# Hipoxemia permisiva: previniendo ROP y otras morbilidades en el prematuro extremo

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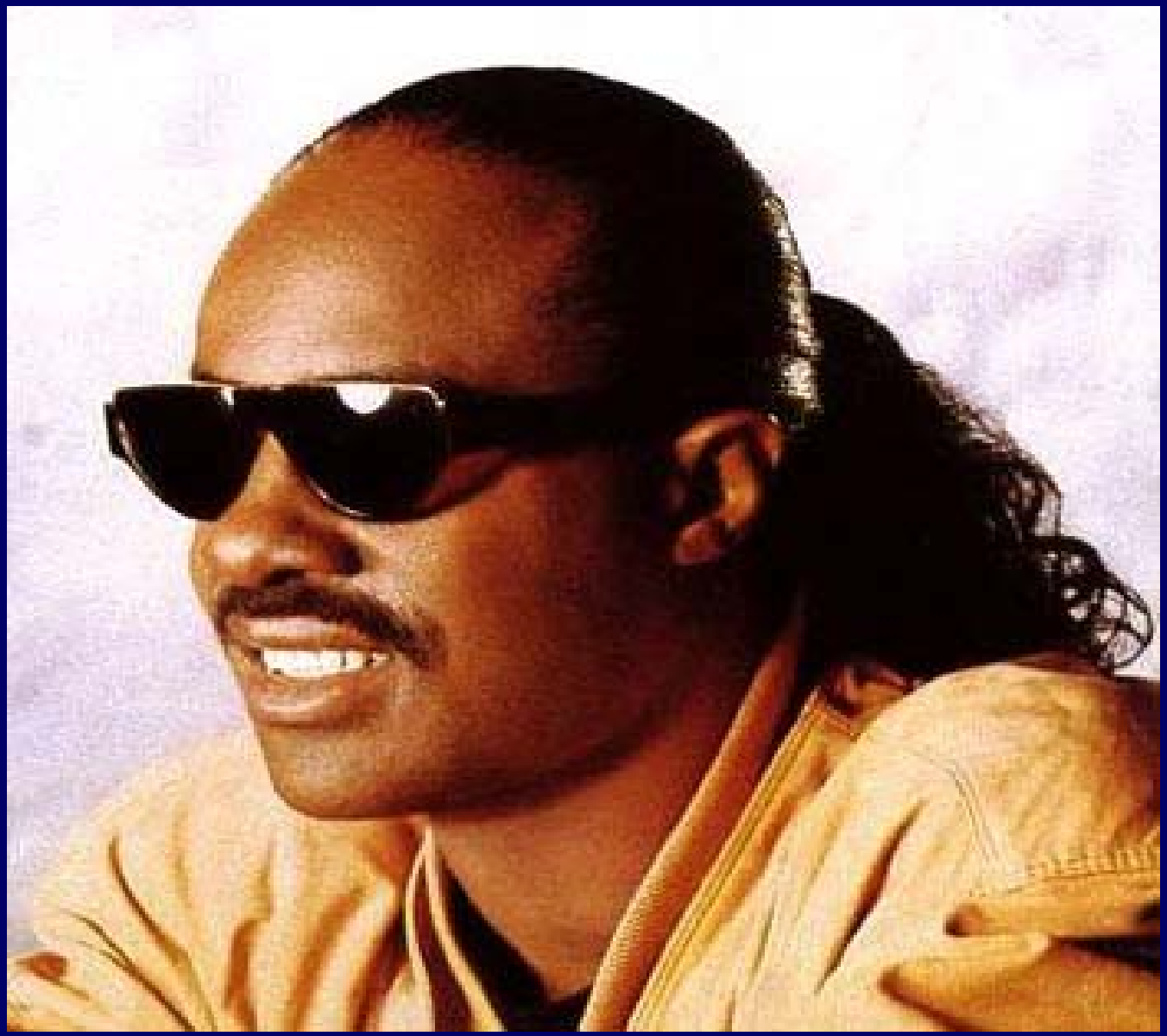
# Stevie Wonder



# Objectives

1. Know the results of the SUPPORT RCT arm of lower versus high oxygen saturation targeting
2. Be able to apply the results of this trial in your daily practice

# Background

- No consensus on targets
- Published “acceptable” levels in neonates are 88-98%
- No standards on assessing “need” in infants
- In contrast, supplemental $O_2$ “need” assessment is standard in COPD patients

**What $PaO_2$ or $SaO_2$ should we target?**

# Does the oxygenation targeting matter?

# Recent Trials of Oxygenation Targets

STOP-ROP Trial

BOOST Trial

SUPPORT Trial

# $SaO_2$ Targets: STOP-ROP Trial

## Methods

| | |
|---|---|
| Design: | Multicenter RCT, not masked |
| Patient population: | 649 preterm infants with prethreshold ROP |
| Treatment group: | $O_2$ sat 96-99% or 89-94% |
| Primary outcome: | Progression to threshold ROP in at least one eye |

STOP-ROP Multicenter Study Group. Pediatrics 105:295, 2000

# $SaO_2$ Targets: STOP-ROP Trial

| | Sats 96 to 99% | Sats 89 to 94% | p value |
|---|---|---|---|
| Threshold ROP | 41% | 48% | <0.05 |
| Pneumonia/BPD exacerbations | 13% | 8% | = 0.07 |
| Prolonged hospitalization* | 13% | 7% | <0.05 |
| Prolonged oxygen* | 47% | 37% | <0.05 |
| Prolonged diuretics* | 36% | 24% | <0.05 |
| Death | 3% | 2% | NS |

* At 3 months corrected age

STOP-ROP Multicenter Study Group. Pediatrics 105:295, 2000

# $SaO_2$ Targets: BOOST Trial

## Methods

| | |
|---|---|
| Design: | Multicenter RCT, double blind |
| Patient population: | 358 infants born at < 30 weeks and oxygen dependent at 32 weeks |
| Treatment groups: | $SaO_2$ 95-98% or 91-94% |
| Primary outcome: | Growth and neurodevelopment at 12 months corrected age |

Askie et al. NEJM 349:959, 2003

# $SaO_2$ Targets: BOOST Trial

| | Sats 95-98% | Sats 91-94% | p value |
|---|---|---|---|
| Dev abnormality | 23% | 24% | NS |
| Weight < 10% tile | 33% | 37% | NS |
| Death | 5% | 3% | NS |
| $O_2$ at 36 w | 64% | 46% | <0.001 |
| Home $O_2$ | 30% | 17% | <0.001 |

Askie et al. NEJM 349:959, 2003

# Current $O_2$ Targets and Practice

Design: Prospective multicenter observational study

Patient Population:
- 84 infants <28 week, <96 hours in 14 centers in 3 countries, monitored for 4 weeks
- Birthweight 863 $\pm$ 208 grams
- Gestational age 26 $\pm$ 1 week

Hagadorn et al. Pediatrics 118:1574, 2006

# Current $O_2$ Targets and Practice

| | Targets | Actual |
|---|---|---|
| Upper limit | 92 to 98% | 97% (75 % tile) |
| Lower limit | 83 to 92% | 91% (25 % tile) |
| Range | 88%, 95% | 95% (median) |
| Compliance by Center | -- | 16-64% |

Thus, compliance varied widely and was generally poor (50%), and achieved saturations are 34% higher than target

Hagadorn et al. Pediatrics 118:1574, 2006

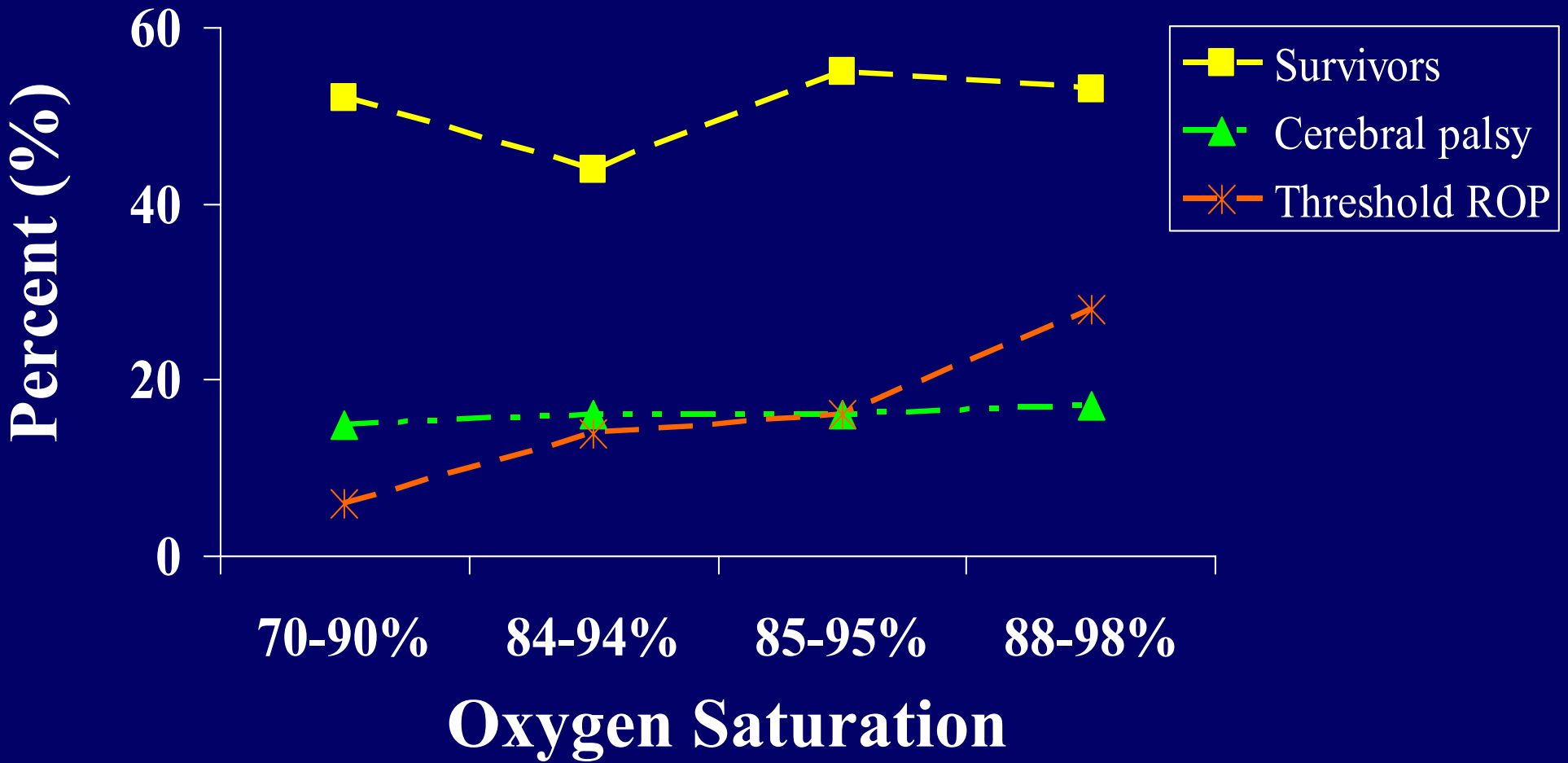
# $SaO_2$ Targets: Retrospective Study

## Methods

- Retrospective review
- Population study - All babies < 28 weeks in several referral units
- Data analyzed by $SaO_2$ targets

Tin et al. Arch Dis Child. 84:F106, 2001

# $SaO_2$ Targets: Retrospective Study




Tin et al. Arch Dis Child. 84:F106, 2001

# $SaO_2$ Targets: Expert Opinion

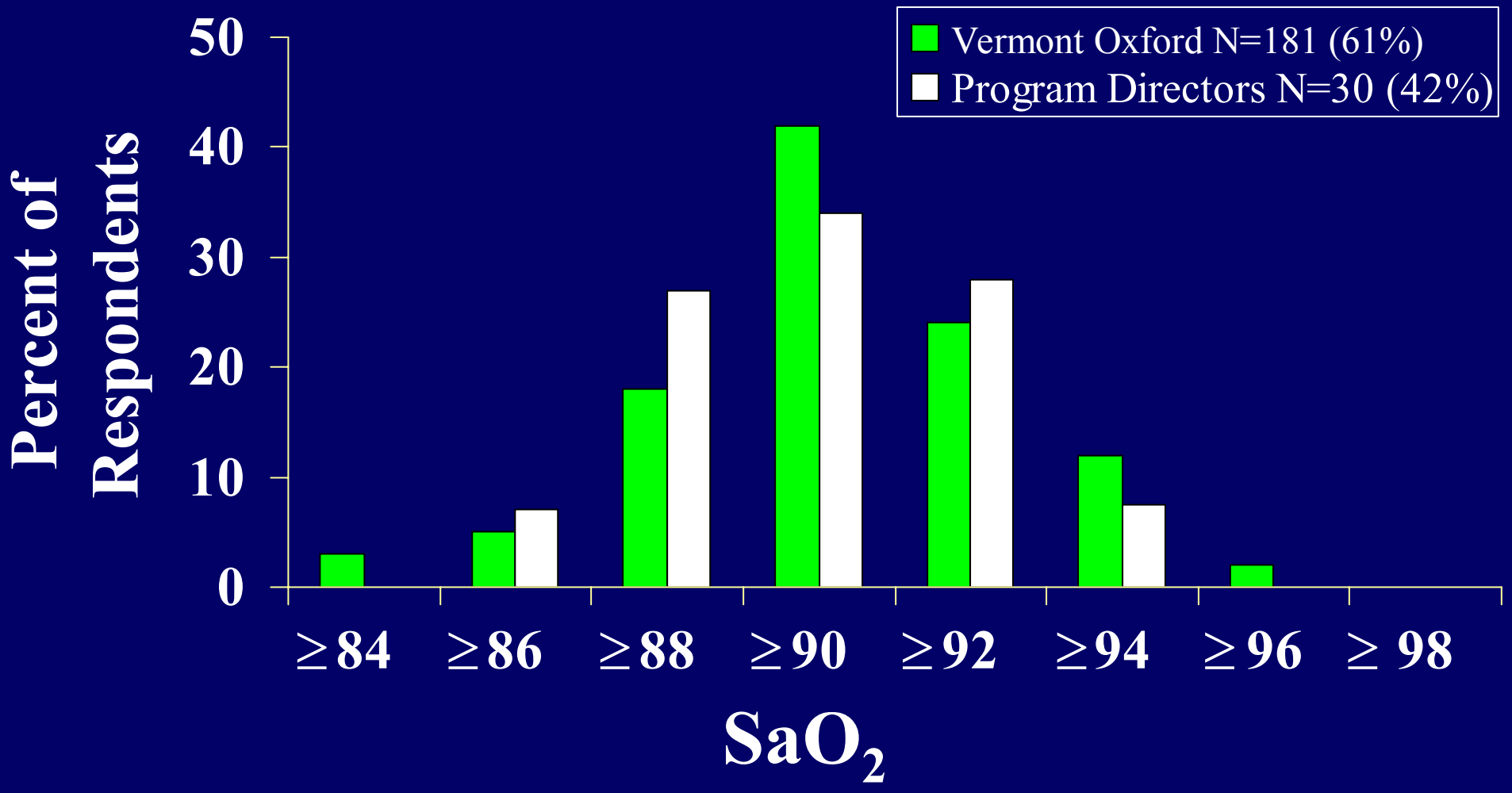
## Methods

Design: Survey of VON Centers and ONTPD

Respondents: 181 (61%) VON Centers and 30 (42%) PD

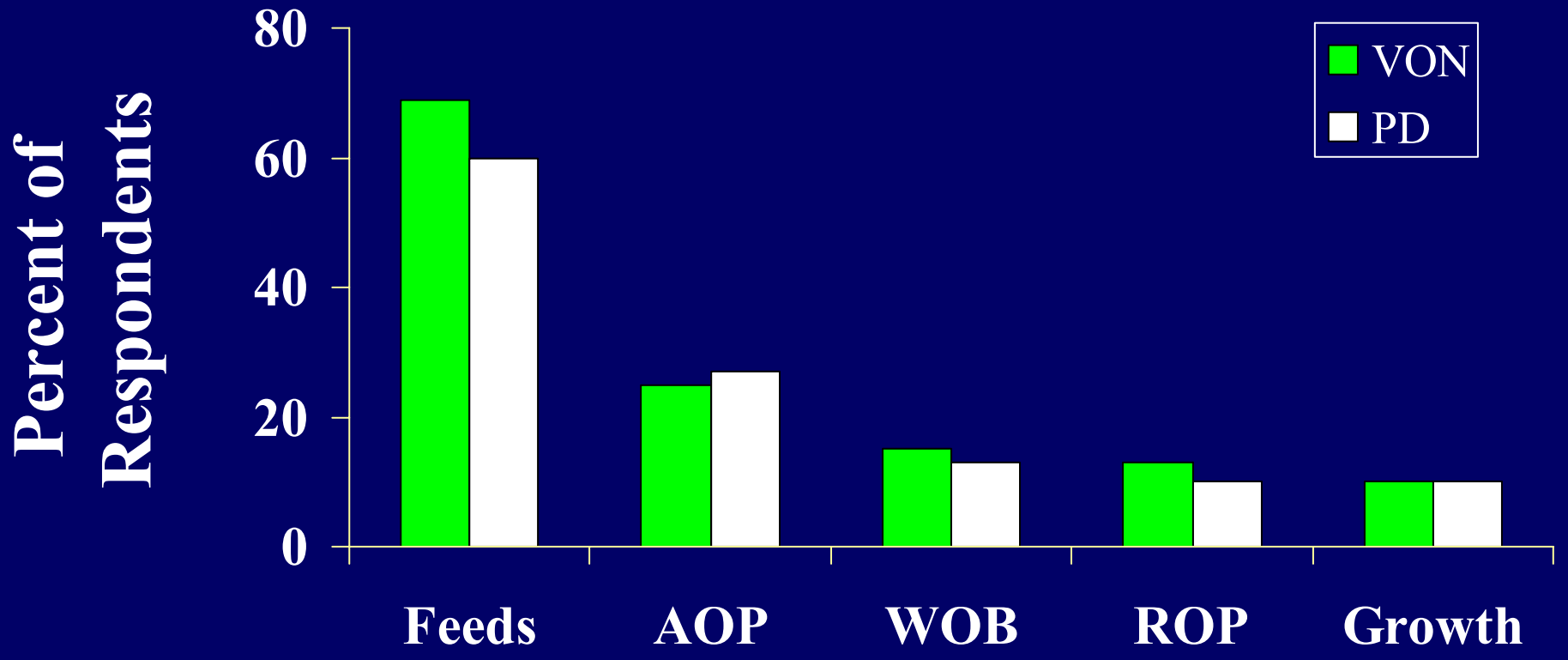
Ellsbury et al. J Pediatr 140:247, 2002

# $SaO_2$ Targets: Expert Opinion



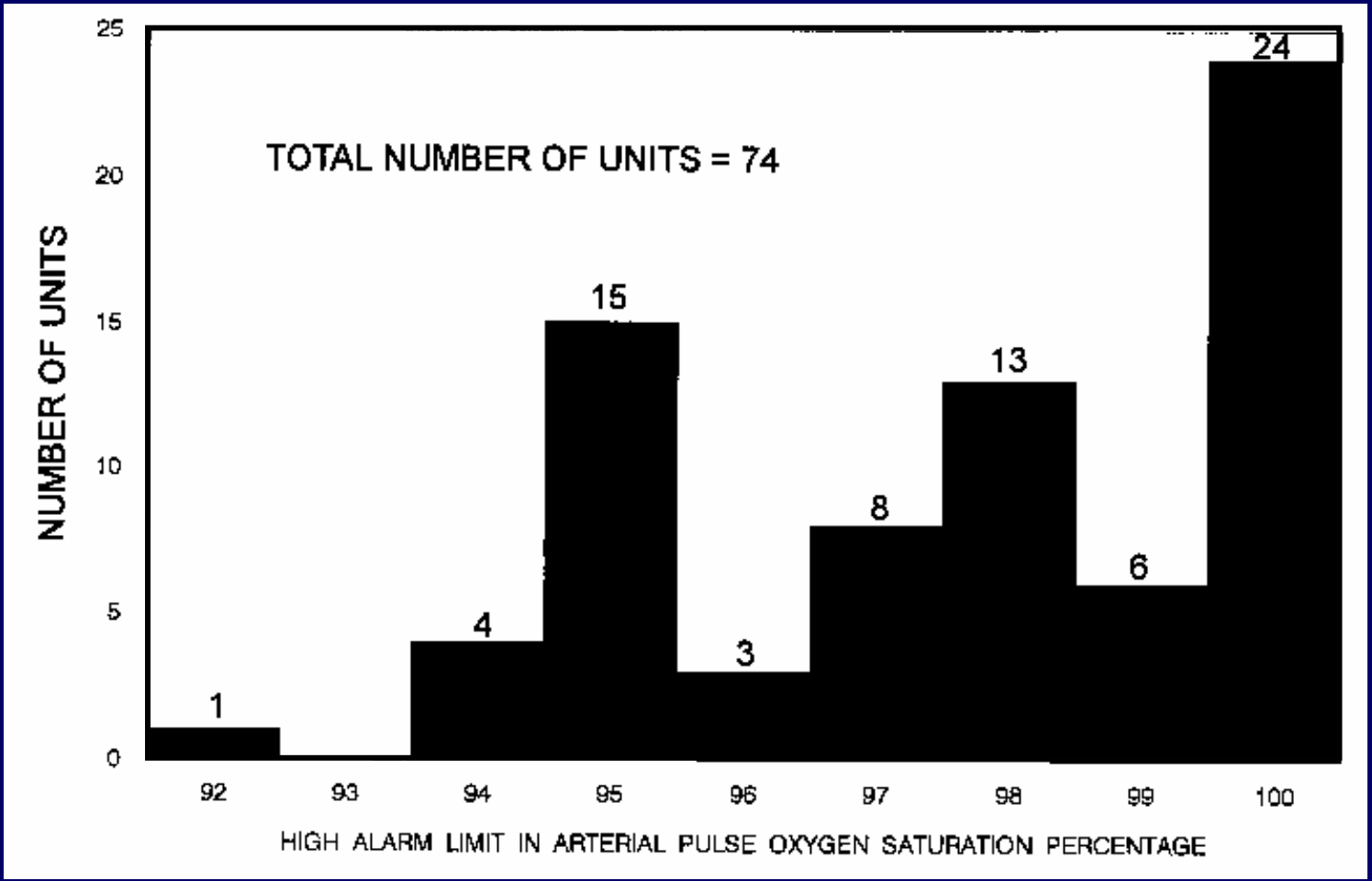

Ellsbury et al. J Pediatr 140:247, 2002

# Indications for Supplemental Oxygen




Ellsbury et al. J Pediatr 140:247, 2002

# Value at Which High Arterial Pulse Oxygen Saturation Alarm is Set




Vijayakumar et al. J Perinatol 17:341, 1997

# Randomized Trial of Oxygen Saturation Targets in Premature Infants - the SUPPORT Trial

The SUPPORT Study Group of the
Eunice Kennedy Shriver NICHD
Neonatal Research Network

UAB
National Heart Lung and Blood Institute
DEPARTMENT OF HEALTH & HUMAN SERVICES · USA
NATIONAL INSTITUTES OF HEALTH
Eunice Kennedy Shriver NICHD
National Institute of Child Health & Human Development

# Background

- Retinopathy of prematurity (ROP) continues to be an important cause of blindness in preterm infants
- Recent observational data suggest that oxygen saturations in the lower limits of common clinical practice (83 or 85%) may reduce ROP but this has not been tested in RCTs
- Furthermore, in RCTs of oxygen supplementation to reduce ROP conducted in the 1950s, restriction of oxygen supplementation resulted in an increased mortality in infants in the lower oxygen group

# Hypothesis

A lower $O_2$ saturation target range (85 to 89%)

compared to

a higher $O_2$ saturation target range (91 to 95%)

reduces

the incidence of the composite outcome of severe ROP or death

among

infants of 24 $^{0/7}$ to 27 $^{6/7}$ weeks gestational age

# Method – Patients

- Inborn infants of 24 $^{0/7}$ to 27$^{6/7}$ weeks gestation for whom a decision had been made to provide full resuscitation were eligible
- Parental consent was obtained antenatally
- Enrollment was conducted from February 2005 to February 2009
- Randomization was stratified by center and by gestational age:
  - 24 and 25 weeks
  - 26 and 27 weeks

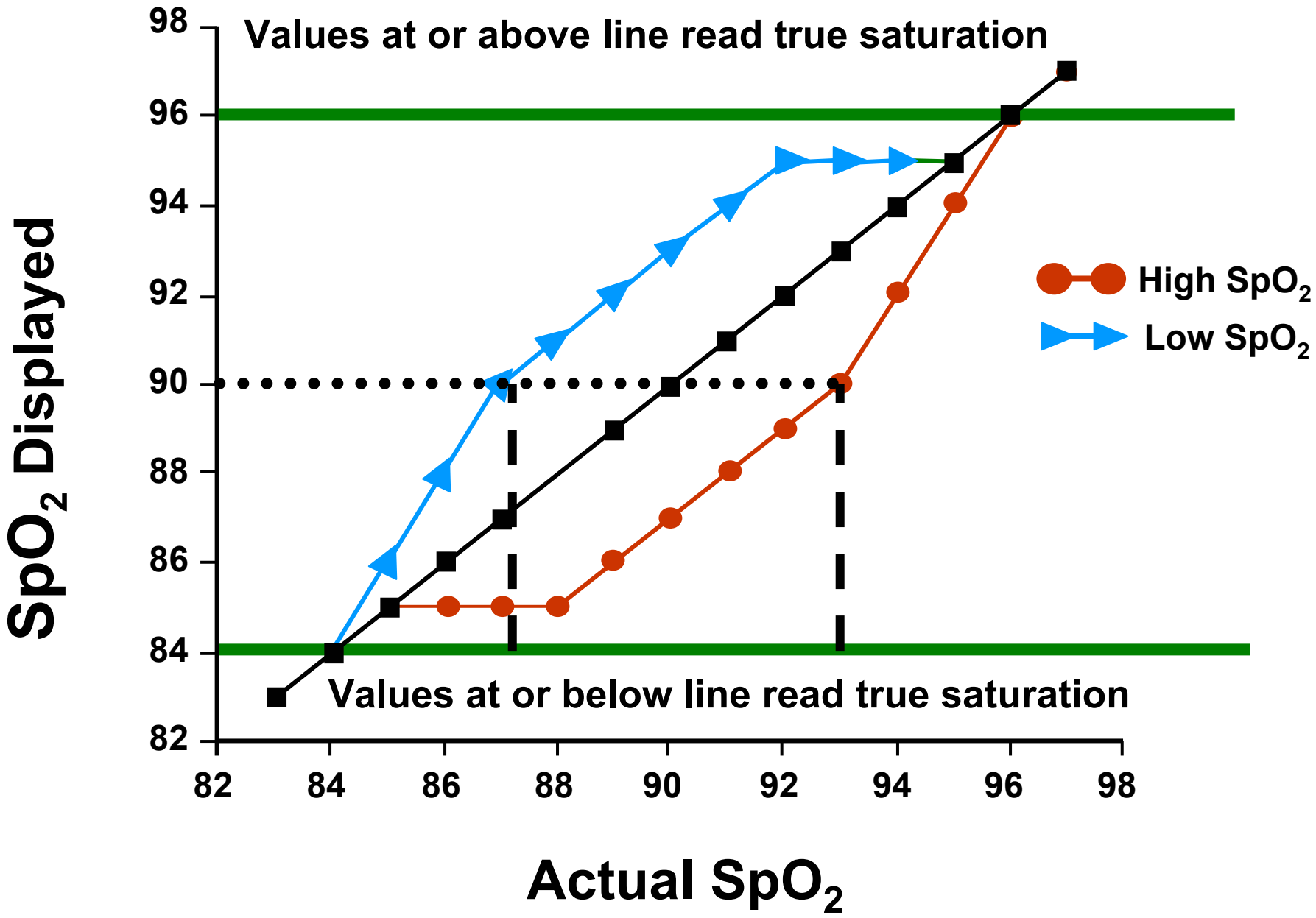
# Methods – Intervention (1)

- Infants were randomized to:
  - lower saturation targeting (85 to 89%) or;
  - higher saturation targeting (91 to 95%)

- Oxygen saturations were monitored with electronically-altered Masimo Radical Pulse Oximeters

| $SpO_2$ Group | Displayed | Actual Target | Alarm Values |
|---|---|---|---|
| Low $SpO_2$ | 88-92% | 85-89% | <84 and >96% |
| High $SpO_2$ | 88-92% | 91-95% | <84 and >96% |

# Actual vs Low and High Reading $SpO_2$



# Recent Trials of Oxygenation Targets

| | Experimental | Control |
|---|---|---|
| SUPPORT | 85-89% | 91-95% |
| STOP-ROP | 96-99% | 89-94% |
| BOOST | 95-98% | 91-94% |

# Methods – Intervention (2)

- Oxygen saturation targeting was initiated within the first two hours after birth and was continued until 36 weeks post-menstrual age or until the infant remained on room air and off the ventilator/CPAP for >72 hours, whichever occurred first
- Adjustments in supplemental oxygen to maintain the displayed saturation within the target range of 88 to 92% were performed by the clinical staff, not the researchers

# Methods – Factorial Design

Infants were also randomized to CPAP started at birth or intubation with surfactant

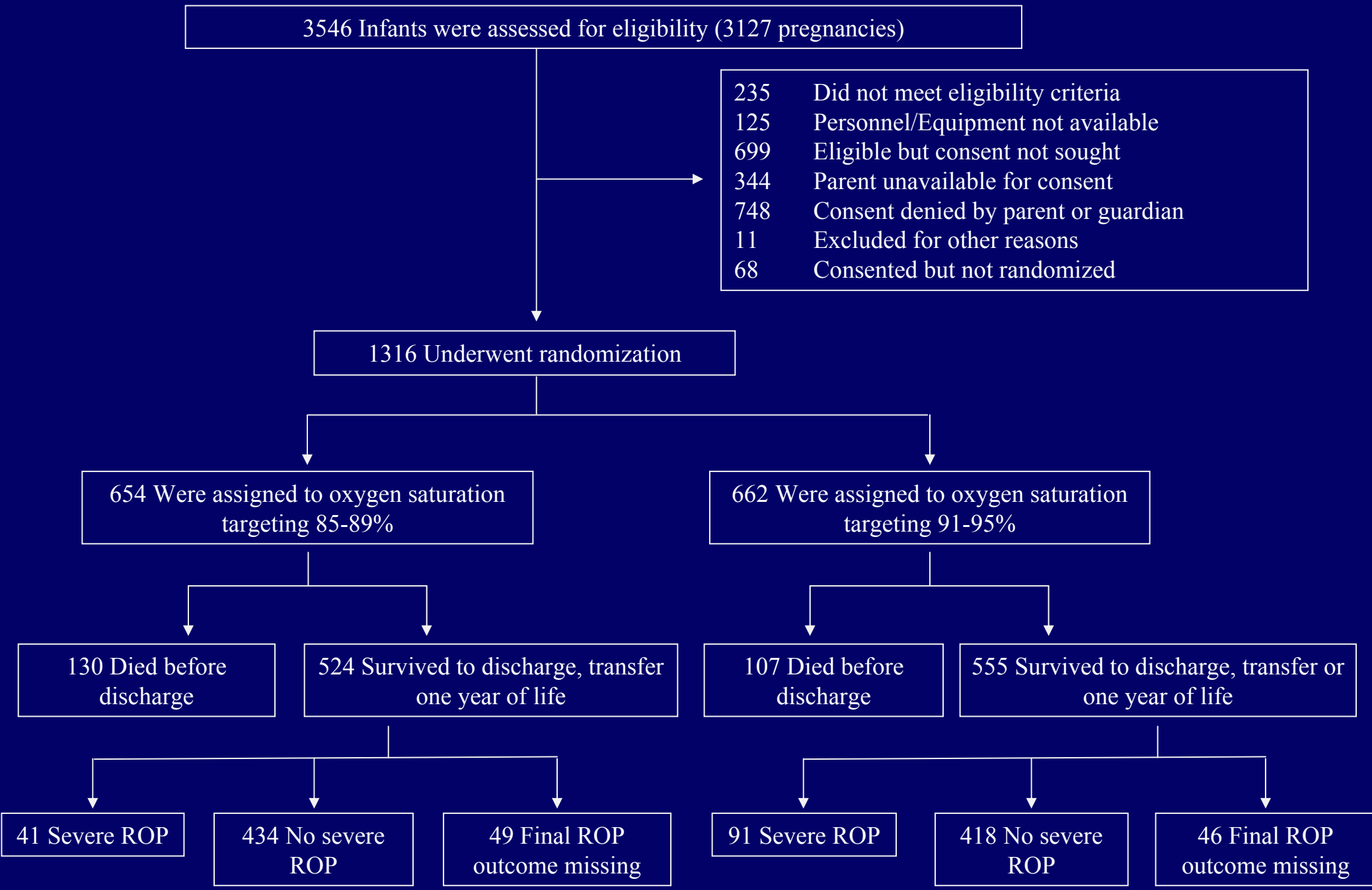
# Methods – ROP Assessments

- Trained ophthalmologists followed the infants until the study endpoint of severe retinopathy *or* fully vascularized retinas *or* immature vessels in zone III for two consecutive exams in each eye were documented

- Severe retinopathy was defined as:
  - threshold retinopathy if any of the following were present:
    - In zone I: stage 3 ROP; plus disease with any stage of ROP or
    - In zone II: plus disease with stage 2 or 3 ROP or
  - If ophthalmologic surgery and/or bevacizumab ROP treatment was used

# Methods – Sample Size Monitoring and Analysis

- Based on an absolute difference of 10% in the primary outcome, sample size was 1310
- An independent DSMC reviewed primary outcomes and adverse events at 25%, 50%, and 75% of outcome assessment
- The DSMC evaluated compliance with oxygen saturation targeting
- Adjustment was performed for pre-specified stratification (center and GA) and for familial clustering as multiple births were randomized to the same treatment arms

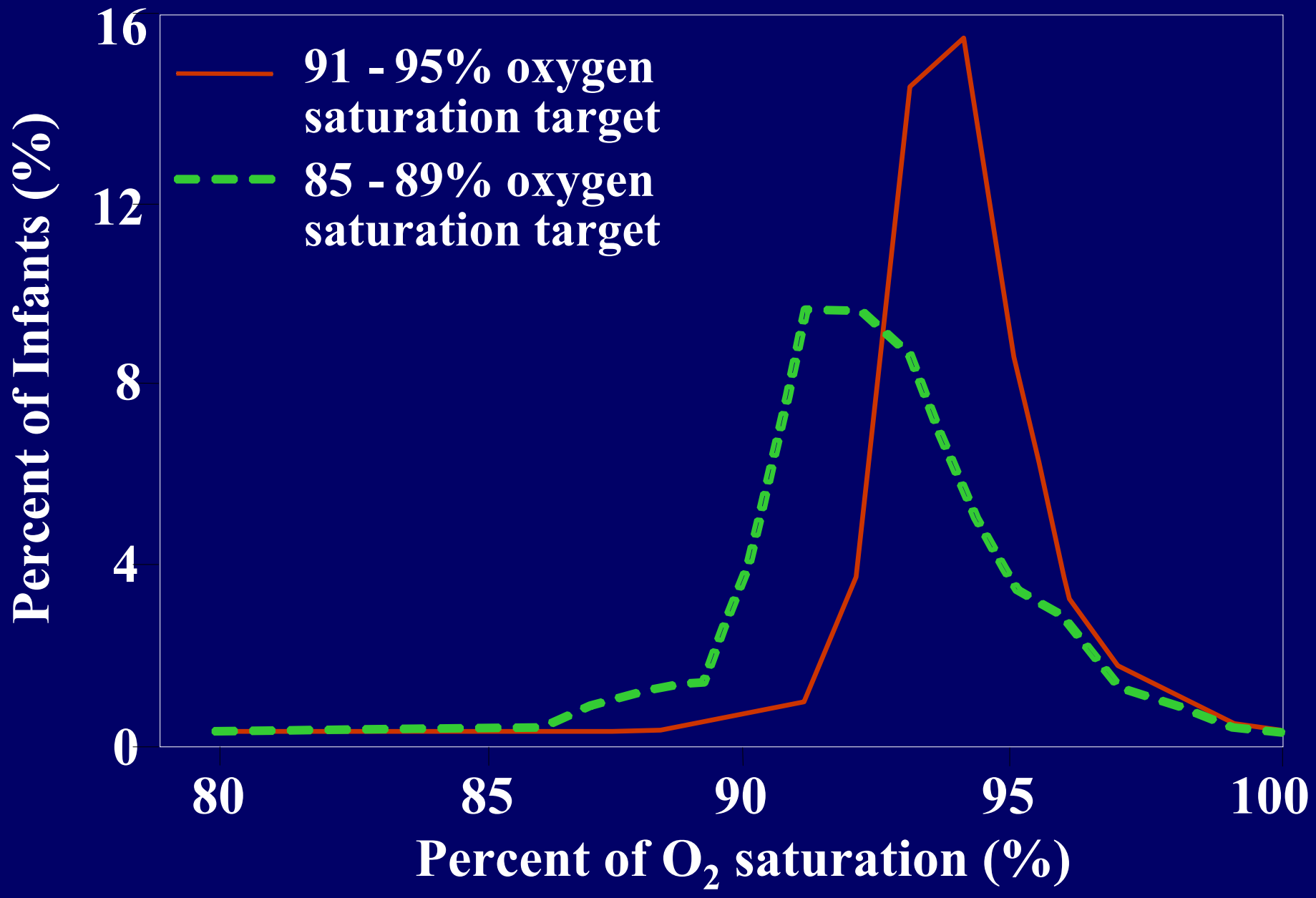

3546 Infants were assessed for eligibility (3127 pregnancies)
235 Did not meet eligibility criteria
125 Personnel/Equipment not available
699 Eligible but consent not sought
344 Parent unavailable for consent
748 Consent denied by parent or guardian
11 Excluded for other reasons
68 Consented but not randomized
1316 Underwent randomization
654 Were assigned to oxygen saturation targeting 85-89%
662 Were assigned to oxygen saturation targeting 91-95%
130 Died before discharge
524 Survived to discharge, transfer one year of life
107 Died before discharge
555 Survived to discharge, transfer or one year of life
41 Severe ROP
434 No severe ROP
49 Final ROP outcome missing
91 Severe ROP
418 No severe ROP
46 Final ROP outcome missing

# Results – Patient Population*

| | Lower Saturation Group (N = 654) | Higher Saturation Group (N = 662) |
|---|---|---|
| Birth weight | 836±193 grams | 825±193 grams |
| Gestational age | 26±1 weeks | 26±1 weeks |
| Race, White/Black/Hispanic | 37/39/20% | 42/35/19% |
| Antenatal corticosteroids | 96.8% | 95.6% |
| Multiple births | 24.6% | 26.6% |

*All p values >0.05

# Actual Median Oxygen Saturation (%)



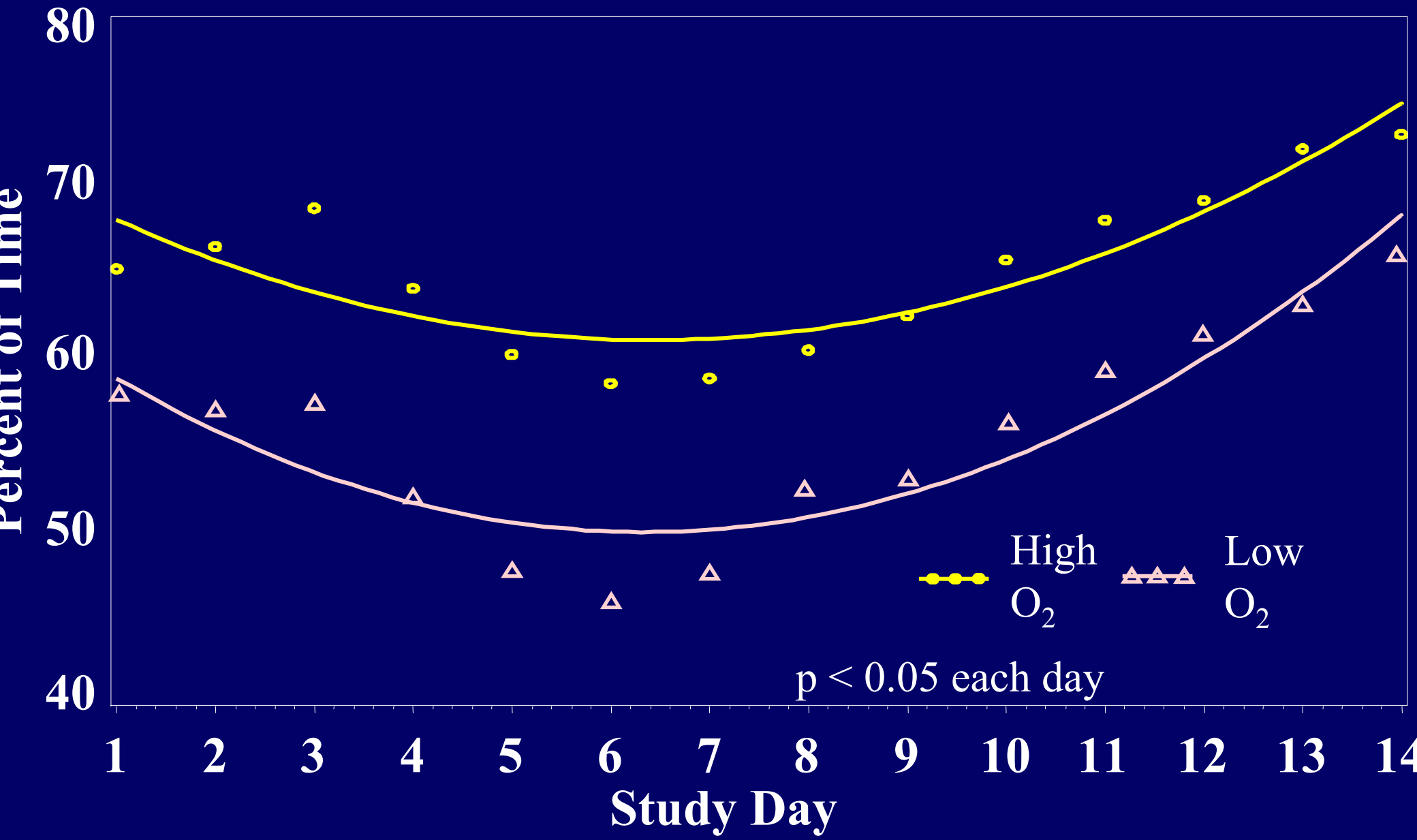
# Mean Percent of Time Spent in $SpO_2$ Ranges While on Supplemental Oxygen

| $SpO_2$ range | Lower Saturation Group Mean % of time in range (95% CI) | Higher Saturation Group Mean % of time in range (95% CI) | p value |
|---|---|---|---|
| >96% | 20.1 (18.8, 21.3) | 23.2 (22.0, 24.5) | 0.001 |
| <85% | 7.3 (6.6, 8.1) | 5.5 (4.8, 6.3) | 0.001 |
| <75% | 4.5 (3.8, 5.2) | 3.6 (2.9, 4.3) | 0.049 |
| <70% | 2.5 (1.9, 3.1) | 2.1 (1.5, 2.7) | 0.409 |

# Median Percent of Time Spent in $SpO_2$ Ranges While on Supplemental Oxygen

| $SpO_2$ range | Lower Saturation Group Median % of time in range | Higher Saturation Group Median % of time in range | p value |
|---|---|---|---|
| >96% | 16.0 | 19.6 | <0.001 |
| <85% | 5.9 | 3.9 | <0.001 |
| <75% | 3.3 | 2.1 | <0.001 |
| <70% | 1.5 | 0.9 | <0.001 |

# Percent of Time on Oxygen by Day and Group



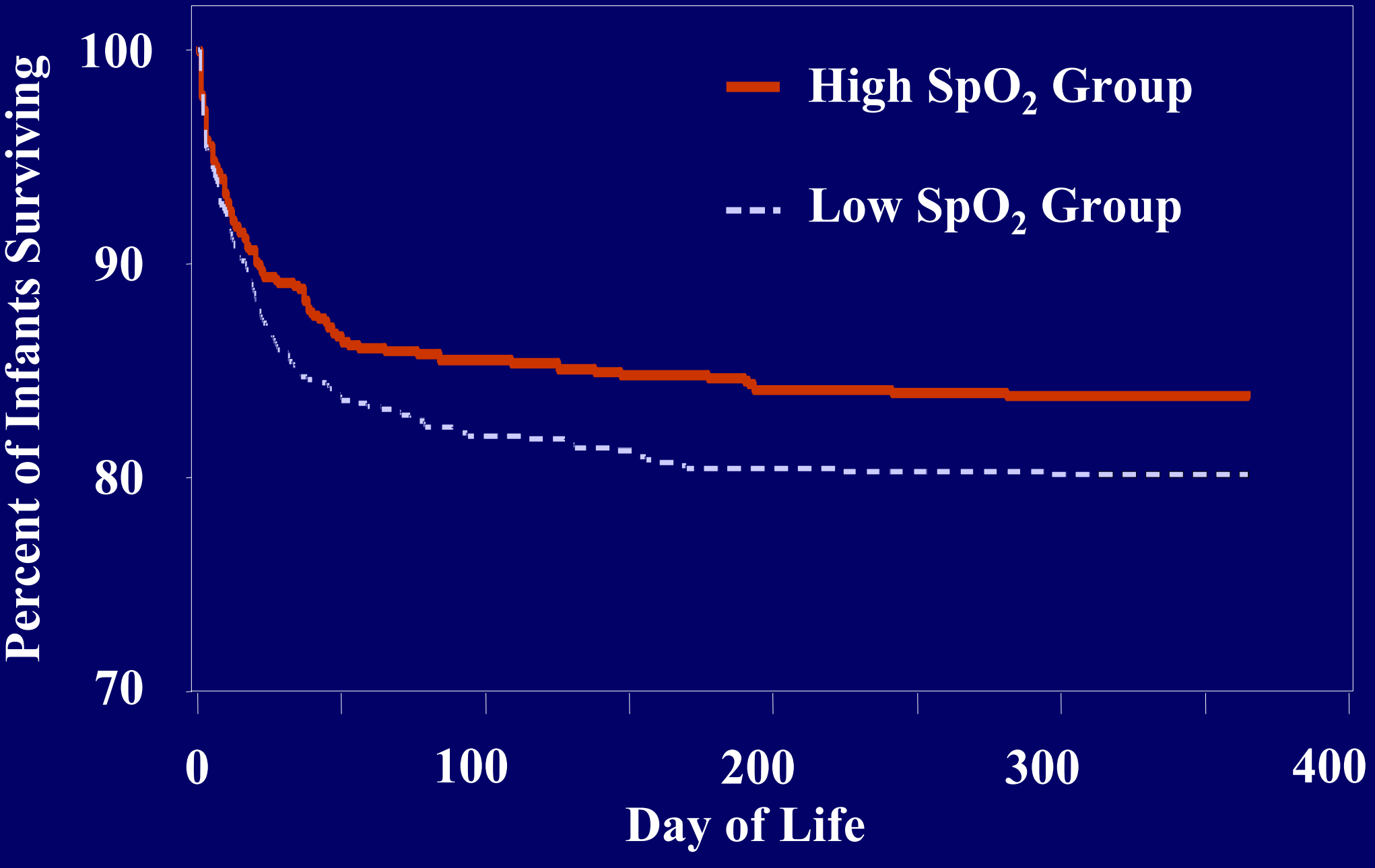
# Results – Primary Outcome

| | Lower Saturation Group N=654 | Higher Saturation Group N=662 | Adjusted Relative Risk (95% CI) | |
|---|---|---|---|---|
| Severe ROP/death | 28.3% | 32.1% | 0.90 (0.76, 1.06) | |
| Severe ROP | 8.6% | 17.9% | 0.52 (0.37, 0.73) | NNT=11 |
| Death | 19.9% | 16.2% | 1.27 (1.01, 1.60) | NNH=27 |

# Results – ROP Adjudication Analysis

| | Lower Saturation Group N=654 | Higher Saturation Group N=662 | Relative Risk for Low $SpO_2$ vs. High $SpO_2$ (95% CI) | |
|---|---|---|---|---|
| Severe ROP | 8.6% | 17.9% | 0.52 (0.37, 0.73) | NNT=11 |
| Severe ROP with adjudication (98.6%) | 8.0% | 16.6% | 0.52 (0.37, 0.73) | NNT=12 |
| Severe ROP with ROP if lost to F/U (100%) | 10.1% | 17.5% | 0.62 (0.45, 0.84) | NNT=14 |

# Survival Curve



# Results – BPD and Other Pulmonary Outcomes

| | Lower Saturation Group N=654 | Higher Saturation Group N=662 | Adjusted Relative Risk (95% CI) |
|---|---|---|---|
| BPD ($O_2$ use at 36 w) | 37.6% | 46.7% | 0.82 (0.72, 0.93) |
| BPD ($O_2$ use) or death, 36 w | 48.5% | 54.2% | 0.91 (0.83, 1.01) |
| BPD (phys), 36 w | 38.0% | 41.7% | 0.92 (0.81, 1.05) |
| BPD (phys) or death, 36 w | 48.8% | 50.0% | 0.99 (0.90, 1.10) |
| Pneumothorax | 7.2% | 6.5% | 1.12 (0.74, 1.68) |
| Any air leaks (14 days) | 7.8% | 6.3% | 1.23 (0.83, 1.83) |
| Postnatal steroids for BPD | 9.6% | 10.7% | 0.91 (0.67, 1.24) |

# Results – PDA

| | Lower Saturation Group N=654 | Higher Saturation Group N=662 | Adjusted Relative Risk (95% CI) |
|---|---|---|---|
| PDA | 47.9% | 50.0% | 0.96 (0.86, 1.07) |
| Medical $R_x$ for PDA | 34.5% | 36.1% | 0.95 (0.82, 1.09) |
| Surgical $R_x$ for PDA | 11.4% | 10.5% | 1.09 (0.80, 1.48) |

# Results – Other Major Outcomes

| | Lower Saturation Group N=654 | Higher Saturation Group N=662 | Adjusted Relative Risk (95% CI) |
|---|---|---|---|
| IVH, grade 3 or 4 | 13.2% | 12.7% | 1.06 (0.80, 1.40) |
| PVL | 3.8% | 4.7% | 0.83 (0.49, 1.42) |
| NEC, stage ≥ 2 | 11.9% | 10.8% | 1.11 (0.82, 1.51) |
| Late onset sepsis | 36.5% | 35.6% | 1.03 (0.89, 1.18) |

# Summary

- $O_2$ saturation targeting in the range of 85-89% did not affect severe ROP/death
- $O_2$ saturation targeting in the range of 85-89% resulted in a significant reduction in severe ROP (17.9 to 8.6%, NNT = 11)
- However, mortality was significantly increased in the 85-89% target group (19.9 versus 16.2%, NNH = 27)

# Conclusions

- Lower oxygen saturation targeting, as conducted in this trial, did not reduce severe ROP/death
- Lower oxygen saturation targeting, as conducted in this trial, decreased severe ROP
- The potential to reduce the risk of severe ROP must be carefully weighed against the possibility of increased risk of death
- Follow up of these infants and data from the similarly designed ongoing trials will be important

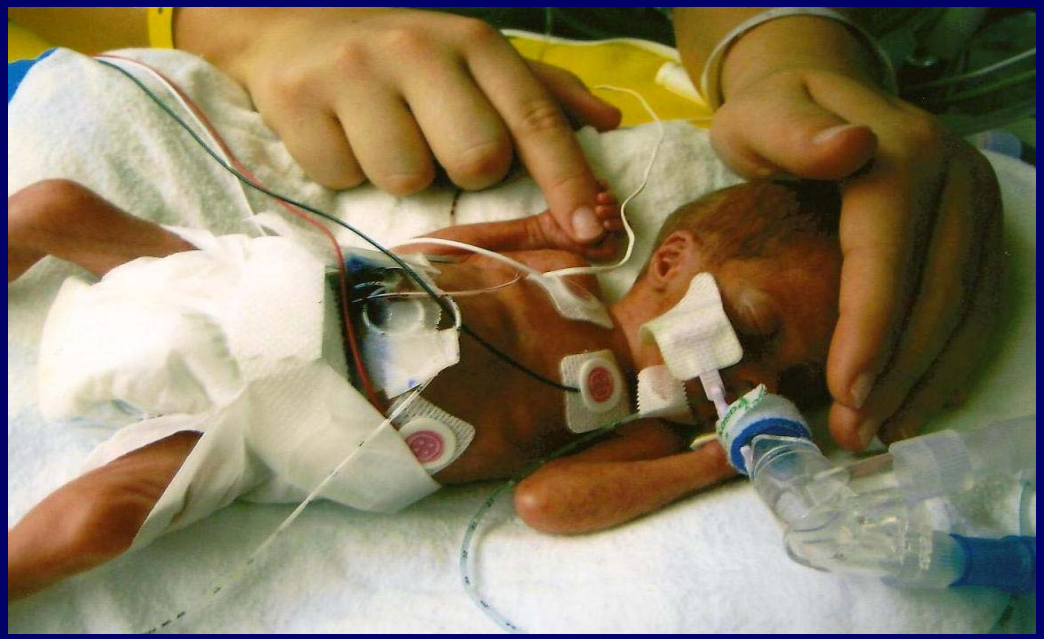
# Take Home Message

- Current $SaO_2$ targets and high alarm limits are too high
- Most current data suggest that oxygen saturation in the low 90s is sufficient to preterm infants
- Additional oxygen supplementation increases ROP and may worsen pulmonary outcomes
- Lower oxygen supplementation may increase the risk for mortality

# Consider Changes in Practice

- Use high saturation alarm at 95% if the baby is on oxygen supplementation and at 99% if the baby is on room air, but at risk for getting oxygen.
- Do physiologic assessment of oxygen “needs” as daily practice.

# Thanks to the many infants, parents, and NICU staff



# Thanks to the members of the Neonatal Research Network

# NICHD Neonatal Research Network Centers (2005-2009)

- Brown University
- Case Western Reserve University
- Duke University
- Emory University
- Indiana University
- RTI International
- Stanford University
- Tufts Medical Center
- University of Alabama – Birmingham
- University of California – San Diego
- University of Cincinnati
- University of Iowa
- University of Miami
- University of New Mexico
- University of Rochester
- University of Texas, Southwestern – Dallas
- University of Texas – Houston
- University of Utah
- Wake Forest University
- Wayne State University
- Yale University

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