Optimal Oxygenation of the Newborn

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CITY
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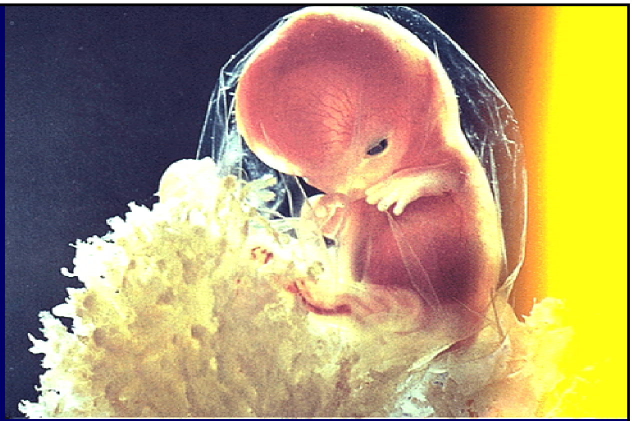
Oxygenation of the Newborn
resolved and unresolved questions



- FiO_2 for resuscitation of term infants
- FiO_2 during chest compressions
- Effect of hypothermia after normoxic resuscitation
- FiO_2 for resuscitation of preterm infants < 33 weeks
- Oxygenation of preterm infants (ELBWI) beyond the delivery room

OXYGEN

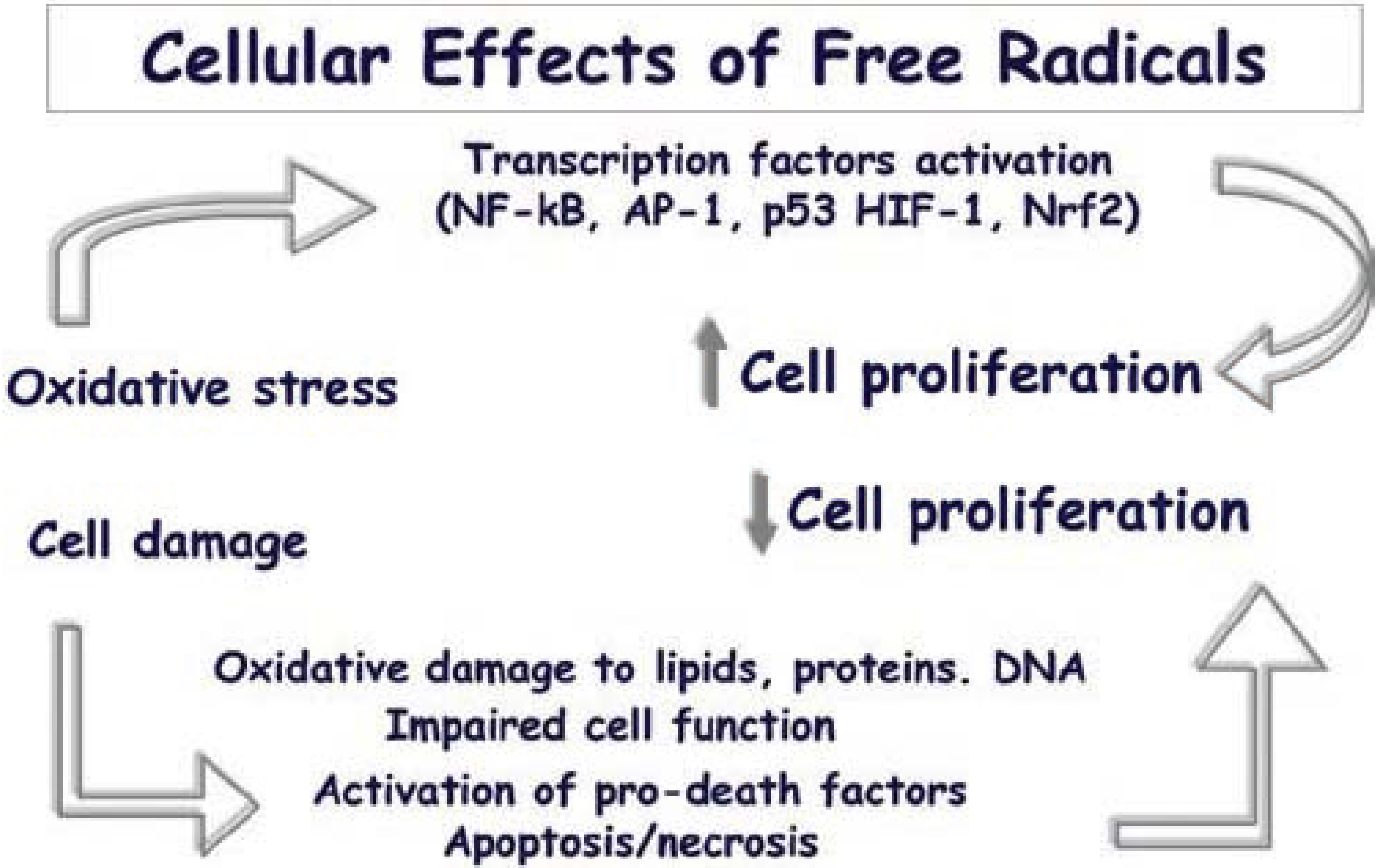
ESSENTIAL FOR LIFE VS **POTENTIALLY TOXIC AND MUTAGENIC**

- **It is completely available**
- **It can easily diffuse accross biological membrane**
- **It can bind heme in protein (Hemoglobin and Cytocrome)**

Over production of Free Radicals

Oxidative stress

Solberg R et al The Journal of Maternal-Fetal and Neonatal Medicine, 2012; 25(S(1)): 41–44



Solberg R, Perrone S, Saugstad OD, Buonocore G JMFNM 2012; 25(S(1)):41–44

Oxygenation of term and preterm babies in the delivery room

Ventilation term/near term babies after birth

Treatment Recommendation

In term infants receiving resuscitation at birth with positive pressure ventilation, it is best to begin with air rather than 100% oxygen.

ILCOR 2010

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association
Learn and Live

Newborn resuscitation – term babies

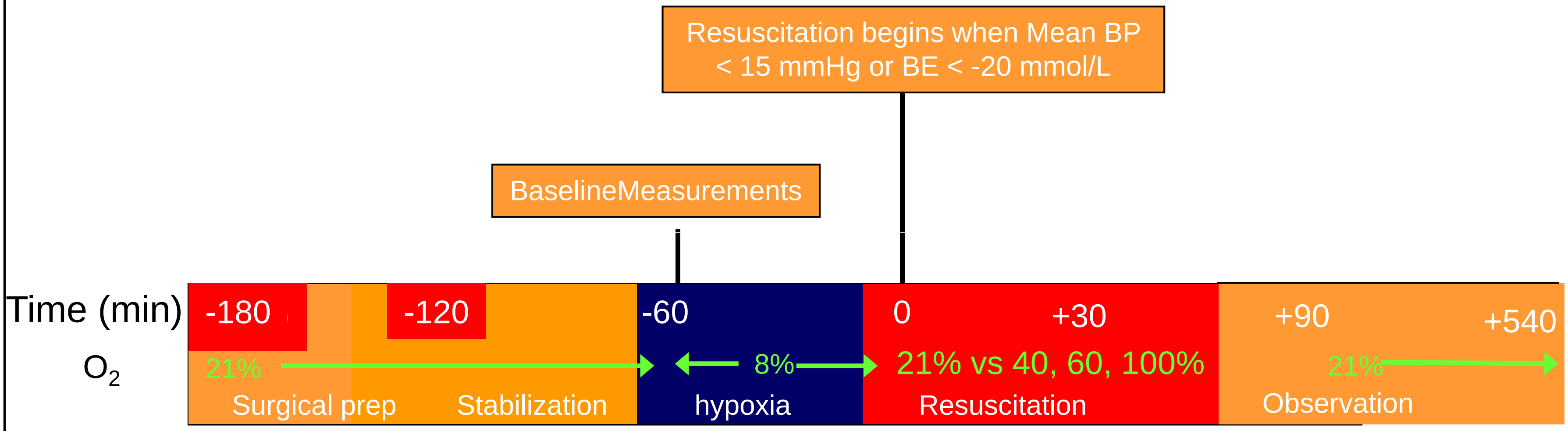
Air versus Oxygen

Why is it best to start with air?

Experimental Protocol

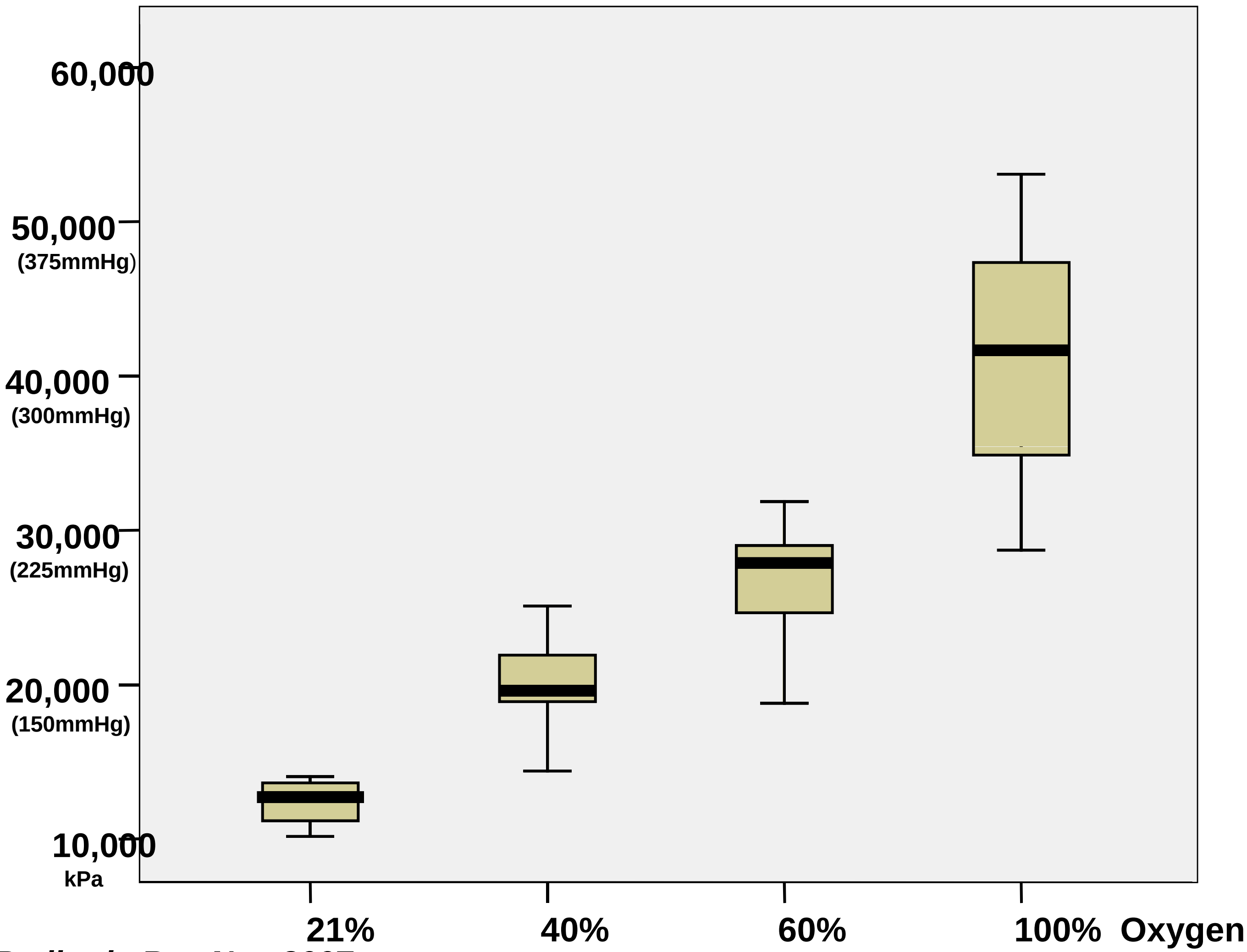
1-2 d old piglets: Hypoxia-Reoxygenation

Jannicke Andresen
Rønnaug Solberg



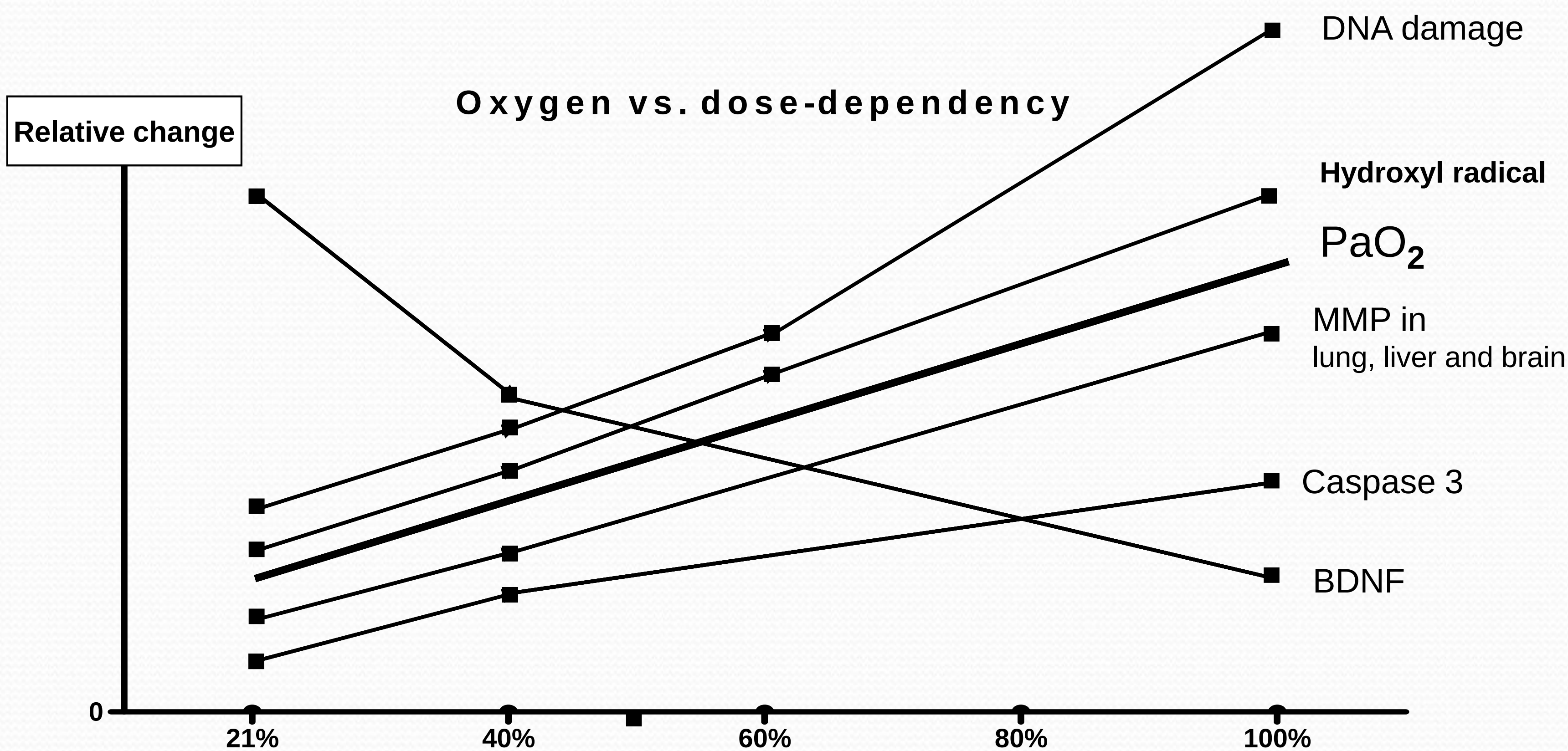
The newborn pig brain resembles the human brain before 3 days of age

PaO_2 after Hypoxia and 15 Minutes Resuscitation with Different FiO_2



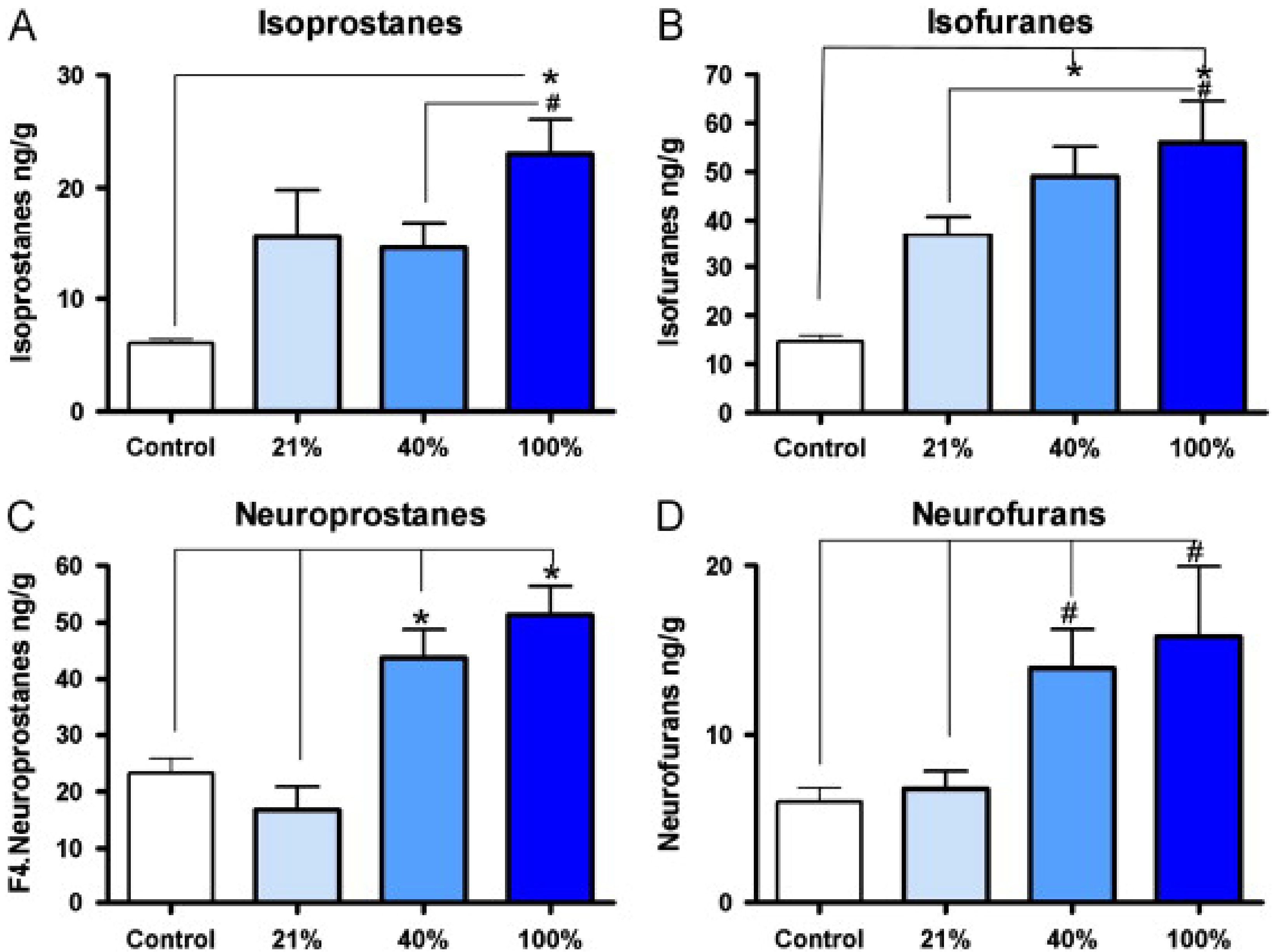
Solberg et al Pediatric Res Nov 2007

Summary of Findings Regarding FiO_2



Saugstad, Sejersted, Solberg, Wollen Bjørås, Neonatology 2012 101;315

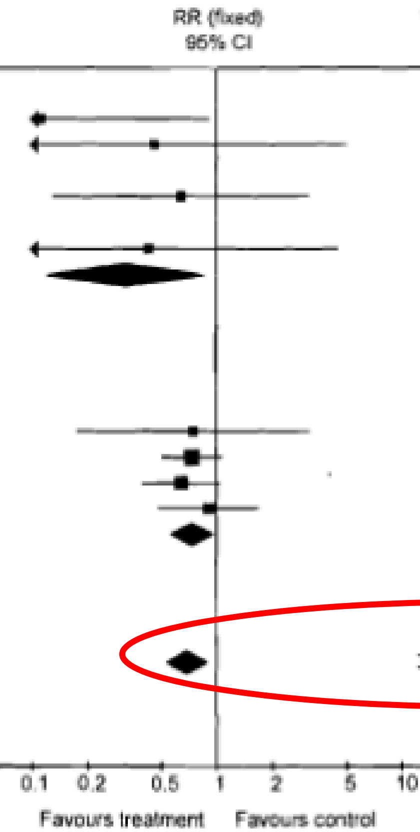
Resuscitation of newborn pigs - effect on the brain of 21- 40 or 100% O2



Solberg, Longini, Proietti, Vezzosi, Saugstad, Buonocore Free Radical Biol Med 2012;53:1061-67

Neonatal Mortality after 21% or 100% O_2 Resuscitation
10 studies including 2134 infants

Study or sub-category	Treatment n/N	Control n/N	Weight %	RR (fixed) 95% CI
01 Randomized Trials				
VENTO 2001	1/300	7/238	5.90	0.11 [0.01, 0.91]
VENTO 2001A	1/55	2/51	1.57	0.46 [0.04, 4.96]
TOMA 2005	0/27	0/27		Not estimable
VENTO 2005	2/17	4/22	2.64	0.65 [0.13, 3.13]
TOMA 2006	0/20	0/24		Not estimable
TOMA 2007	1/30	2/26	1.62	0.43 [0.04, 4.51]
Subtotal (95% CI)	449	388	11.73	0.32 [0.12, 0.85]
Total events: 5 (Treatment), 15 (Control)				
Test for heterogeneity: Chi² = 1.86, df = 3 (P = 0.60), I² = 0%				
Test for overall effect: Z = 2.30 (P = 0.02)				
02 Quasi-randomized Trials				
RAMJI 1993	3/42	4/42	3.02	0.75 [0.18, 3.15]
SAUGSTAD 1998	40/280	60/311	42.98	0.74 [0.51, 1.07]
RAMJI 2003	24/204	39/214	28.78	0.65 [0.40, 1.03]
BAJAJ 2005	17/107	17/97	13.48	0.91 [0.49, 1.67]
Subtotal (95% CI)	633	664	88.27	0.74 [0.57, 0.95]
Total events: 84 (Treatment), 120 (Control)				
Test for heterogeneity: Chi² = 0.74, df = 3 (P = 0.86), I² = 0%				
Test for overall effect: Z = 2.35 (P = 0.02)				
Total (95% CI)	1082	1052	100.00	0.69 [0.54, 0.88]
Total events: 89 (Treatment), 135 (Control)				
Test for heterogeneity: Chi² = 4.15, df = 7 (P = 0.76), I² = 0%				
Test for overall effect: Z = 2.98 (P = 0.003)				



814 000 asphyxic deaths:
252,000 (95% CI: 146,000 - 374,000) saved lives

Saugstad, Ramji, Soll, Vento. ***Neonatology 2008***

When is oxygen supplementation needed?

Preterm infants: IlCOR recommends blended oxygen

Chest compressions: ILCOR has no recommendations

Newborn piglets with cardiac arrest
Chest compressions and ventilated with air or 100% oxygen:

Group	time to ROSC (median and interquartile range) s
21% O2	150 s (115–180)
100% O2	135 s (113–168)

p = 0.80

ROSC: return of spontaneous circulation, ie heart rate > 100 bpm

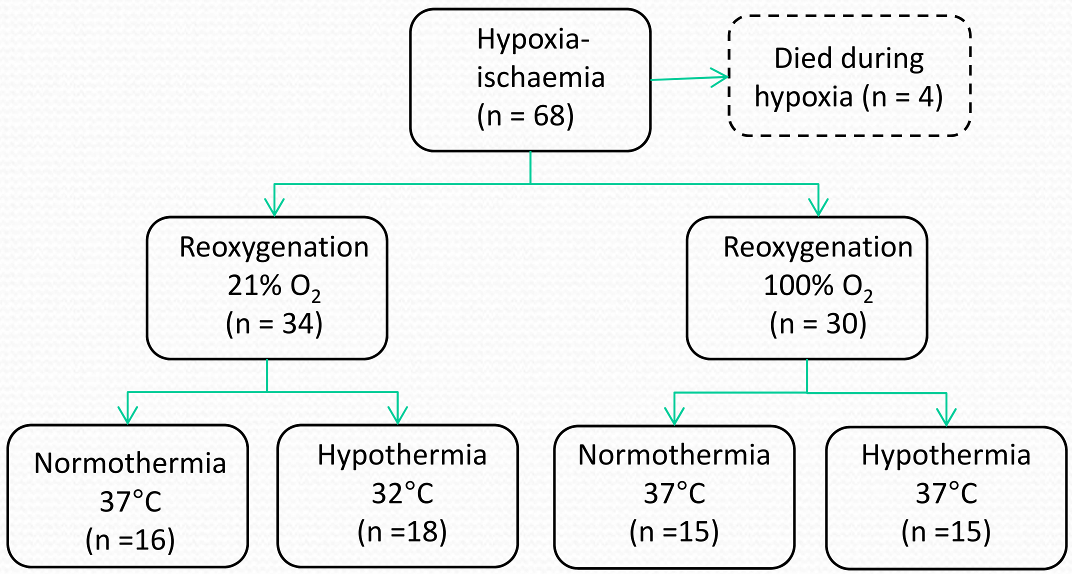
Solevaag et al Neonatology. 2010;98:64-72

Is the effect of hypothermia related to initial oxygenation?

- The babies enrolled in the randomized trials on hypothermia were resuscitated with 100% oxygen
- Hyperoxia induces inflammation in the brain
- Is hypothermia more or less protective if initial resuscitation is carried out in normoxia?

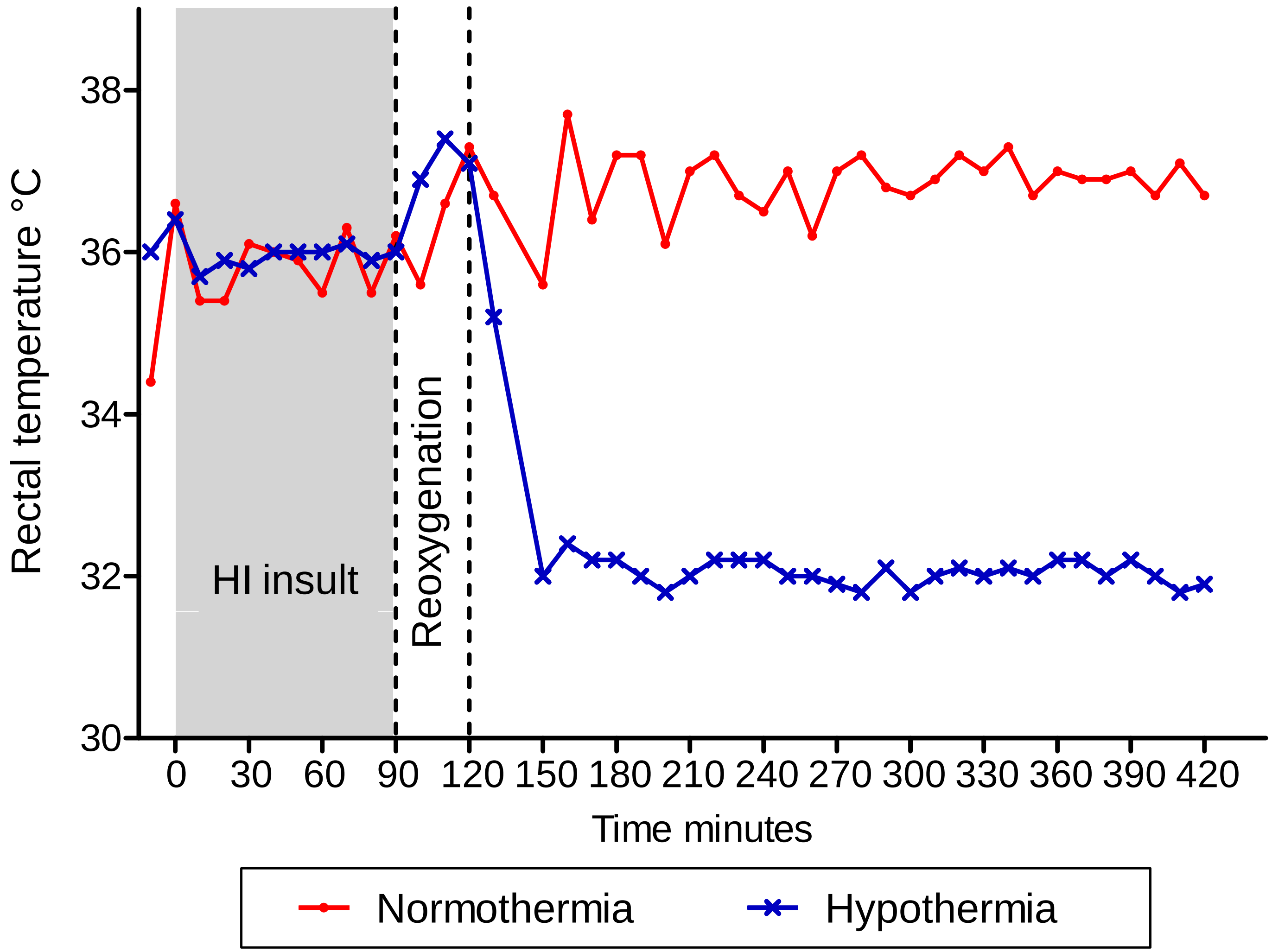
Experimental design

7-day-old Wistar rats of both sex
Hypoxia/ischemia 90 min – Reoxygenation 30 min – Hypothermia/Normothermia 5 h
One-week survival
Reflex performance testing - Histopathology



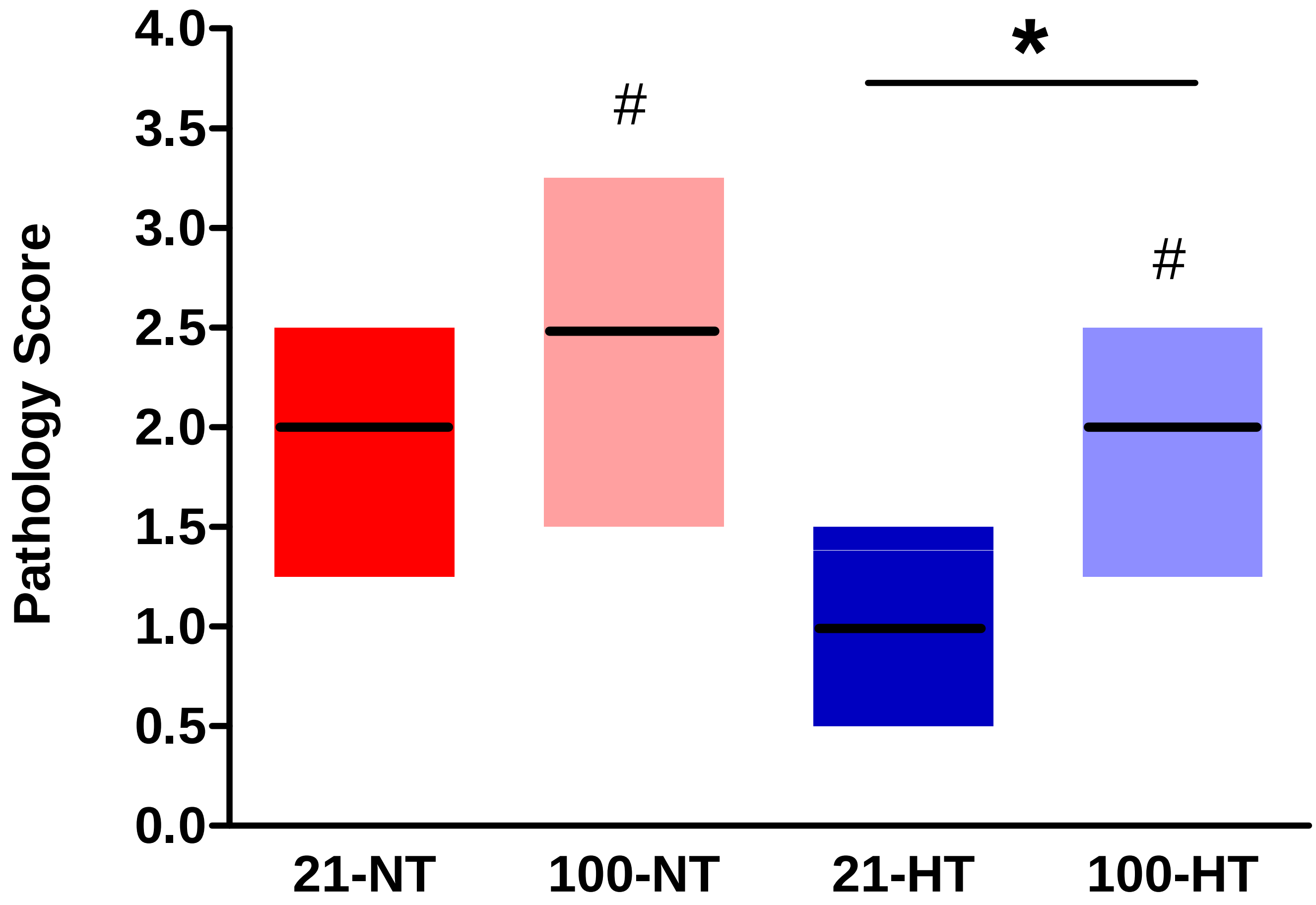
Dalen, Liu, Elstad, Løberg, Saugstad, Rootwelt, Thoresen, Pediatric Res, 2012

Results



Dalen, Liu, Elstad, Løberg, Saugstad, Rootwelt, Thoresen, Pediatric Res 2012

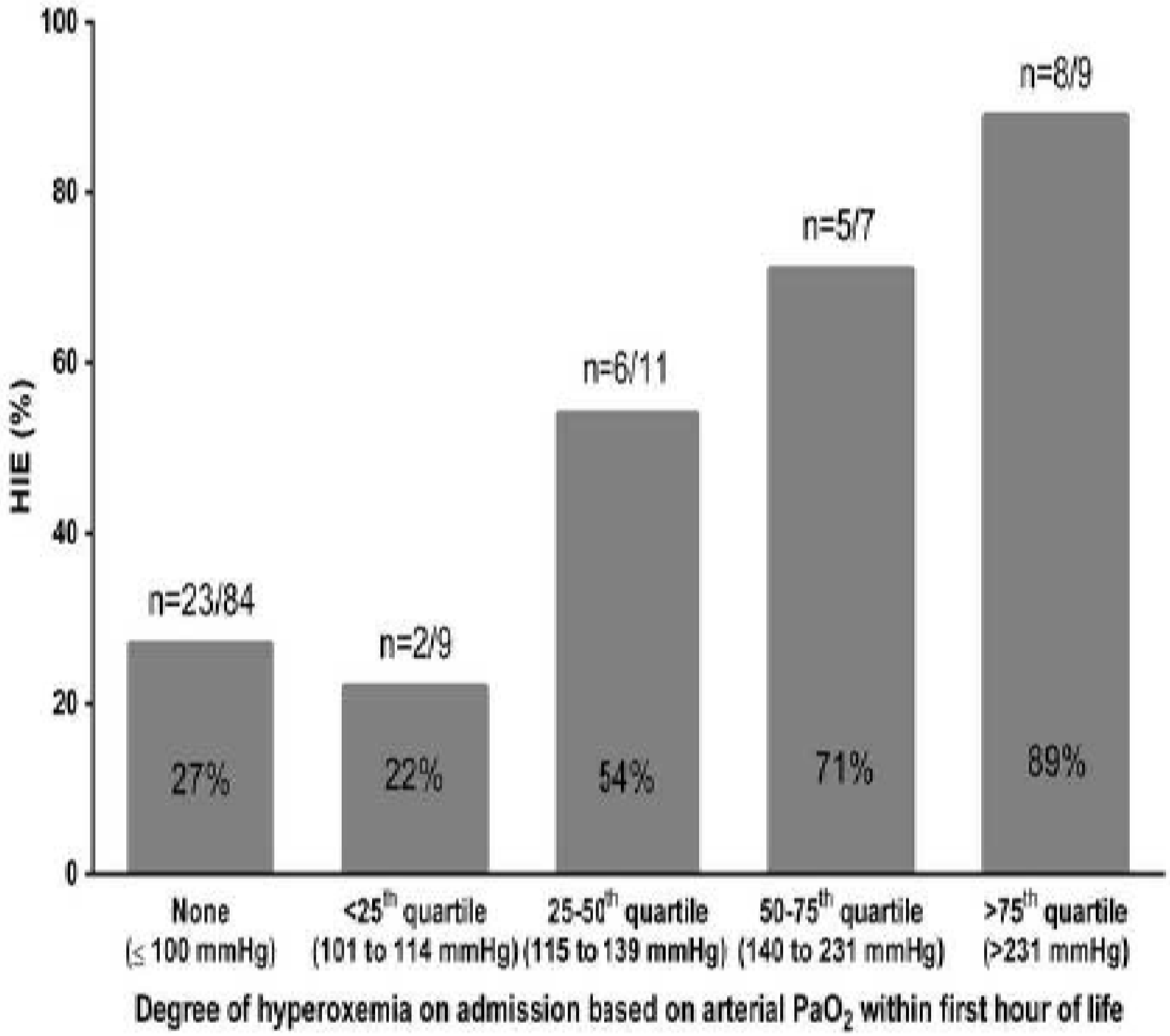
Pathology Scores in Hippocampus



*HT (p=0.018)
O_2 (p=0.033)

Dalen, Liu, Elstad, Løberg, Saugstad, Rootwelt, Thoresen, Pediatric Res 2012

Relationship between degree of hyperoxemia on admission and incidence of moderate/severe HIE.



Moderate/Severe HIE is directly associated with the degree of hyperoxemia ($p<0.001$).

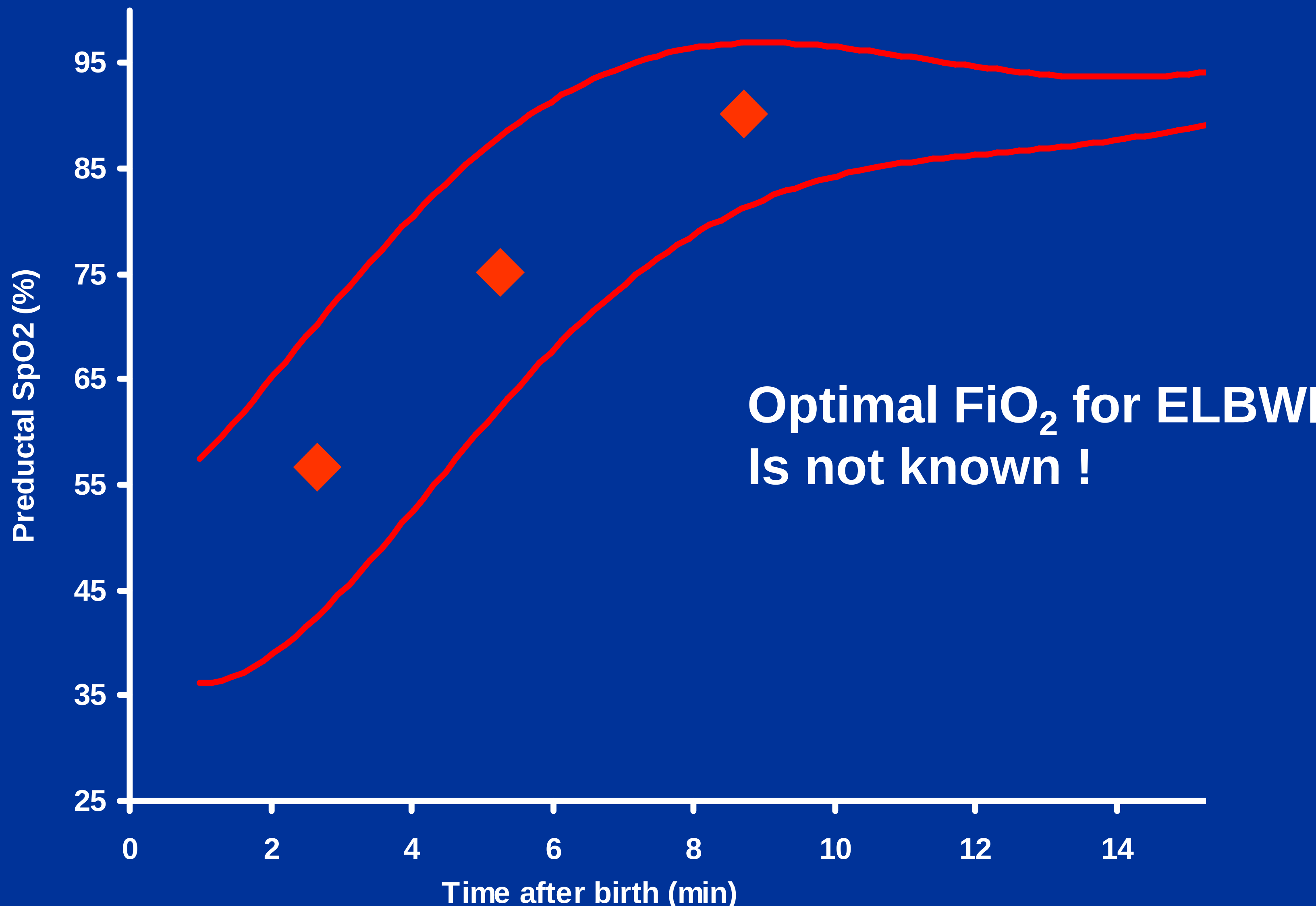
Kapadia VS et al,
J Pediatrics, 2013

How to resuscitate/stabilise premature infants?

High or low initial FiO_2 ?

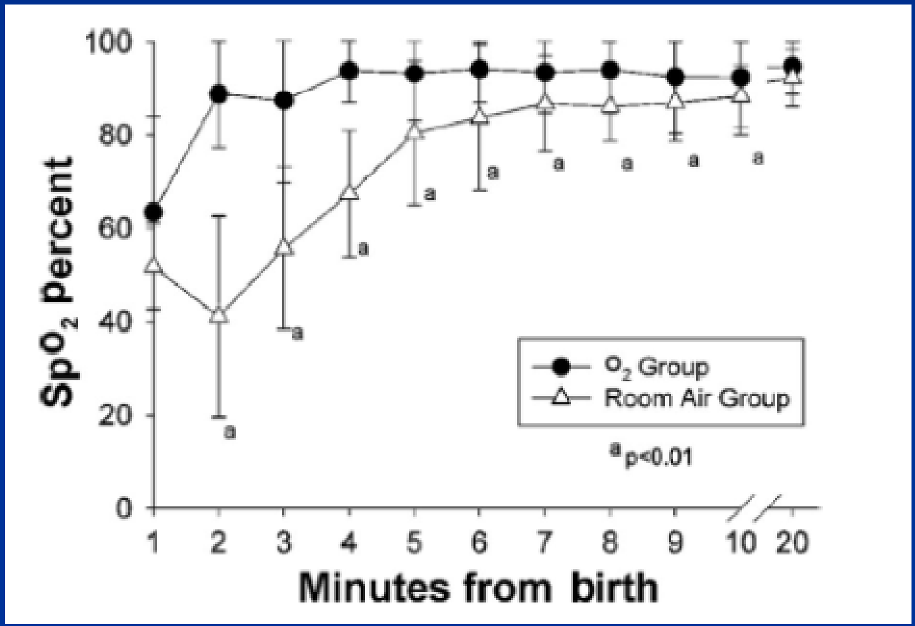
SpO_2 polynomial adjustment curve in "control" ELBWIs ≤ 28 w GA

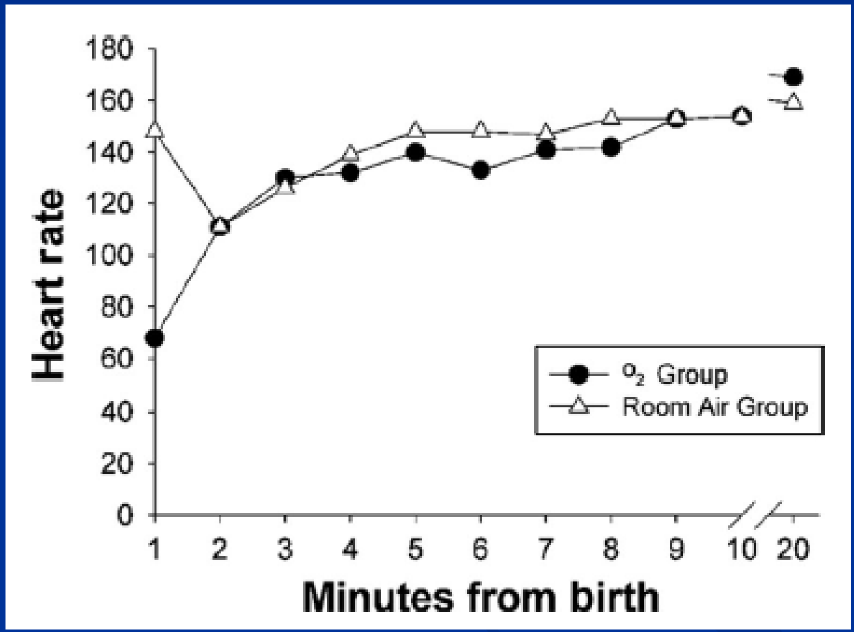
(n=29, ± SD)



Vento M, Saugstad OD SFNM 2010

Resuscitation of preterm neonates <32 w using 21% or 100% oxygen.



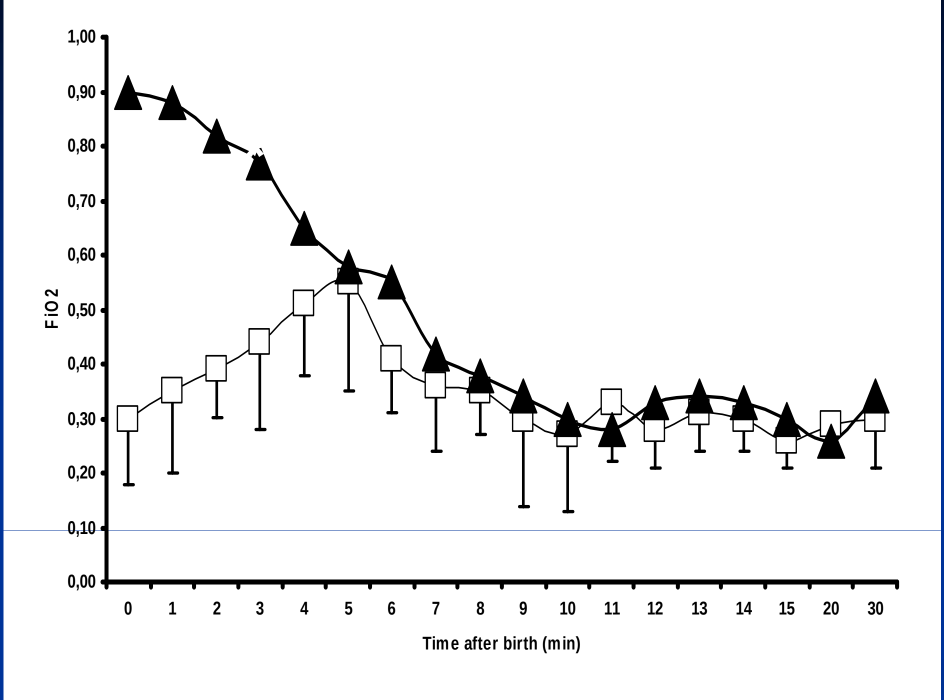


Wang CL et al Pediatrics 2009

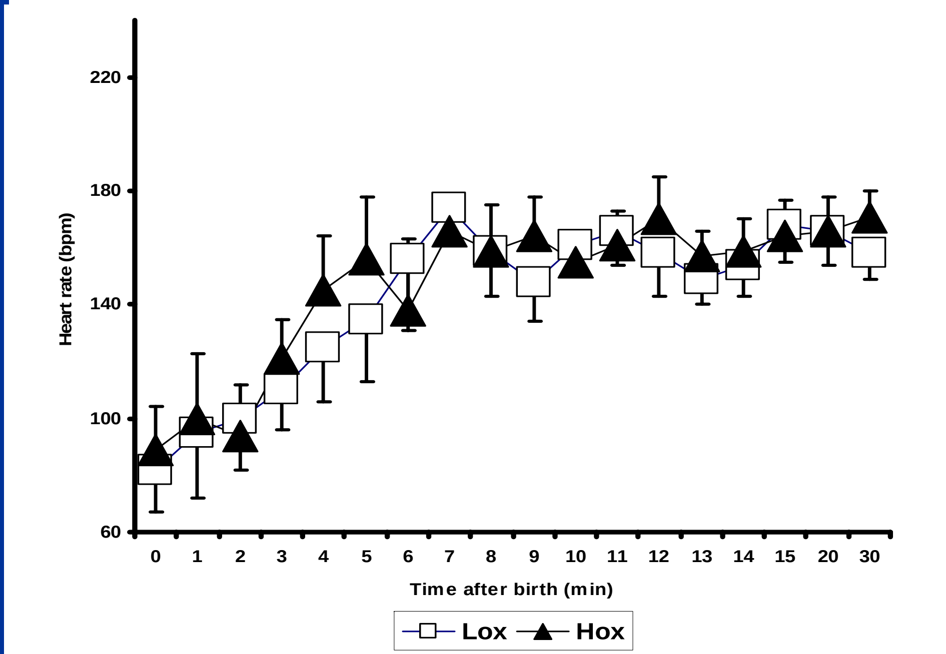
Newborns< 29 weeks randomized to initial 90% or 30% oxygen

Initial FIO_2

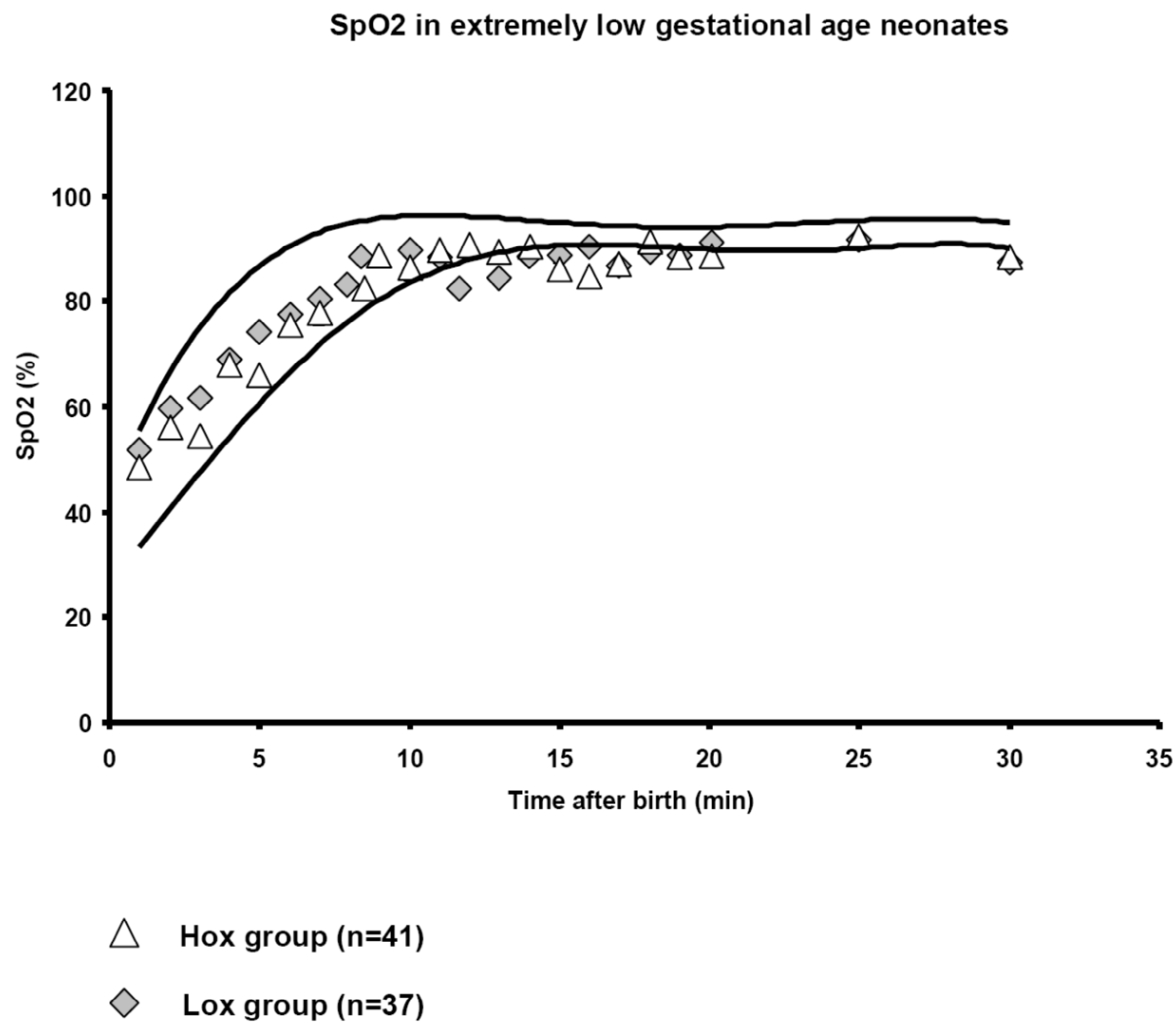
High: 0.9
Low: 0.3



HEART RATE



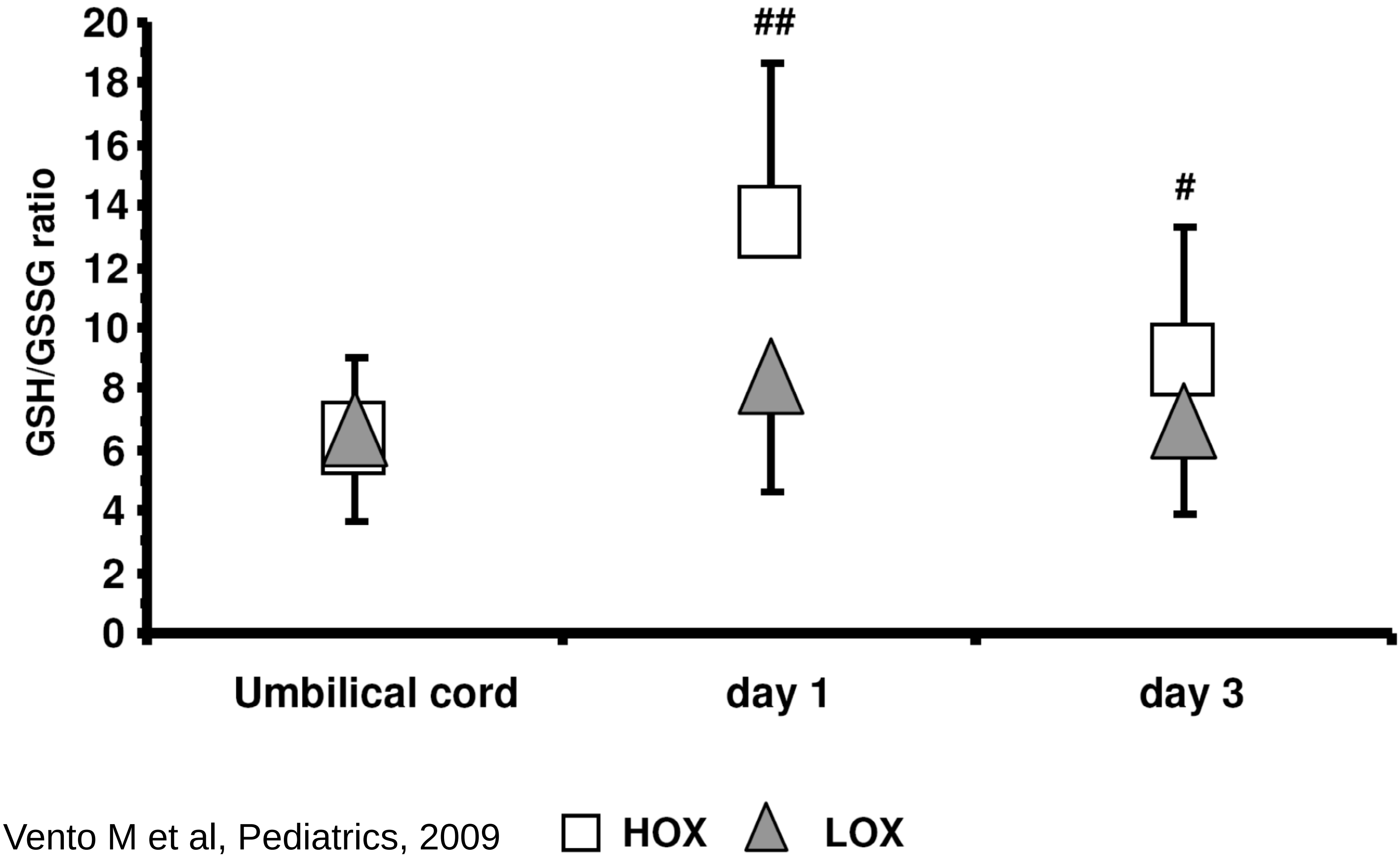
Esriq, Vento et al, 2009



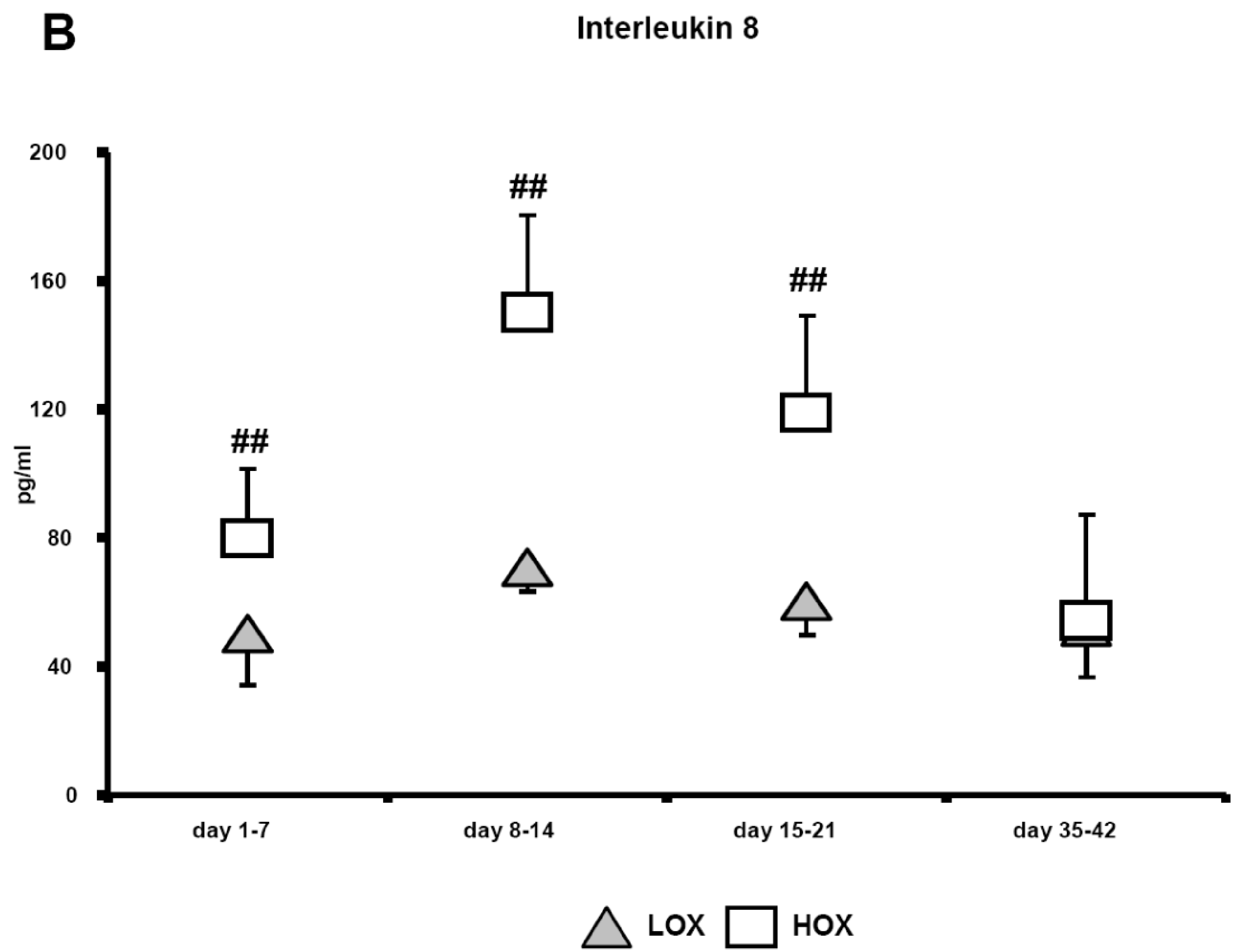
Vento M et al, Pediatrics, 2009

Effect of high (FiO_2 0.9) or low (FiO_2 0.3)
24-28 weeks GA

Oxidized to reduced glutathione ratio



Vento M et al, Pediatrics, 2009

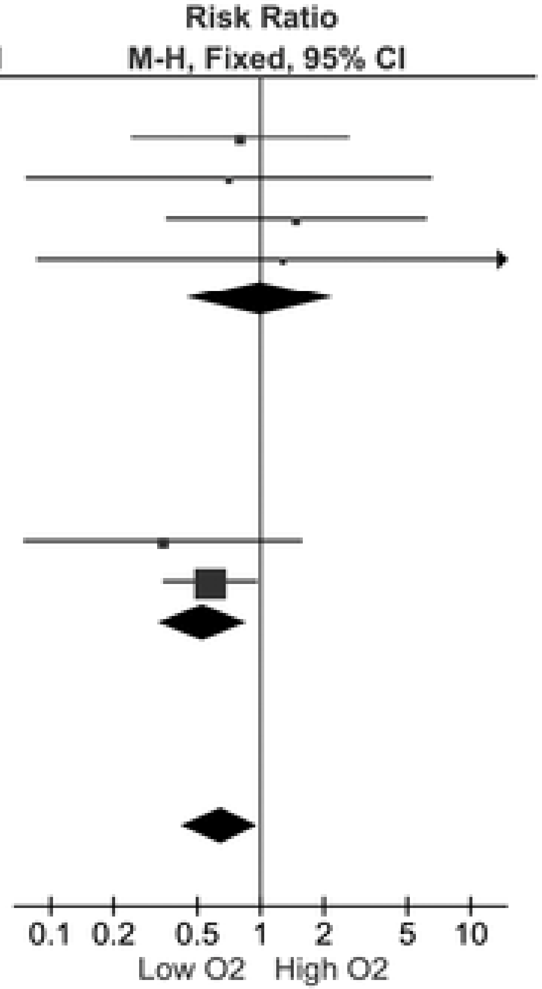


Vento M et al,Pediatrics, 2009

Lower versus Higher Oxygen Concentration for Delivery Room Stabilisation of Preterm Neonates: Systematic Review.

Meta-analysis of effect on mortality prior to hospital discharge.

Study or Subgroup	Low O2 Events	Low O2 Total	High O2 Events	High O2 Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Trials with allocation concealed						
Harling 2005	4	26	5	26	11.4%	0.80 [0.24, 2.65]
Rabi 2011	1	34	3	72	4.4%	0.71 [0.08, 6.54]
Vento 2009	4	37	3	41	6.5%	1.48 [0.35, 6.17]
Wang 2008	1	18	1	23	2.0%	1.28 [0.09, 19.06]
Subtotal (95% CI)		**115**		**162**	**24.2%**	**1.00 [0.45, 2.24]**
Total events	10		12			
Heterogeneity: $Chi^2 = 0.55$, df = 3 (P = 0.91); $I^2 = 0\%$						
Test for overall effect: Z = 0.01 (P = 0.99)						
1.1.2 Trials without allocation concealment						
Lundstrom 1995	2	34	6	35	13.5%	0.34 [0.07, 1.58]
Saugstad 1998	16	70	27	68	62.3%	0.58 [0.34, 0.97]
Subtotal (95% CI)		**104**		**103**	**75.8%**	**0.53 [0.33, 0.88]**
Total events	18		33			
Heterogeneity: $Chi^2 = 0.40$, df = 1 (P = 0.53); $I^2 = 0\%$						
Test for overall effect: Z = 2.48 (P = 0.01)						
Total (95% CI)		**219**		**265**	**100.0%**	**0.65 [0.43, 0.98]**
Total events	28		45			
Heterogeneity: $Chi^2 = 2.51$, df = 5 (P = 0.78); $I^2 = 0\%$						
Test for overall effect: Z = 2.04 (P = 0.04)						
Test for subgroup differences: $Chi^2 = 1.72$, df = 1 (P = 0.19), $I^2 = 41.7\%$						



Brown JVE, Moe-Byrne T, Harden M, McGuire W (2012) PLoS ONE 7(12): e52033. doi:10.1371/journal.pone.0052033

Resuscitation of premature infants < 33 weeks GA with low (0.21-0.30) or high (0.60-1.0) oxygen

Lundstrøm KE et al Oxygen at birth and prolonged cerebral vasoconstriction in preterm infants. Arch Dis Childhood 1995;73:F81-F86

Escrig R et al Achievement of targeted saturation values in extremely low gestational age neonates resuscitated with low or high oxygen concentrations: a prospective, randomized trial. Pediatrics. 2008;121:875-81.

Wang CL et al. Resuscitation of preterm neonates by using room air or 100% oxygen. Pediatrics. 2008;121:1083-9.

Vento M et al Preterm resuscitation with low oxygencauses less oxidative stress, inflammation, and chronic lung disease. Pediatrics.2009;124:e439-49.

Harling et al Does the use of 50% oxygen at birth in preterm infants reduce lung injury? Arch Dis Child Fetal Neonatal Ed. 2005;90:F401-5

Rabi Y, et al. Room-air versus oxygen administration for resuscitation of preterm infants: the ROAR study. Pediatrics. 2011;128:e374-81.

See KS et al. Feasibility of a multinational trial of targeted oxygen saturation versus 100% oxygen in the resuscitation of premature infants and their developmental outcome (To2rpido).PSAZN 2009 (abstr).

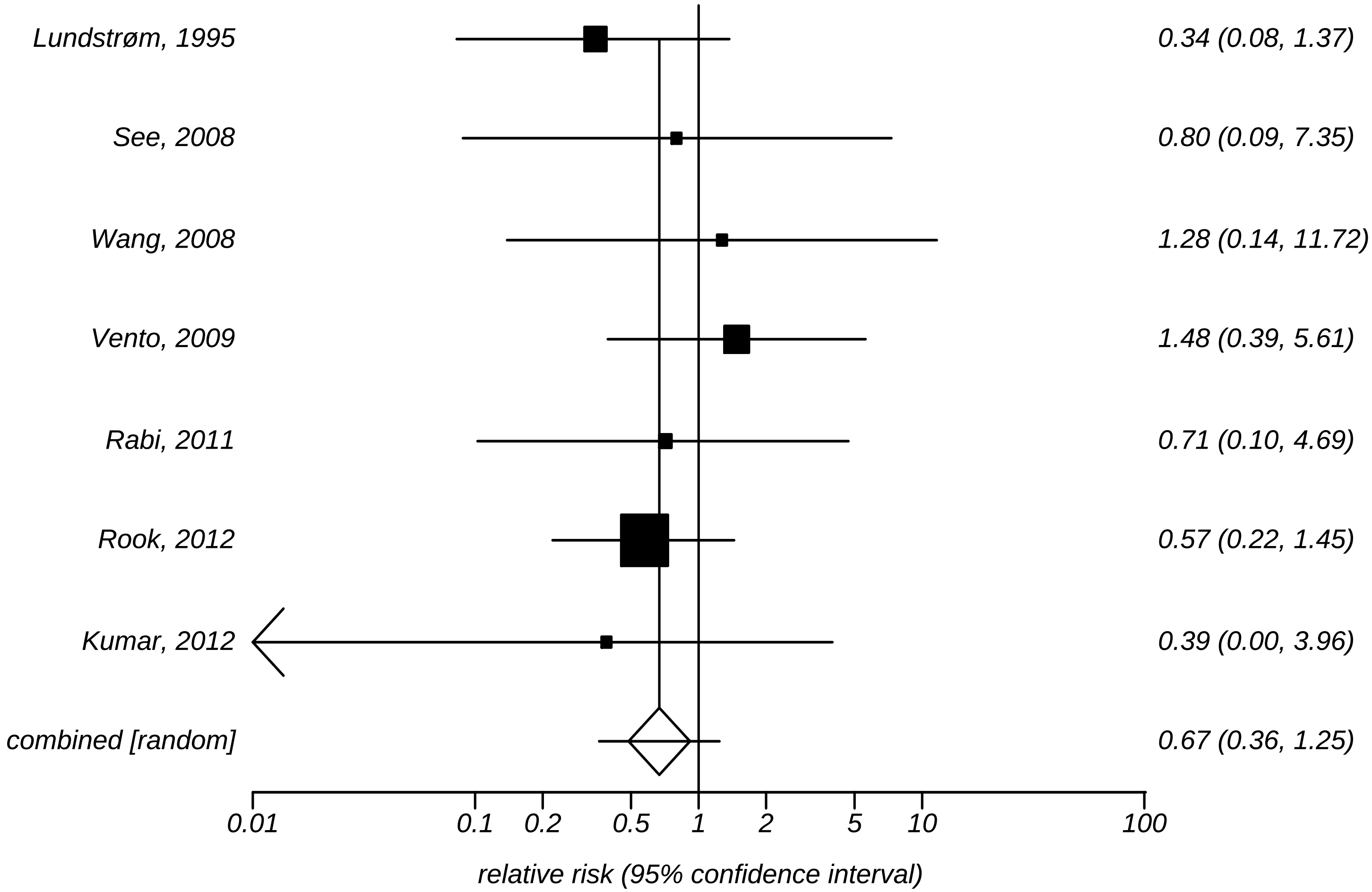
Rook D et al Randomized Controlled Trial on the Resuscitation of Preterm Infants with 30% Versus 65% Oxygen at Birth Arch Dis Child 2012; 97(Suppl 2): Abstr 385

Kumar VH et al. Randomized trial of varying levels of oxygen (21%, 40% and 100%) at resuscitation in premature infants < 32 weeks GA. E-PAS2012:4525.352

Saugstad, Aune, Finer, Vento, submitted

Mortality in low versus high $iFiO_2$

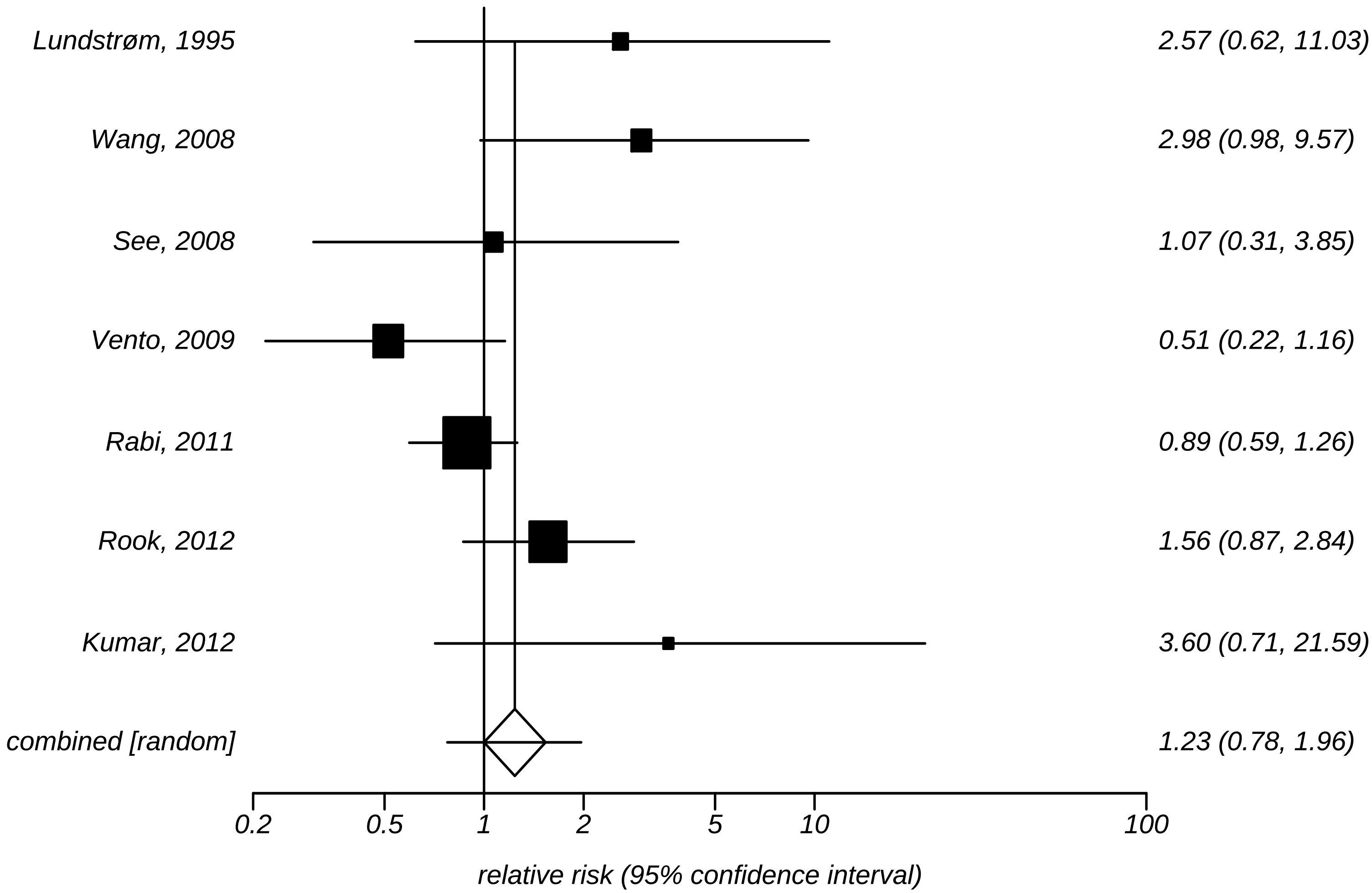
Relative risk meta-analysis plot (random effects)



Saugstad, Aune, Finer, Vento submitted

BPD in low versus high iFiO$_2$

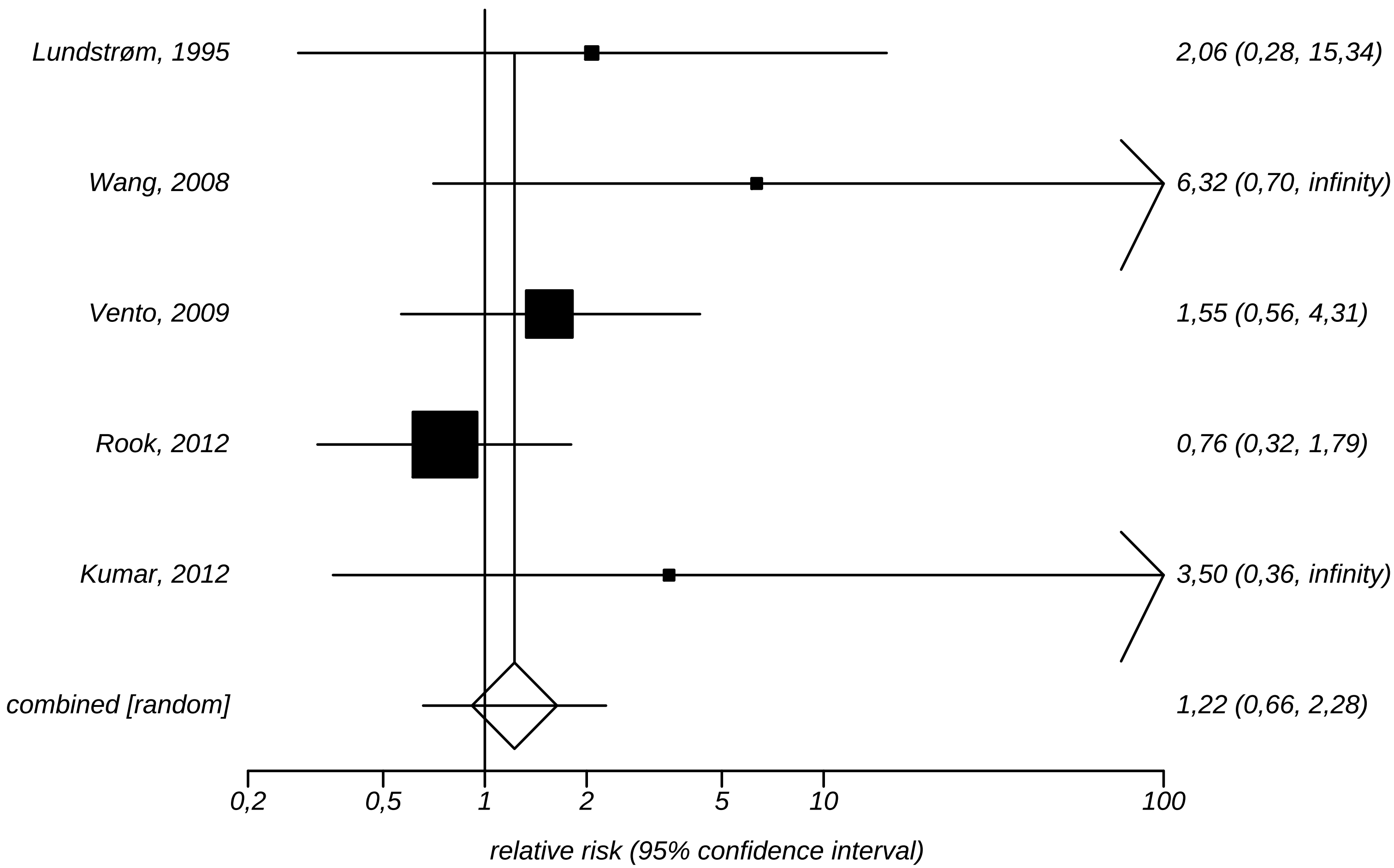
Relative risk meta-analysis plot (random effects)



Saugstad, Aune, Finer, Vento submitted

IVH in low versus high $iFiO_2$

Relative risk meta-analysis plot (random effects)



Saugstad, Aune, Finer, Vento submitted

The TO_2RPIDO and the Presox Studies

Randomize premature infants to low or high FiO_2

TO_2RPIDO: <31 completed weeks gestation with either 21% or 100% oxygen

PRESOX: < 29 weeks with either 21% or 60% oxygen

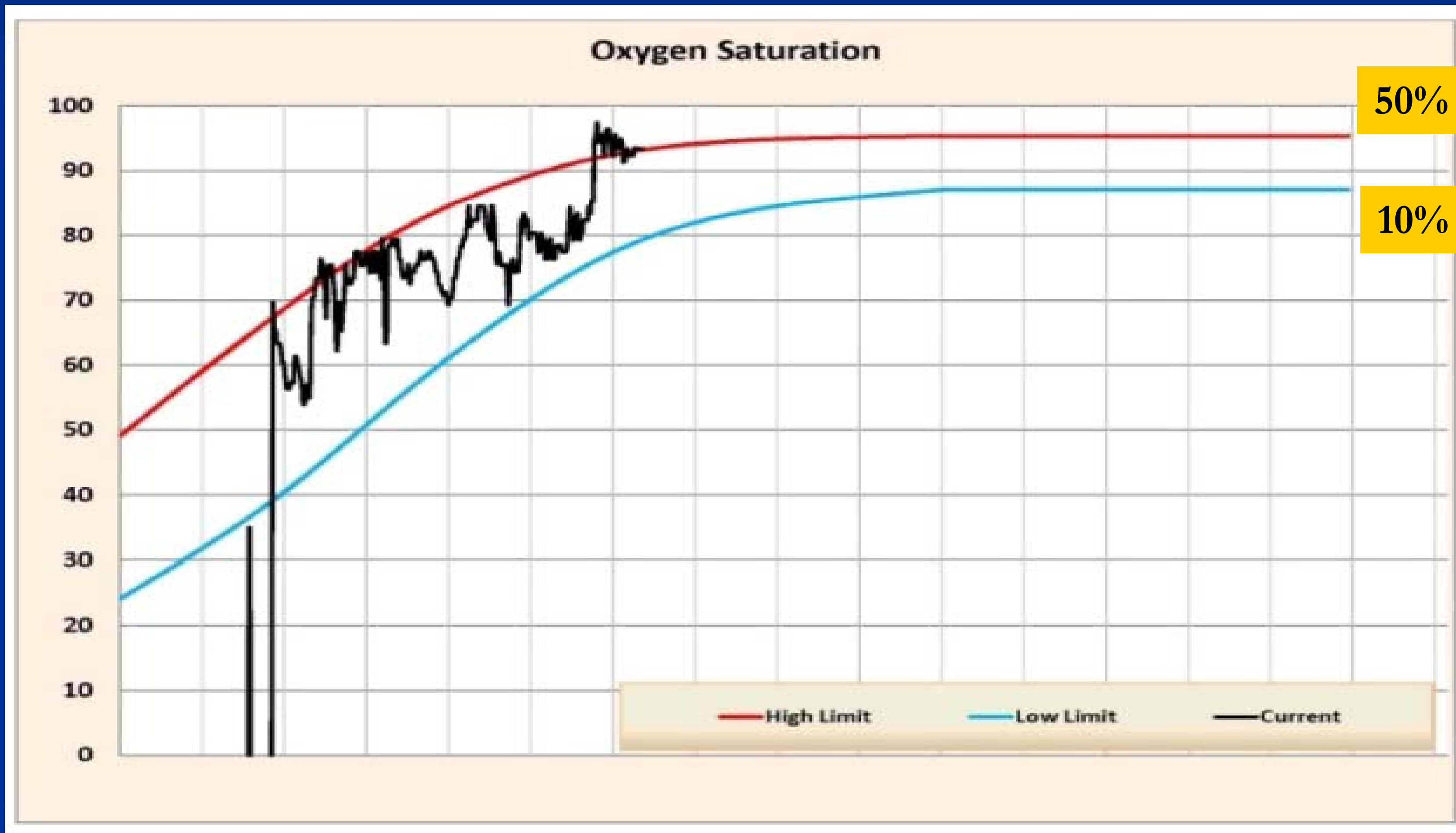
- Neonatal morbidities and mortality
  - BPD/ROP/NEC etc
  - Death
  - Major developmental disability at 18 months
- Acute oxidative stress

- Enrollment finished 2015?

Resuscitation of preterm infants < 33 weeks GA:

Start low (21-30% O_2)

Adjust FiO_2 according to preductal SpO_2 allowing to individualize FiO_2 avoiding hyper/hypoxia



Rich W et al ,2011

How to oxygenate ELBWIs beyond the delivery room?

What is the effect of oxygen saturations on mortality, BPD and ROP?

At least 13 studies have been published investigating the effect on BPD and ROP of low or high oxygen saturation in VLBWI or ELBWIs.

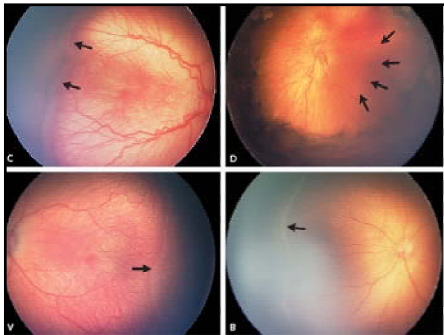
Of these 7 are randomized !

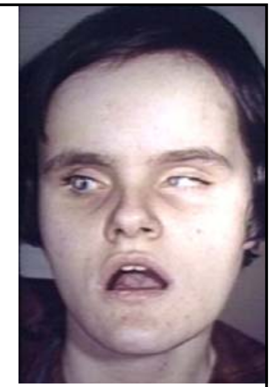
Studies regarding high or low SpO2 targets in VLBWI or ELBWIs – Characterisation of Studies

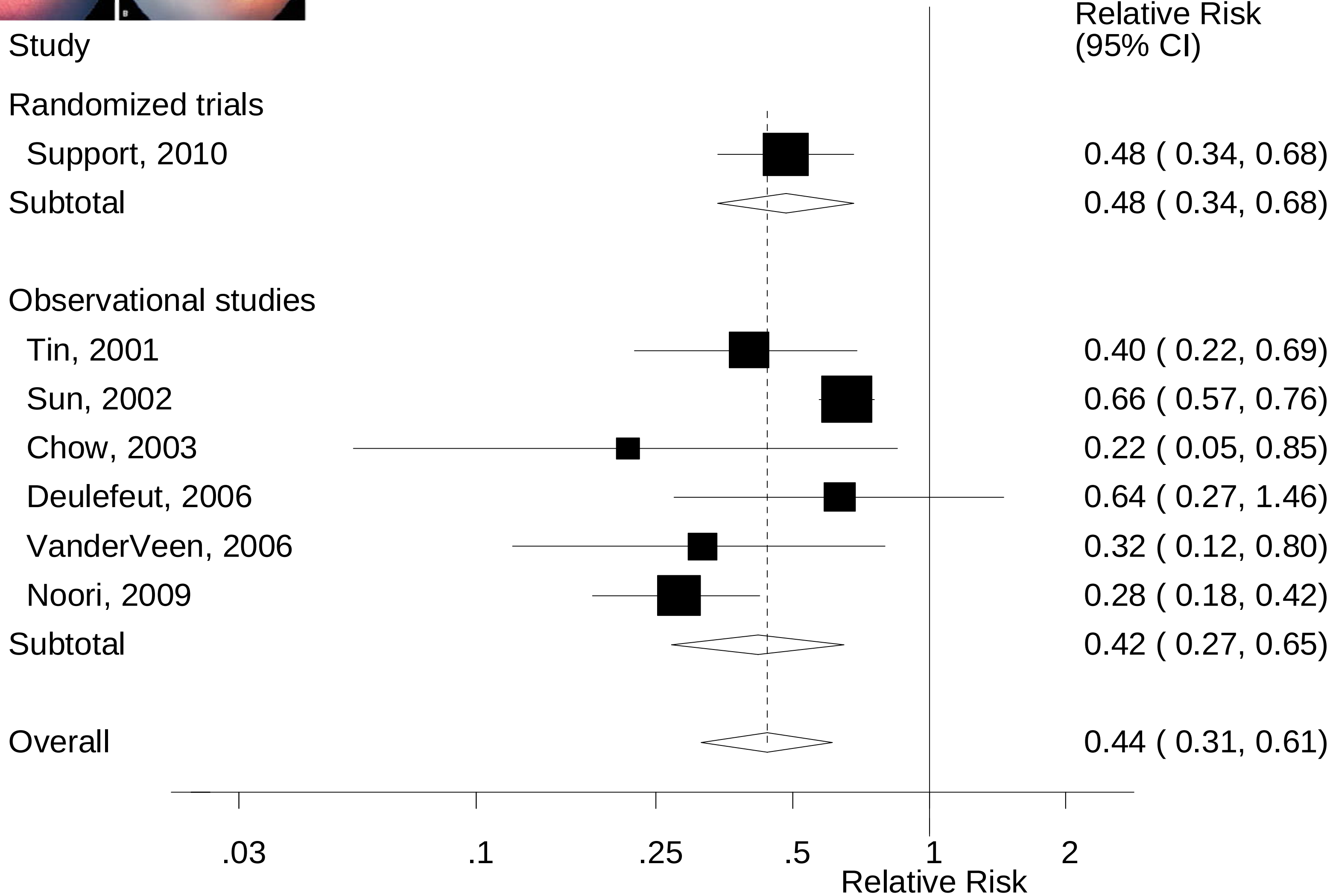
Study	GA w/BW g	Study design	High SaO_2	Low SaO_2
STOP ROP 2000	Mean 25.4 w	Randomized	96-99	89-94
Tin 2001	<28 weeks	Observational	88-98	70-90
Sun 2002	500-1000gr	Survey	>95	≤ 95
BOOST 1 2003	<30 weeks	Randomized	95-98	91-94
Chow 2003	500-1500 gr	Observational	90-98	85-93
VanderVeen 2006	≤28 weeks ≤ 1250 gr	Historical control	87-97	85-93
Deulofeut 2006	≤ 1250 gr	Historical control	92-100	85-93
Noori 2009	< 1000 gr	Historical control	89-94	83-89
SUPPORT 2010	24-28 weeks	Randomized	91-95	85-89

Saugstad and Aune, Neonatology 2010;100:1-8.

Severe ROP and SpO_2







Saugstad and Aune, Neonatology 2010;100:1-8.

NEOPROM

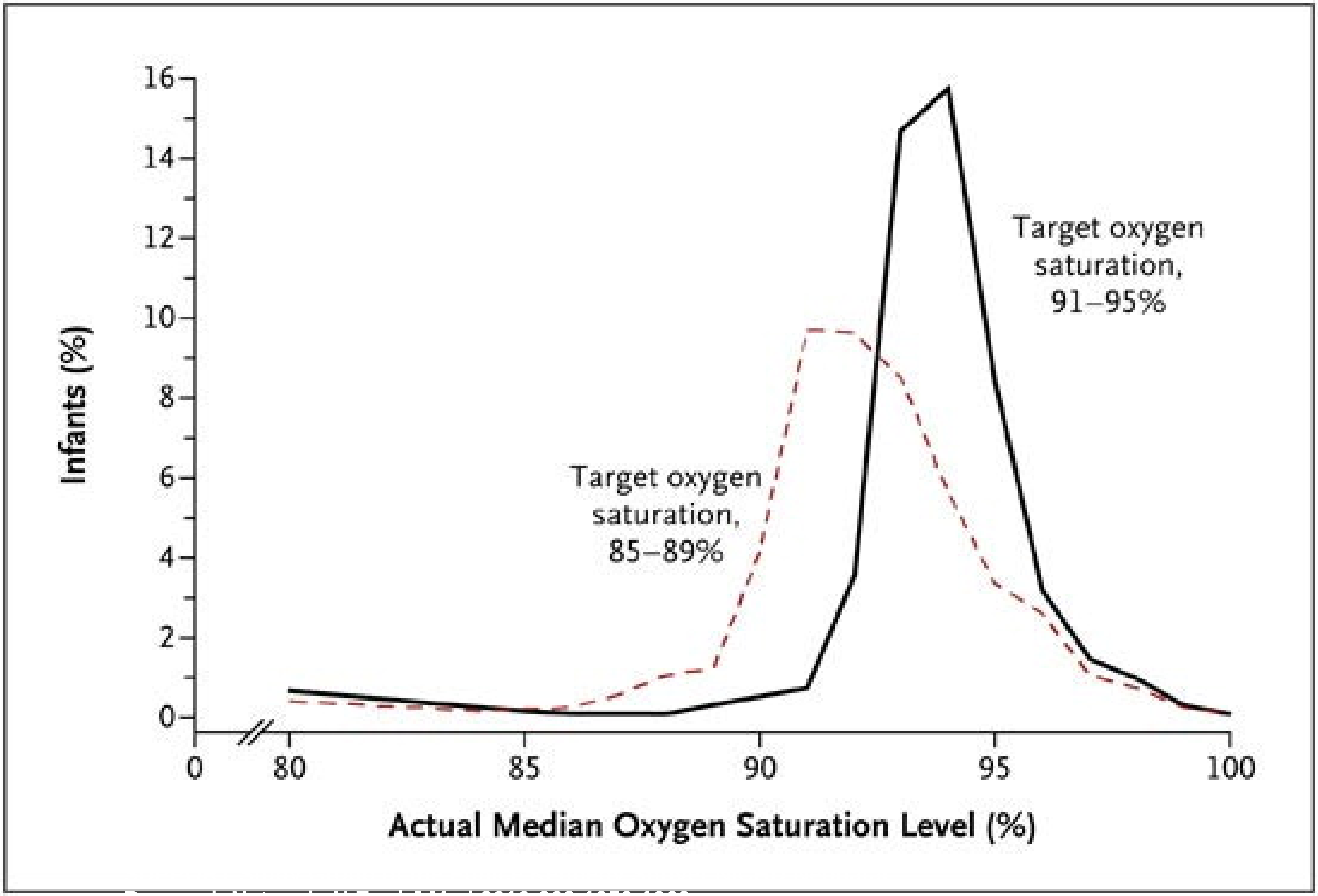
Combination of 5 large studies, <28 weeks GA

Study	Published	Trial Registry number
Support *Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial*	NEJM 2010;362:1959 -69	NCT 00233324
BOOST II *Benefits Of Oxygen Saturation Targeting Trial*	NEJM 2013	ISRCTN00842661
COT *Canadian Oxygen Trial*	JAMA 2013;309:	NCT 00637169

Randomized to Oxygen Targets:

Low arm: SpO_2 85-89 %

High arm: SpO_2 91-95 %



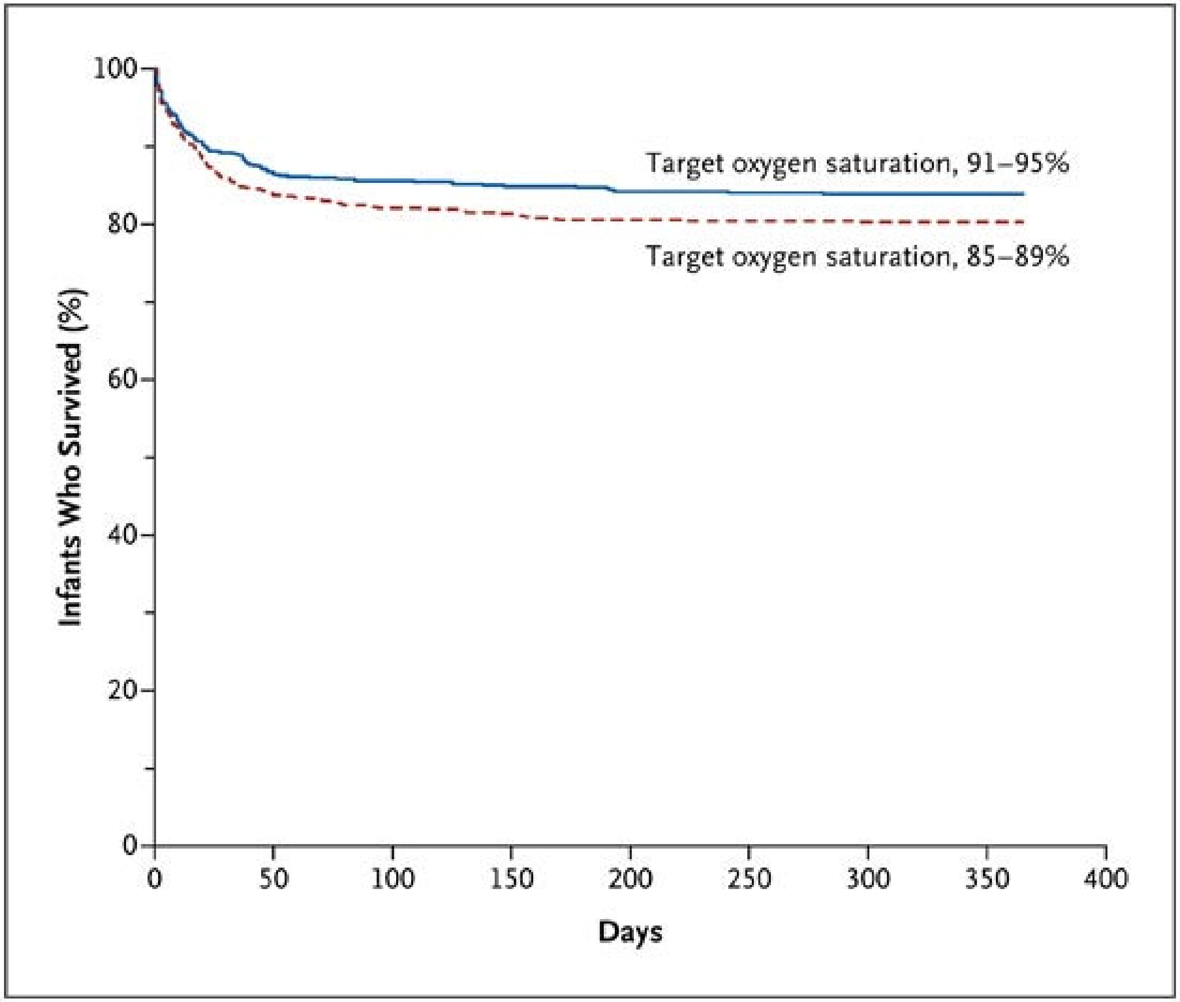
Infants (%)
16
14
12
10
8
6
4
2
0
0
80
85
90
95
100
Actual Median Oxygen Saturation Level (%)
Target oxygen saturation, 91–95%
Target oxygen saturation, 85–89%

Neoprom

	SUPPORT		BOOST 2		COT	
	low	high	low	high	low	high
GA w	26(1)	26(1)	26.0(1.2)	26.0 (1,2)	25,6 (1,2)	25,6 (1,2)
BW g	836 (193)	825 (193)	826(184)	837(189)	827 (190)	844 (199)
AS %	96.8%	95,6	89,6	90,7	88,2	90,0
Number	**654**	**662**	**1224**	**1224**	**578**	**569**

Enrolled
Low: 2456
High: 2455

The SUPPORT TRIAL- Survival

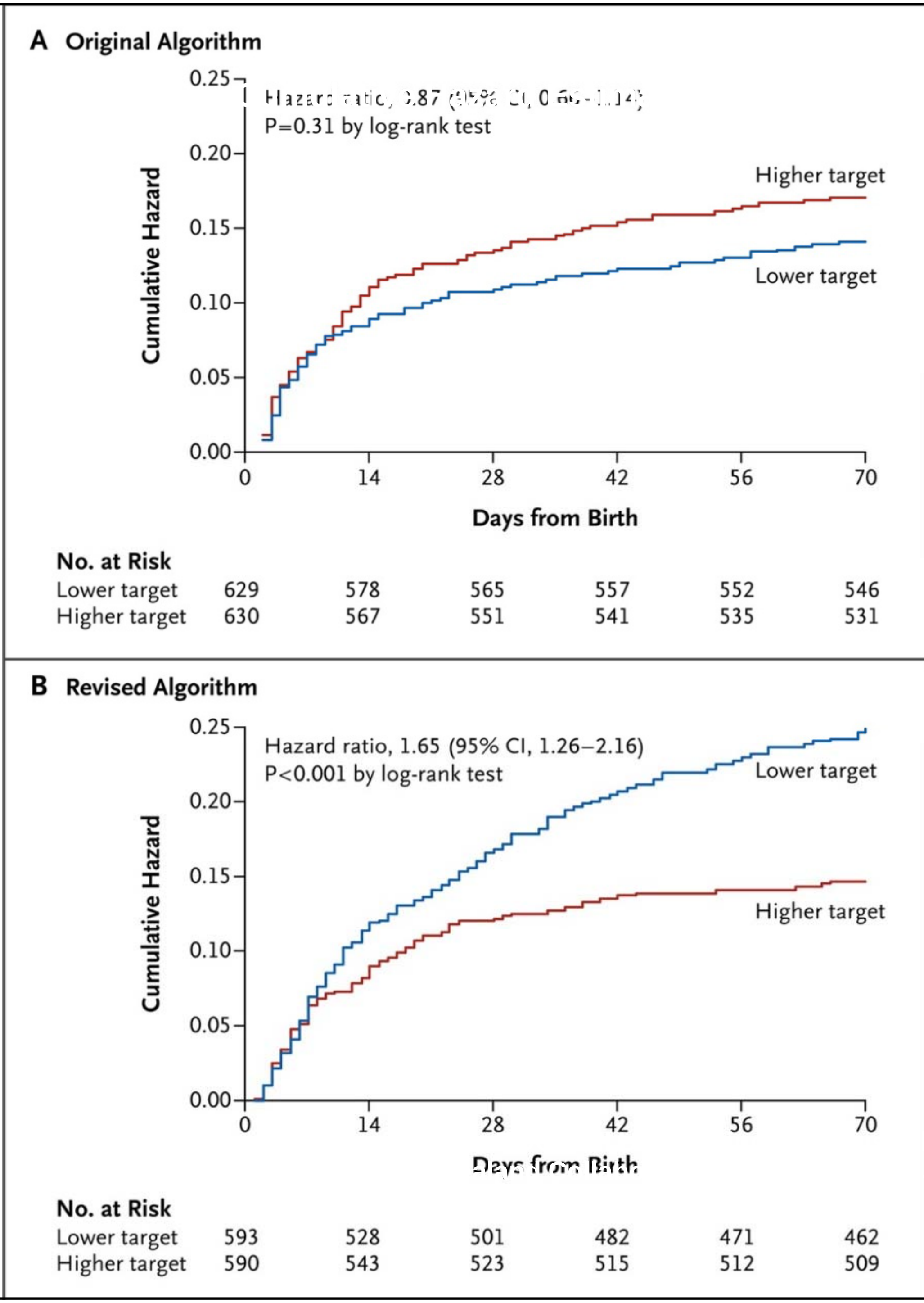


SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network
N ENGL J MED 2010; 362:1959-1969

Neoprom

	SUPPORT		BOOST 2		COT	
	low	high	low	high	low	high
Death^	**19,9**	**16,2**	**23,1**	**16,6**	**16,6**	**15.3**
BPD *	**37,6**	**46,7**	**44,1**	**48,9**	**31,8**	**33,1**
IVH**	**13,2**	**12,7**	**10,6**	**12,3**		
ROP #	**8,6**	**17,9**	**12,1**	**15,7**	**12,8**	**13,1**

Mortality data from BOOST 2 (UK)

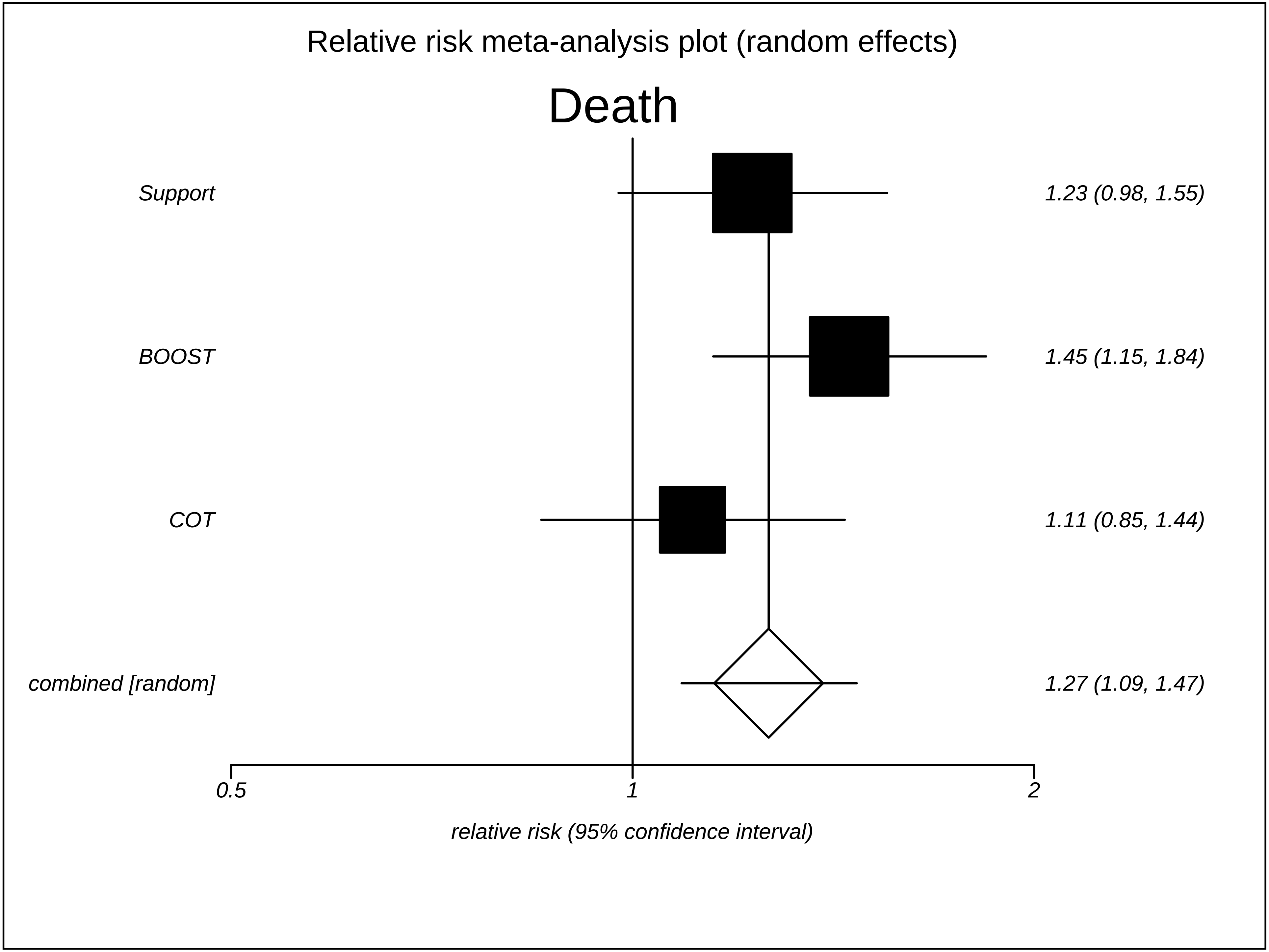


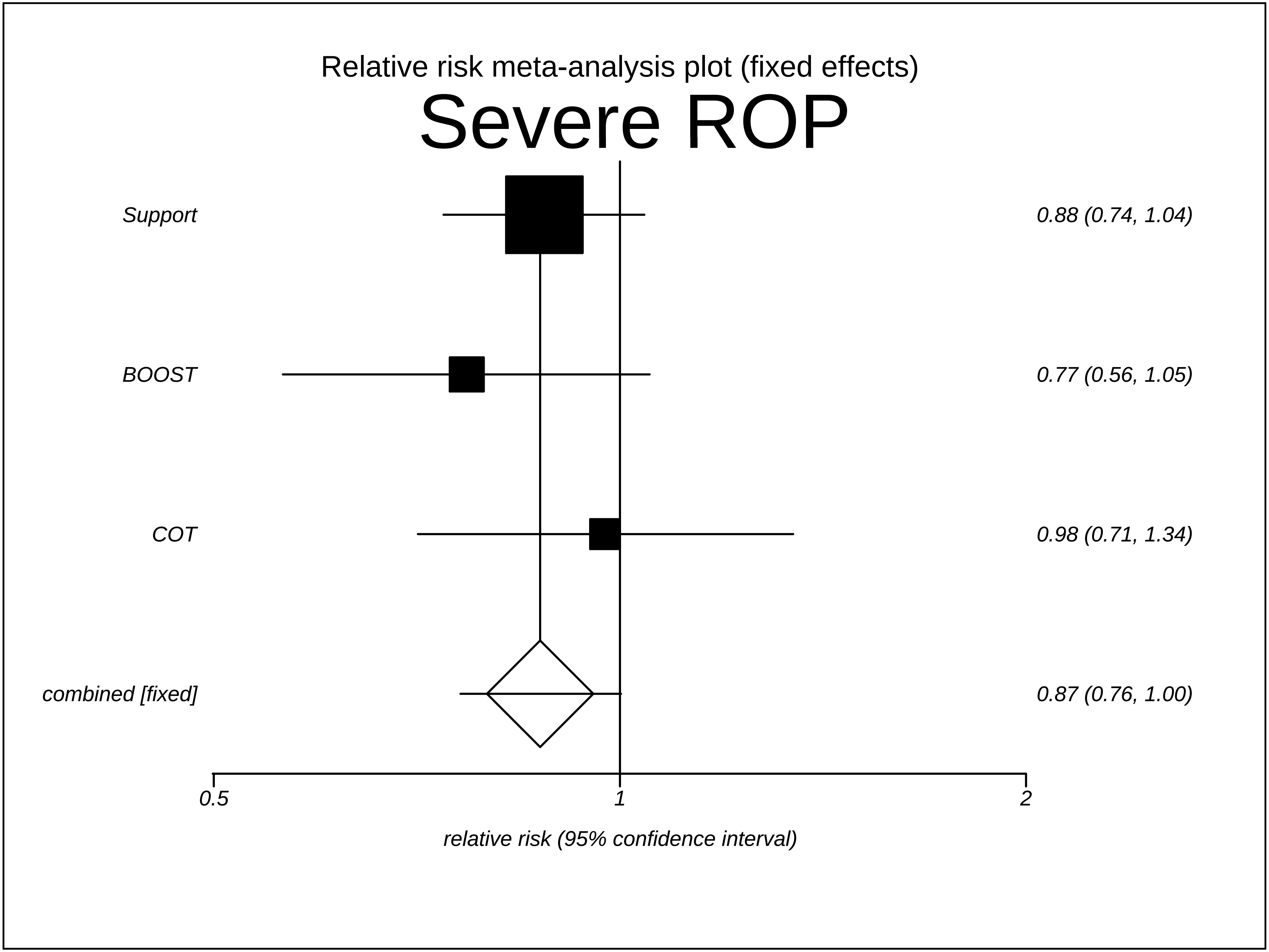
Mortality difference between low and high saturations increases up to 70 days after birth

Neoprom

	low	high	OR (95%CI
Death (%)	**366/1801 (20,3)**	**289/1829 (15,8)**	**1,27 (1,09 -1,47)**
Severe ROP (%)	**293/1584 (18,5)**	**344/1628 (21,1)**	**0,87 (0,76-1.00)***
NEC (%)	**205/1785 (11.5)**	**165/1878 (8.8)**	**1.35 (1.09 -1.67)**

* P = 0,05


Relative risk meta-analysis plot (random effects)
Death
Support
BOOST
COT
combined [random]
1.23 (0.98, 1.55)
1.45 (1.15, 1.84)
1.11 (0.85, 1.44)
1.27 (1.09, 1.47)
0.5
1
2
relative risk (95% confidence interval)



Relative risk meta-analysis plot (fixed effects)
Severe ROP
Support
0.88 (0.74, 1.04)
BOOST
0.77 (0.56, 1.05)
COT
0.98 (0.71, 1.34)
combined [fixed]
0.87 (0.76, 1.00)
0.5
1
2
relative risk (95% confidence interval)

Oxygen saturation in ELBWIs

Unanswered questions and updated recommendations

Did Neoprom add to our enlightenment in this matter?

COT Vs Support and BOOST which data should we ”believe” in?

What about babies > 27 w GA

Do we need separate data for SGA?

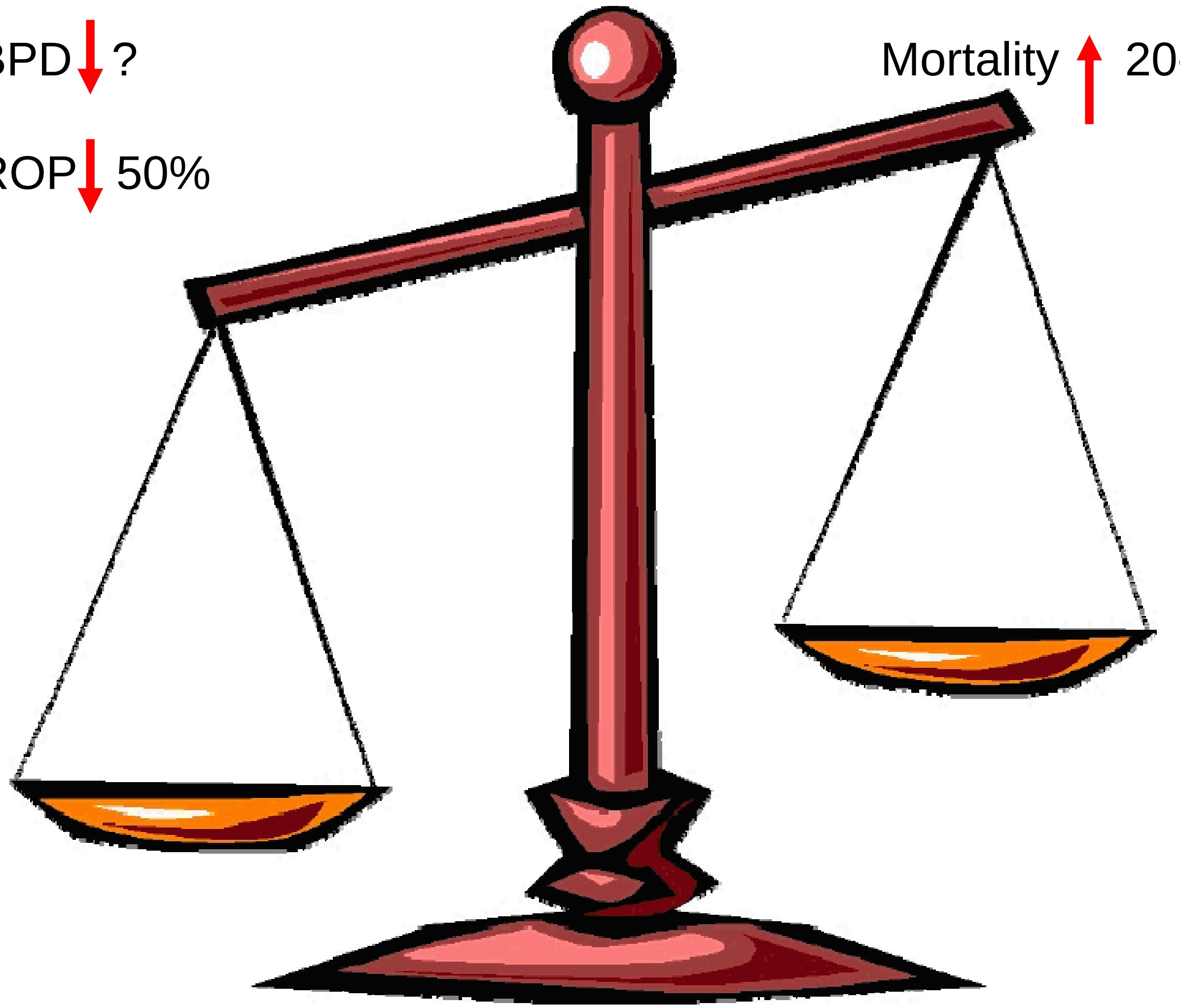
Should SpO_2 be kept constant throughout the postnatal period?

SpO_2 of ELBWIs should not be targeted at 85-89 % until further data become available. 91-95% is best choice. (2011)

SpO_2 of ELBWI should be targeted between 90-95% (European Guidelines on RDS 2013)

The SpO_2 targets describing the optimal balance between mortality and ROP and BPD is presently not known

SpO_2 85-89% Vs 91-95 %



Low SpO_2 (85-89%) beyond the DR probably reduces ROP but may increase mortality.
Keep SpO_2 90-95% (European guidelines 2013)

Conclusions

- It is best to initiate resuscitation of term babies with air
- Optimal FiO_2 during chest compressions is not known
- Keep oxygen normal before admission, Hyperoxia may increase risk of HIE and reduce the effect of hypothermia
- The optimal FiO_2 for resuscitation of < 33 w GA is not known. Start low (21-30%), increase if needed
- Low SpO_2 for ELBWIs (85-89%) beyond the DR probably reduces ROP but may increase mortality
- Keep SpO_2 between 90-95% (European guidelines 2013)
- **Still there are a number of unanswered questions!**

Thank you for your attention