased risk of death. (Funded by the Australian National Health and Medical Research Council and others; BOOST II Current Controlled Trials number, ISRCTN00842661; and Australian New Zealand Clinical Trials Registry numbers, ACTRN12605000055606 and ACTRN12605000253606.)

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The optimum range for oxygen saturation in preterm infants is unknown. Trials in the 1950s showed that unrestricted oxygen increased the rate of severe retinopathy of prematurity. However, when oxygen was subsequently restricted, increased mortality was observed.[1] The first Benefits of Oxygen Saturation Targeting (BOOST) trial showed that in preterm infants who were still receiving oxygen at 32 weeks' gestation, targeting a higher oxygen-saturation range prolonged oxygen dependence.[2] Observational studies suggested that higher oxygen-saturation levels may increase rates of retinopathy of prematurity.[3-5]

In five randomized, masked trials with similar protocols conducted in the United States,[6] Australia, New Zealand, Canada, and the United Kingdom[7] involving infants born before 28 weeks' gestation, investigators are evaluating the effects of targeting a range of oxygen saturation of 85 to 89%, as compared with a range of 91 to 95%, on survival and neurodevelopmental outcomes at 18 months to 2 years after term. In all five trials, Masimo Radical pulse oximeters were used to measure oxygen saturation.

During the trials, investigators in the United Kingdom found that standard Masimo Radical oximeters returned fewer oxygen-saturation values in the range of 87 to 90% than expected.[8] We investigated this oximeter finding, because such a discrepancy might affect the study groups differently, and we found that there was a shift up in the oximeter-calibration curve between 87% and 90%. This reduced the frequency of displayed oxygen-saturation values ranging from 87 to 90% and caused values ranging from 87 to 96% to read 1 to 2% higher. Masimo supplied software with a revised calibration algorithm that eliminated the problem and was similar to the calibration of other oximeters.[8]

Approximately halfway through the trials, between December 2008 and May 2009, oximeters in the United Kingdom and Australian trials were changed to the new calibration algorithm, and the new algorithm was used for all infants who were subsequently enrolled. The New Zealand trial oximeters were not changed because recruitment had nearly finished. Analysis of oxygen-saturation distributions showed that the revised calibration algorithm improved oxygen-saturation targeting, with clearer separation in oxygen-saturation patterns between the two study groups and more time in the intended oxygen-saturation range (Fig. 1, and Tables S1.1 through S1.4 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

In 2010, in the Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT),[6] investigators reported that infants treated with the use of an oxygen-saturation target of 85 to 89%, as compared with a target of 91 to 95%, had decreased rates of retinopathy of prematurity (8.6% vs. 17.9%, $P<0.001$) but increased rates of death (19.9% vs. 16.2%, $P=0.045$). At that time, patients were being recruited for the BOOST II trials, and after analyzing data from the original trials, the data and safety monitoring committees did not advise stopping recruitment.[9]

In December 2010, the data and safety monitoring committees in the United Kingdom, Australian, and New Zealand undertook a pooled interim safety analysis,[10] including data from the 2315 infants enrolled in the three BOOST II trials and the 1316 infants enrolled in SUPPORT.[6] The sole outcome that the committees analyzed was survival at 36 weeks' gestation. Guidelines prespecified that the results would not be released to the investigators unless a difference in survival in all infants or in those recruited after the oximeter-calibration changes exceeded 3 SE ($P<0.003$). In the three trials reported here, mortality at 36 weeks showed heterogeneity between the original oximeter-calibration algorithm and the revised algorithm ($P=0.006$ for interaction). Among the 1260 infants for whom the original oximeter algorithm was used, there was no significant between-group difference in mortality. However, in the 1055 infants for whom the revised algorithm was used, infants with an oxygen-saturation target of 85 to 89%, as compared with those with a target of 91 to 95%, had an increased rate of death at 36 weeks (21.8% vs. 13.3%, $P<0.001$). At that time, recruitment to the present trials in the United Kingdom and Australia was closed.[10] The present New Zealand trial had finished recruiting.

The primary outcome of the Neonatal Oxygenation Prospective Meta-analysis (NeOProM) Collaboration[7] is death or severe neurosensory disability at 18 months to 2 years of age, corrected for prematurity. SUPPORT recently reported no difference in this composite outcome but an increased rate of death at 18 to 22 months in

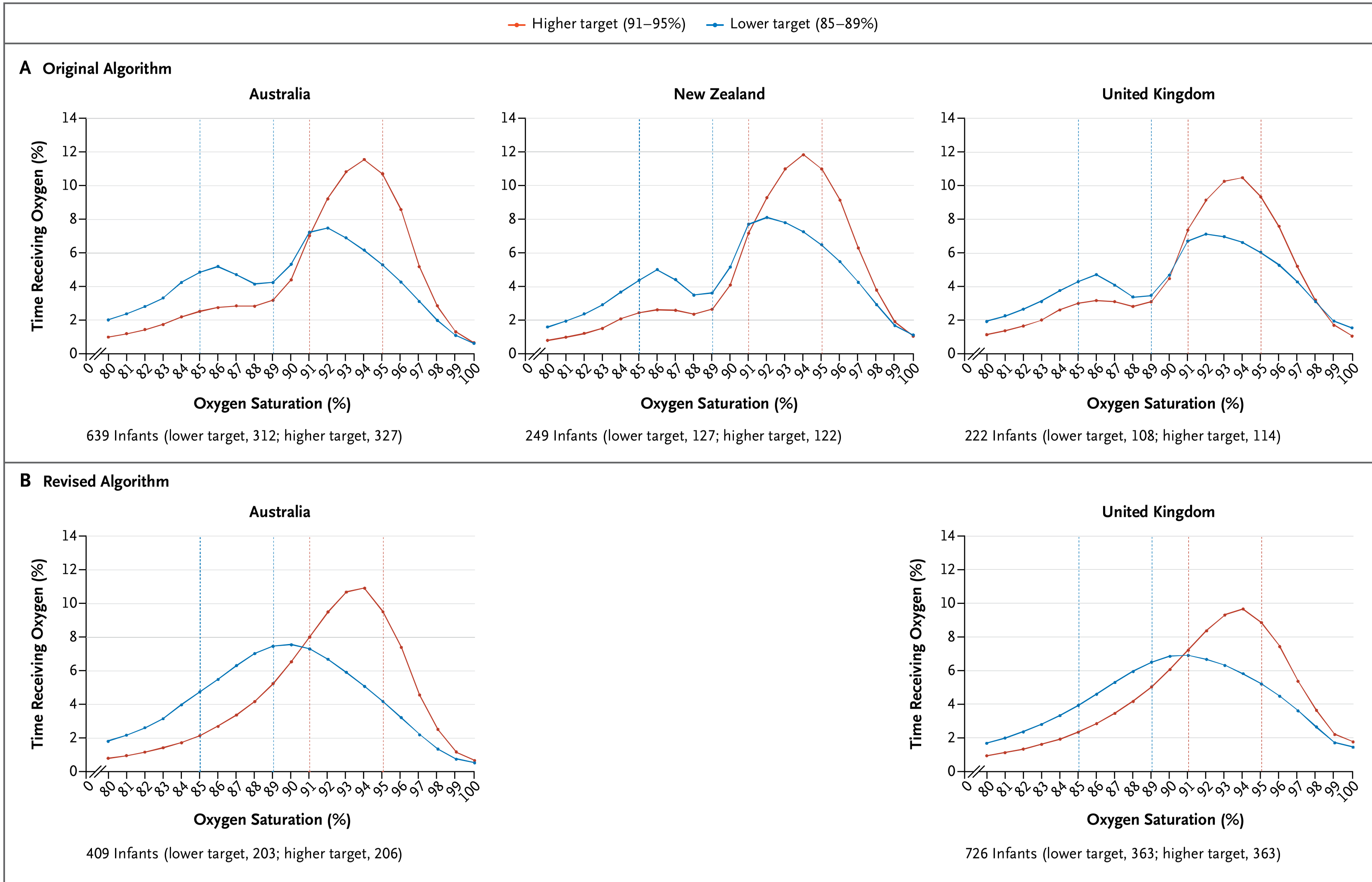


Figure 1. Pooled Frequency Histograms for Time Infants Spent at Each Oxygen-Saturation Level from 80 to 100% while Receiving Supplemental Oxygen.

For trials in the United Kingdom and Australia, separate histograms are provided for infants whose treatment used the original oximeter-calibration algorithm and those whose treatment used the revised algorithm, according to whether they were assigned to receive a higher target of oxygen saturation (91 to 95%) or a lower target (85 to 89%). Revised oximeters were not used in the New Zealand trial.

infants in the group with a lower oxygen-saturation target.[11] Because a finding of increased mortality with a lower oxygen-saturation target could have an influence on clinical practice,[10,11] we now report a pooled analysis of individual patient data with respect to outcomes at hospital discharge in the United Kingdom, Australian, and New Zealand BOOST II trials.

METHODS

PATIENTS

The planned study sample sizes were 1200 infants each for the United Kingdom and Australian trials and 340 infants for the New Zealand trial. Infants were enrolled from March 1, 2006, until December 24, 2010. Randomization was performed centrally by computer and separately for each trial. In the United Kingdom, a minimization procedure was used to balance study-group assignment according to sex, gestational age, and center. In Australia and New Zealand, randomization was stratified according to sex, gestational age, center, single birth or multiple births, and whether birth took place in the hospital where enrollment took place. Infants were eligible if they had been born within the past 24 hours and before 28 weeks' gestation. Infants were excluded if they were considered to be unlikely to survive, had a major congenital abnormality, or would not be available for follow-up.

The ethics committee at each center approved the study before randomization. All parents provided written informed consent.

ENROLLMENT AND TREATMENT

Infants were randomly assigned to treatment with the use of an oxygen-saturation target of 85 to 89% (lower-target group) or 91 to 95% (higher-target group). To mask the intervention, the study oximeters were modified internally so that readings of 85 to 95% showed an oxygen saturation that was either 3% higher or 3% lower than the actual value. Thus, a displayed reading of 90% corresponded to an actual oxygen saturation of 87% in one group and 93% in the other. To achieve the intended oxygen-saturation range in either group, clinical staff members targeted displayed readings in the range of 88 to 92%. Displayed oxygen-saturation values gradually reverted to actual values when the measured value was outside the range of 85 to 95%.

Only study oximeters were used from the time of randomization until 36 weeks, unless infants died or were discharged home. If infants were in stable condition while breathing ambient air before 36 weeks, oximetry could be discontinued, but if oximetry resumed before 36 weeks, study oximeters were used. Data regarding oxygen saturation were downloaded and merged with chart data on which staff recorded the inspired oxygen concentration in blocks of either 20 minutes (in the United Kingdom) or 60 minutes (in Australia and New Zealand) to enable assessment of compliance with target ranges.

ASSESSMENTS

Data were recorded on case-report forms at each center and checked centrally. Retinopathy of prematurity was classified according to the International Classification of Retinopathy of Prematurity[12] and is reported if infants were treated according to the Early Treatment for Retinopathy of Prematurity (ETROP) criteria.[13] Necrotizing enterocolitis was listed if it required surgery or caused death. Oxygen treatment at 36 weeks was recorded in all three trials. In the United Kingdom, bronchopulmonary dysplasia was additionally defined as requiring supplemental oxygen at 36 weeks to maintain an actual oxygen saturation of 90%.

When the oximeter-calibration algorithm was revised, infants continued to be treated with the use of the oximeter-calibration version to which they were originally assigned. Clinical staff members were not informed about the nature of the software revision. No further training about oxygen-saturation targeting was provided.

STUDY OVERSIGHT

The BOOST II trials were funded and conducted independently, with similar protocols (available at NEJM.org). The Australian trial was funded by the National Health and Medical Research Council, the United Kingdom trial by the Medical Research Council, and the New Zealand trial by the New Zealand Health Research Council. Masimo supplied the oximeters used in the study under lease, but company representatives were not involved in the design of the study or in the analysis of the data.

STATISTICAL ANALYSIS

A joint analysis plan prespecified that data from the three trials would be pooled and outcomes reported for all infants and for those who underwent randomization before and after the revision of the oximeter-calibration algorithm.

All analyses were performed with the use of Stata SE 11.2 software (StatCorp). All analyses were performed separately by the trial statisticians in the United Kingdom and Australia and were cross-checked. A two-sided P value of less than 0.05 was considered to indicate statistical significance without adjustment for multiple comparisons.

All analyses were performed on the intention-to-treat principle at randomization, regardless of deviations from the protocol. Outcomes were summarized with the use of counts and percentages for categorical variables and of means and standard deviations for normally distributed continuous variables. The magnitude and direction of treatment effects were expressed as relative risks, with 95% confidence intervals adjusted for country. Relative risks were calculated as the event rate in the lower-target group divided by the event rate in the higher-target group. Prespecified subgroup analyses according to the oximeter-calibration algorithm that was used were performed with a statistical test for interaction.

To compare the oxygen-saturation values, the percentage of time spent at each oxygen-saturation value between 60% and 100% was calculated for each infant and pooled for all infants, for time treated with oxygen and for all time evaluated on the oximeter. Offset readings were adjusted back to the actual oxygen-saturation values. We used quadratic interpolation to estimate the distribution of values affected by the transitioning back to actual values of offset readings in which the measured value was outside the range of 85 to 95%. A post hoc survival analysis was performed with the use of cumulative-hazard plots to compare mortality before discharge in the two target groups.

RESULTS

PATIENTS

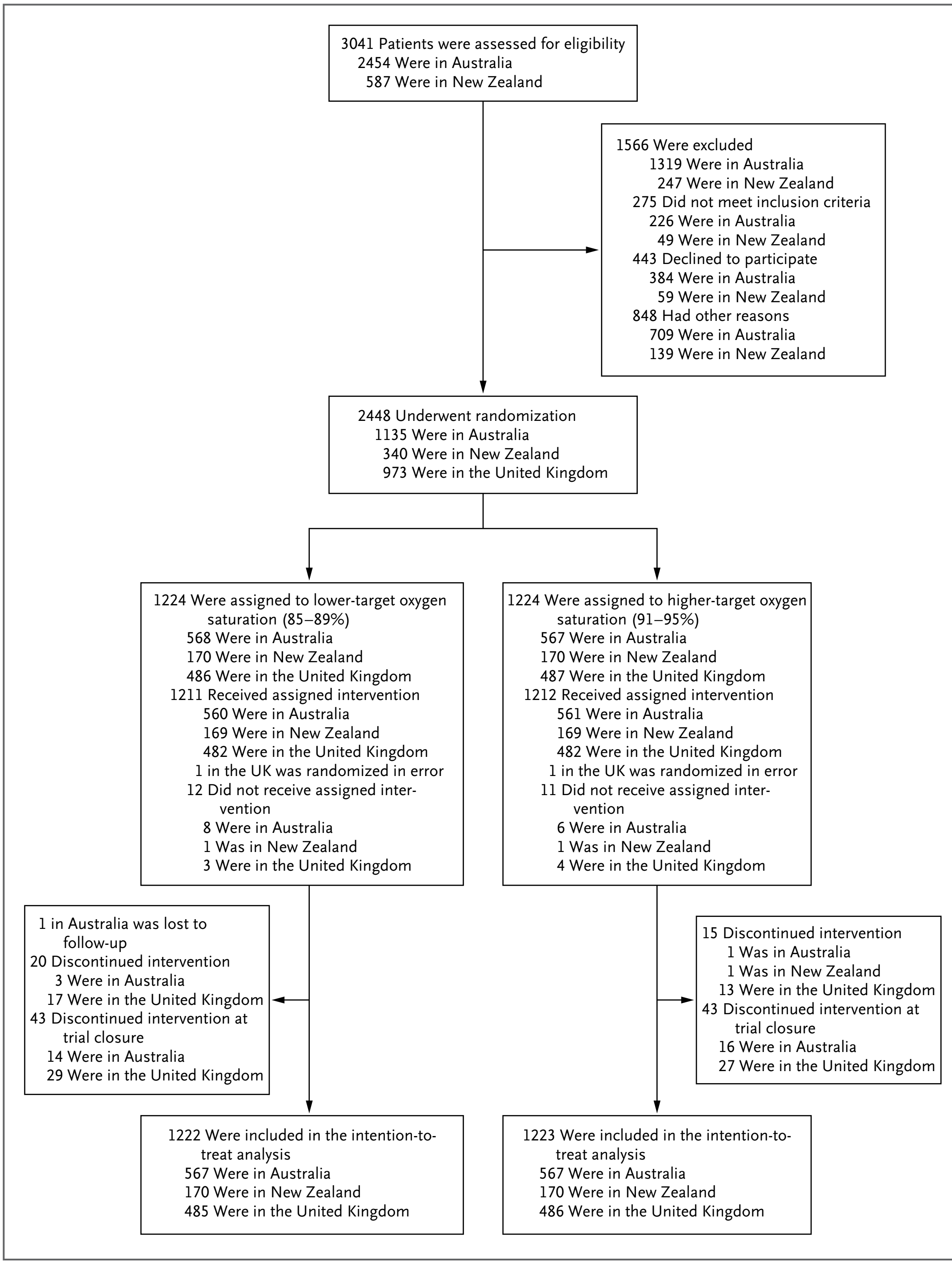
A total of 2448 infants were enrolled in the three trials (973 in the United Kingdom, 1135 in Australia, and 340 in New Zealand). Of these infants, 1261 (51.5%) were treated with the use of the original oximeter-calibration algorithm and 1187 (48.5%) with the use of the revised algorithm (Fig. 2). Baseline demographic and clinical characteristics were similar in the two target groups, among the three trials, and in the two algorithm groups (Table 1). Forest plots of pooled outcomes at hospital discharge are shown in Figure 3. Outcome data from the individual trials are provided in Tables S2.1 and S2.2 in the Supplementary Appendix.

RATE OF DEATH

Among the 1187 infants for whom the revised oximeter-calibration algorithm was used, those in the lower-target group had a higher rate of death than those in the higher-target group at hospital discharge (23.1% vs. 15.9%; relative risk in the lower-target group, 1.45; 95% confidence interval [CI], 1.15 to 1.84; P=0.002). These findings mean that 14 infants would need to be treated with a higher oxygen-saturation target in order to prevent 1 death. Among the 1261 infants for whom the original oximeter-calibration algorithm was used, there were no significant between-group differences in outcomes at hospital discharge. There was heterogeneity between the rates of death among infants whose treatment used the original oximeter-calibration algorithm, as compared with the revised algorithm (P=0.006 for interaction), but not for other outcomes.

In all data combined, there was no significant difference in rate of death in the lower-target group, as compared with the higher-target group (19.2% vs. 16.6%; relative risk, 1.16, 95% CI, 0.98 to 1.37; P=0.09), but infants in the lower-target group had a reduced rate of treatment for retinopathy of prematurity (10.6% vs. 13.5%; relative risk, 0.79; 95% CI, 0.63 to 1.00; P=0.045) and an increased rate of necrotizing enterocolitis requiring surgery or causing death (10.4% vs. 8.0%; relative risk, 1.31; 95% CI, 1.02 to 1.68; P=0.04). Although significantly fewer infants in the lower-target group were treated with oxygen at 36 weeks in the three trials, there was no significant between-group difference in the rate of bronchopulmonary dysplasia, as defined physiologically in the United Kingdom trial.

There were more deaths in the lower-target group, but no single cause dominated the difference (Table S3 in the Supplementary Appendix). Figure 4 shows cumulative hazard plots for mortality before discharge, according to which version of the oximeter-calibration algorithm was used. The difference in the proportions of infants surviving in the two groups accumulated gradually after the first week after birth.



EFFECT OF OXIMETER RECALIBRATION

Figure 1 summarizes pooled distributions of oxygen saturation during the administration of supplemental oxygen (Fig. S1 and Tables S1.1 through S1.4 in the Supplementary Appendix). With the original oximeter-calibration algorithm, there were fewer oxygen-saturation values between 87% and 90% in the two target groups and little separation between the peaks of the oxygen-saturation distributions. With the revised algorithm, the dip in oxygen-saturation values between 87% and 90% was eliminated, and there

Figure 2 (facing page). Enrollment and Outcomes.
In the United Kingdom trial, screening of eligible infants was not recorded. Of the infants who underwent randomization, all were included in the analysis except for the following 3: in the United Kingdom trial, 1 infant in the lower-target group for whom consent was not provided and 1 infant in the higher-target group who was found to be ineligible because of age; and in the Australian trial, 1 infant in the lower-target group whose parents withdrew consent. A total of 23 infants (12 in the lower-target group and 11 in the higher-target group) did not receive the intended allocation at all times, mainly because of errors in oximeter allocation that were rectified later. The intervention was discontinued before it was completed in 35 infants, mainly because of parental or clinician wishes or because the infant was transferred to another center that was unable to continue the intervention. When the trials were stopped early after the interim safety analysis, the intervention was stopped in 43 infants in each of the two study groups.

was clearer separation between the two target groups.

Per-Protocol Analysis and Adverse Events

The results of a per-protocol analysis that excluded 23 infants who did not receive the intended intervention were similar to the findings in the intention-to-treat analysis. The few adverse events that were reported are listed in full in Table S4 in the Supplementary Appendix.

Discussion

The present trials were closed early when a pooled interim safety analysis showed that infants in the group treated with an oxygen-saturation target of 85 to 89%, as compared with 91 to 95%, had an increased rate of death at 36 weeks.[10] This report includes outcomes for all infants until hospital discharge. A substantial difference in mortality persisted, and other important outcomes were influenced significantly by the targeted oxygen-saturation range.

The between-group difference in the rate of death accrued over many weeks of the intervention and was not attributable to any single cause of death. It is unclear why the rate of death was higher in the lower-target group than in the higher-target group. Detailed post hoc analysis of the oxygen-saturation patterns of infants who survived and died will be required to further explore this issue. Interpretation of the results is complicated by the change in oximeter calibration approximately halfway through the trials. This modification rectified an artifact in the original oximeters that appeared to decrease the difference between groups in oxygen-saturation patterns. The revised Masimo oximeter-calibration algorithm may be more relevant to future clinical practice because it resembles the calibration in other commonly used oximeters; the original calibration algorithm is no longer available.[8]

There was significant heterogeneity in treatment effect between the original oximeter-calibration algorithm and the revised algorithm with respect to mortality but not retinopathy of prematurity or necrotizing enterocolitis. This may be because each of these outcomes may be influenced at different oxygen saturations. The oxygen-saturation histograms in Figure 1 show that when the oximeter-calibration algorithm was revised, there was no increase in the proportion of time spent with oxygen-saturation values below 85% in the lower-target group. This suggests that the increase in mortality cannot be attributed to an increase in the time spent with very low oxygen-saturation values.

Infants in the lower-target group had a significant decrease in the rate of treatment for retinopathy of prematurity, a finding that is consistent with the results of trials conducted in the 1950s[1] and SUPPORT.[6,11] Because treatment for this condition is usually effective, blindness was rare, with similar rates in the two target groups in SUPPORT.[11] However, retinopathy of prematurity causes other structural and functional eye abnormalities that can be visually disabling,[14] and these may become more common if the reported survival advantage with a higher oxygen saturation influences clinical practice. Treatment for retinopathy of prematurity was more frequent in the two target groups in the United Kingdom than in Australia and New Zealand, suggesting that treatment thresholds may have differed even though the same criteria were used.[15]

In the pooled data, the lower oxygen-saturation target significantly increased the rate of necrotizing enterocolitis requiring surgery or causing death. This definition excludes milder cases of necrotizing enterocolitis with more subjective features. It is plausible that a lower oxygen saturation might influence bowel ischemia.

The increased proportion of infants receiving

Table 1. Baseline Characteristics of the Infants, According to Trial and Study Group.*

Characteristic	Australia		New Zealand		United Kingdom		Combined Trials	
	Lower Target (N=568)	Higher Target (N=567)	Lower Target (N=170)	Higher Target (N=170)	Lower Target (N=486)	Higher Target (N=487)	Lower Target (N=1224)	Higher Target (N=1224)
Male sex — no./total no. (%)	293/568 (51.6)	295/566 (52.1)	90/170 (52.9)	90/170 (52.9)	258/486 (53.1)	259/487 (53.2)	641/1224 (52.4)	644/1223 (52.7)
Birth weight — g	817±177	833±190	873±202	884±186	818±182	824±188	826±184	837±189
Gestational age — wk	26.0±1.16	26.0±1.18	26.1±1.23	26.1±1.19	26.0±1.30	26.0±1.31	26.0±1.22	26.0±1.23
Multiple births — no./total no. (%)	138/568 (24.3)	135/567 (23.8)	46/170 (27.1)	46/170 (27.1)	138/485 (28.5)	136/486 (28.0)	322/1223 (26.3)	317/1223 (25.9)
Birth outside enrollment hospital — no./total no. (%)	44/568 (7.7)	42/567 (7.4)	11/170 (6.5)	13/170 (7.6)	57/486 (11.7)	60/487 (12.3)	112/1224 (9.2)	115/1224 (9.4)
Use of antenatal glucocorticoids — no./total no. (%)								
Complete regimen	303/568 (53.3)	320/567 (56.4)	94/170 (55.3)	103/170 (60.6)	306/483 (63.4)	301/484 (62.2)	703/1221 (57.6)	724/1221 (59.3)
Incomplete regimen	198/568 (34.9)	199/567 (35.1)	56/170 (32.9)	49/170 (28.8)	137/483 (28.4)	135/484 (27.9)	391/1221 (32.0)	383/1221 (31.4)
Admission temperature — °C	36.0±1.05	36.1±0.93	36.4±1.01	36.4±0.89	36.6±0.93	36.6±0.94	36.3±1.04	36.3±0.96

* Plus–minus values are means ±SD. The oxygen-saturation targets were 85 to 89% (lower-target group) or 91 to 95% (higher-target group).

oxygen at 36 weeks in the higher-target group probably reflects, in part, the increased oxygen needed to achieve the target. As in SUPPORT,[6] when bronchopulmonary dysplasia was defined on the basis of a physiological test in the United Kingdom trial, there was no significant between-group difference in this diagnosis.

With the original oximeters in the present trials, the peak median oxygen-saturation values while infants were receiving supplemental oxygen were approximately 89% in the lower-target group and 92% in the higher-target group, as compared with 91% and 94%, respectively, in SUPPORT.[6] Although the same intended targets were used, quite different oxygen-saturation patterns were achieved in our studies, as compared with those in SUPPORT. When the oximeter-calibration algorithm was revised, the lower-target groups in the present trials spent more time in the intended range, and mortality in these groups increased. With greater or lesser adherence to the intended range, the effect of oxygen-saturation targets on mortality may vary, so the best estimate of the effect of oxygen saturation on mortality is unknown. Other interventions that influence oxygen targeting may influence mortality and should also be researched carefully.[16]

Monitoring of oxygen saturation has largely replaced the practice of monitoring the arterial partial pressure of oxygen (PaO_2)[17,18] and has effectively lowered the range of PaO_2 for preterm infants, as compared with previously recommended PaO_2 targets.[19,20] Infants in the lower-target group may have had times when the PaO_2 was below 40 mm Hg.[19] The optimal measure of oxygenation to guide clinical practice is not known.

Without the pooled interim safety analysis,[10] continued recruitment to the present trials might have resulted in potentially avoidable deaths in the lower-target group. Consensus is needed about the roles of data and safety monitoring committees of simultaneous, similar, independent trials in respect to patient safety. The use of an interim analysis carries a statistical risk that, by chance, the observed effect might not represent the true effect that would have been shown if the trial had continued.[21] Thus, the prespecified criteria for unmasking the results of the interim safety analysis[11] required a difference in survival of 3 SE (99.73% confidence interval).

Outcome	Lower Target	Higher Target	Relative Risk (95% CI)	P Value
	no. of patients/total no.			
Death at discharge				
Original algorithm	98/629	109/630	0.90 (0.70–1.15)	0.39
Revised algorithm	137/592	94/590	1.45 (1.15–1.84)	0.002
Pooled (P=0.006 for heterogeneity)	235/1221	203/1220	1.16 (0.98–1.37)	0.09
Death at gestational age of 36 wk				
Original algorithm	85/629	98/630	0.87 (0.66–1.13)	0.29
Revised algorithm	131/592	82/590	1.59 (1.24–2.04)	<0.001
Pooled (P=0.001 for heterogeneity)	216/1221	180/1220	1.20 (1.00–1.44)	0.045
Retinopathy of prematurity				
Original algorithm	52/556	61/535	0.79 (0.56–1.12)	0.19
Revised algorithm	58/479	80/509	0.77 (0.57–1.06)	0.11
Pooled (P=0.91 for heterogeneity)	110/1035	141/1044	0.79 (0.63–1.00)	0.045
Necrotizing enterocolitis				
Original algorithm	55/629	39/630	1.42 (0.96–2.10)	0.08
Revised algorithm	72/592	58/587	1.23 (0.89–1.71)	0.21
Pooled (P=0.59 for heterogeneity)	127/1221	97/1217	1.31 (1.02–1.68)	0.04
Intraventricular hemorrhage				
Original algorithm	66/624	54/625	1.23 (0.88–1.73)	0.23
Revised algorithm	74/579	72/586	1.04 (0.77–1.41)	0.79
Pooled (P=0.48 for heterogeneity)	140/1203	126/1211	1.12 (0.89–1.41)	0.32
Other brain injury				
Original algorithm	48/564	54/562	0.89 (0.61–1.28)	0.52
Revised algorithm	66/515	59/520	1.13 (0.81–1.57)	0.47
Pooled (P=0.34 for heterogeneity)	114/1079	113/1082	1.01 (0.79–1.30)	0.91
Patent ductus arteriosus				
Original algorithm	315/629	303/629	1.04 (0.93–1.16)	0.49
Revised algorithm	266/590	250/590	1.06 (0.93–1.21)	0.37
Pooled (P=0.83 for heterogeneity)	581/1219	553/1219	1.05 (0.97–1.15)	0.23
Oxygen dependence at 36 wk				
Original algorithm	193/542	216/530	0.89 (0.77–1.03)	0.13
Revised algorithm	201/456	245/501	0.90 (0.79–1.03)	0.14
Pooled (P=0.83 for heterogeneity)	394/998	461/1031	0.90 (0.81–0.99)	0.03
Bronchopulmonary dysplasia				
Original algorithm	47/91	41/84	1.06 (0.79–1.42)	0.71
Revised algorithm	113/262	131/292	0.96 (0.80–1.16)	0.68
Pooled (P=0.59 for heterogeneity)	160/353	172/376	0.99 (0.85–1.16)	0.91

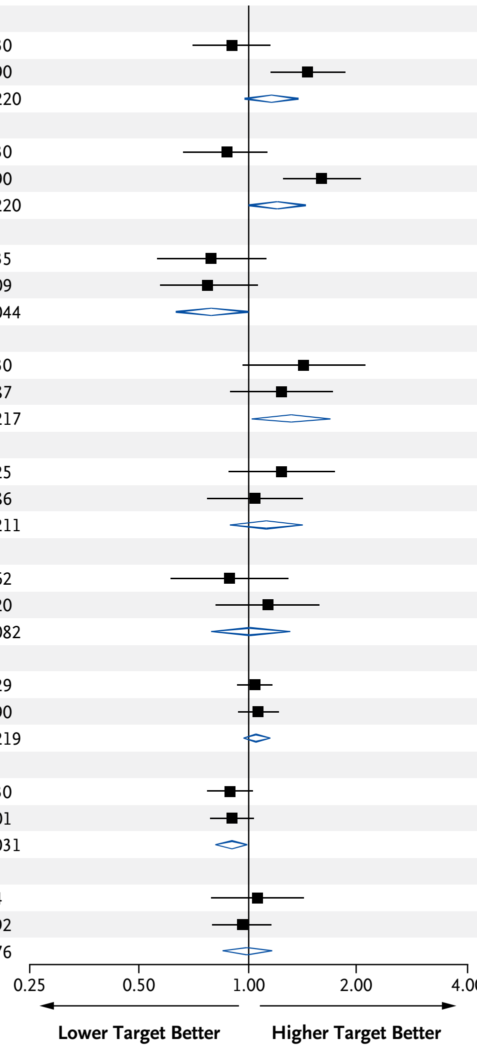


Figure 3. Combined Discharge Outcomes from the Three Trials, According to Oxygen-Saturation Target and Status of the Oximeter-Calibration Algorithm.

Shown are discharge outcomes for all infants in the lower-target group for oxygen saturation (85 to 89%) and the higher-target group (91 to 95%) on the basis of whether their treatment involved the original algorithm for oximeter calibration or the revised algorithm. Also shown are P values for heterogeneity for such algorithm use, as calculated with the use of chi-square tests. Oxygen dependence at a gestational age of 36 weeks was measured in all three trials. In the United Kingdom trial, bronchopulmonary dysplasia was additionally defined as requiring supplemental oxygen to maintain an actual oxygen saturation of 90% or more. Intraventricular hemorrhage was defined as only grade III or IV events, and patent ductus arteriosus was defined as a condition requiring medical or surgical treatment. The category of "other brain injury" included porencephaly, ventriculomegaly, post-hemorrhagic hydrocephalus requiring a shunt or reservoir, periventricular leukomalacia, and cerebral atrophy. Relative risks and P values were adjusted for country.

The optimum oxygen-saturation range for extremely preterm infants is unknown and may vary with advancing gestational and postnatal age. The present trials and the SUPPORT trial suggest that targeting a range of 91 to 95% is safer than targeting a range of 85 to 89%, but other ranges have not been investigated. The follow-up results from SUPPORT show no significant difference in rates of later disability.[11] The ongoing NeOProM Collaboration[7] will even-

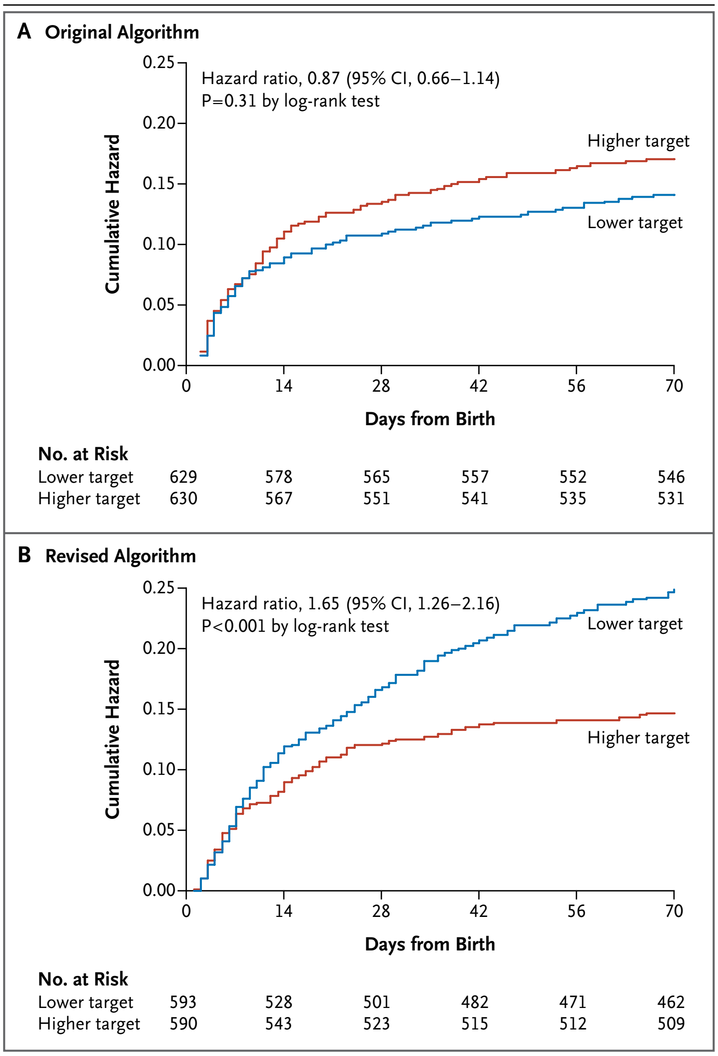


Figure 4. Cumulative Hazard Estimates for Death before Discharge.

Data from the three BOOST II trials have been pooled and are plotted separately for infants who were treated with the use of the original oximeter-calibration algorithm (Panel A) or the revised algorithm (Panel B). Cumulative hazard values were calculated with the use of the Nelson–Aalen estimator.

tually provide follow-up data on approximately 5000 infants and may further inform clinical practice.

In conclusion, preterm infants born before 28 weeks' gestation with a target oxygen saturation of 85 to 89% had a significantly higher rate of death than did those with a target of 91 to 95% in a subgroup whose treatment involved an oximeter-calibration algorithm similar to that in current use.[8] Our findings strongly favor the avoidance of targeting an oxygen saturation of less than 90% among such infants, according to readings on current oximeters.[6,10,11,22]

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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APPENDIX

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