

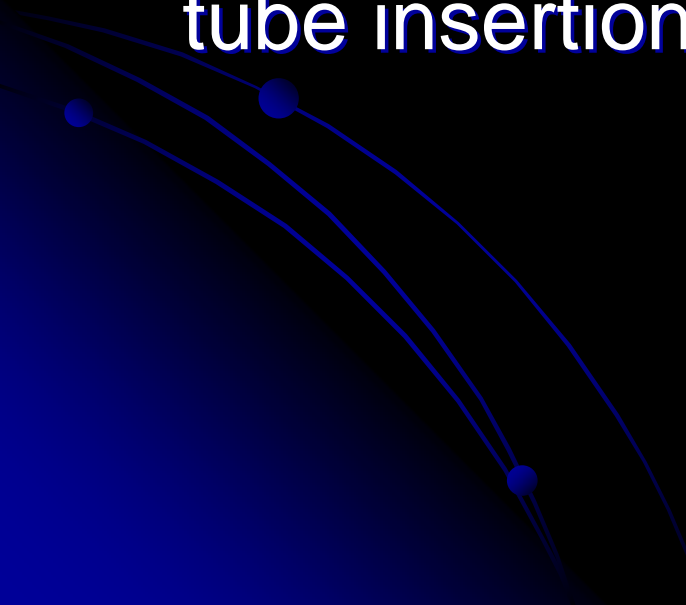
EBM presentation

Kaohsiung Medical University Hospital
Department of Pediatrics

Present by Resident : Ko-Hsin Chen

Instructed by Attending Physician : San-Nan Yang

Brief history

- Preterm male neonate with GA=25+2 wks, BBW=670 gm, Apar score 1"→5": 3→5
 - Newborn resuscitation with Endotracheal tube insertion for respiratory distress
- 

Brief history

- Respiratory distress syndrome grade III with ventilator support and surfactant 2 doses supplement in 24hrs after birth
- Respiratory system: on ETT with ventilator use till now



Brief history

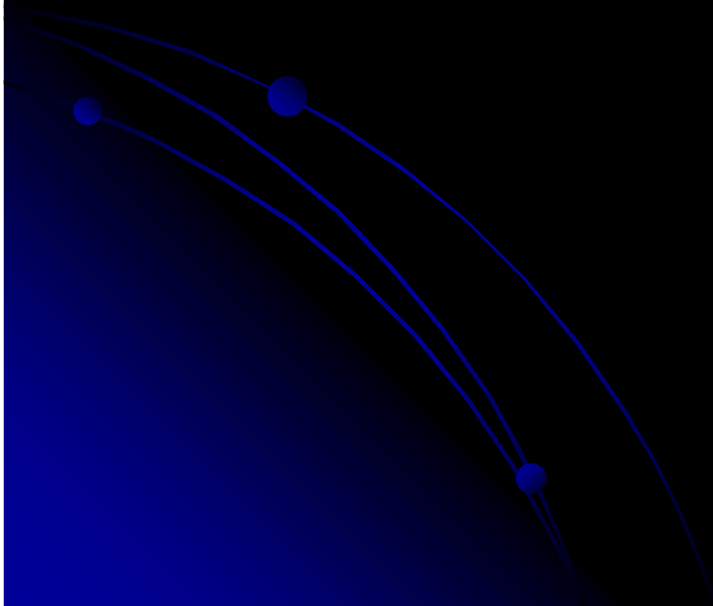
- Current setting: IMV mode, rate=26/min, FiO₂=35%, PIP=18 mmHg, PEEP=5
- Ventilator-dependent state
- Is the treatment of **Dexamethasone** for **chronic lung disease** get **adverse outcome ???**

Introduction

- In 1983, the first randomized trial
 - the benefit of postnatal glucocorticoid therapy in infants with chronic lung disease
- Several subsequent clinical trials showed postnatal glucocorticoid therapy administered systemically :
 - improved lung function and outcome of infants with established BPD and prevented BPD in high-risk preterm infants (ie, infants with a birth weight less than 1250 g or a gestational age less than 30 weeks)

Asking an answerable question

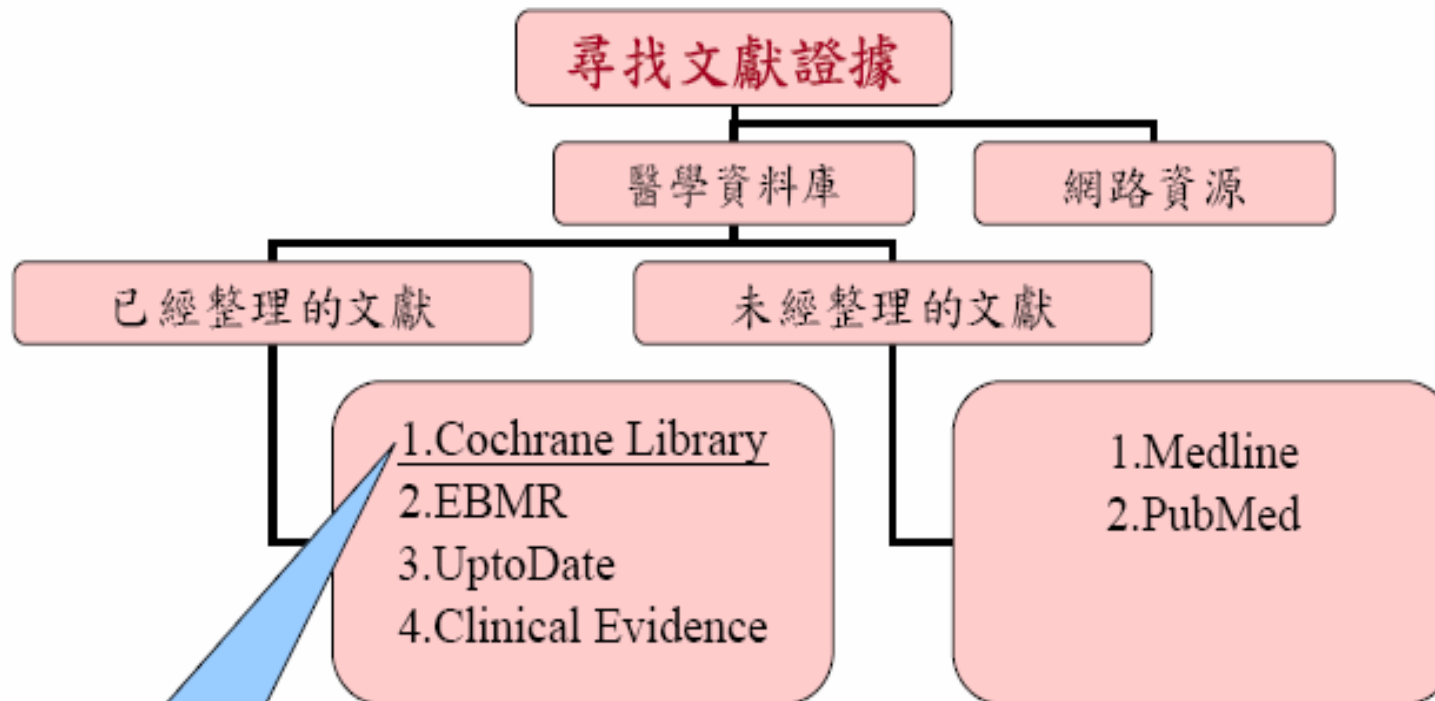
- Is the treatment of **Dexamethasone** for **chronic lung disease** get **adverse outcome** (neurodevelopmental deficit, infection, GI bleeding...)???



PICO

- **Patient ~**
preterm infant with chronic lung disease
- **Intervention ~**
Dexamethasone
- **Comparison ~**
No treatment or placebo
- **Outcome ~**
adverse outcome: neurodevelopmental deficit, infection, GI bleeding

Accessing-Searching evidences



使用此data
base 來搜尋





The Cochrane Library

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LP Brion, RA Primhak, I Ambrosio-Perez
Year: 2002

[Record](#) [Review](#)



Protein containing synthetic surfactant versus animal derived surfactant extract for the prevention and treatment of respiratory distress syndrome
RH Pfister, RF Soll, T Wiswell
Year: 2007

[Record](#) [Review](#)



Cromolyn sodium for the prevention of chronic lung disease in preterm infants
GY Ng, A Ohlsson
Year: 2001

[Record](#) [Review](#)



Elective high frequency jet ventilation versus conventional ventilation for respiratory distress syndrome in preterm infants
T Bhuta, DJ Henderson-Smart
Year: 1998

[Record](#) [Review](#)



Early administration of inhaled corticosteroids for preventing chronic lung disease in ventilated very low birth weight preterm neonates
V Shah, A Ohlsson, HL Halliday, MS Dunn
Year: 2007

[Record](#) [Review](#)



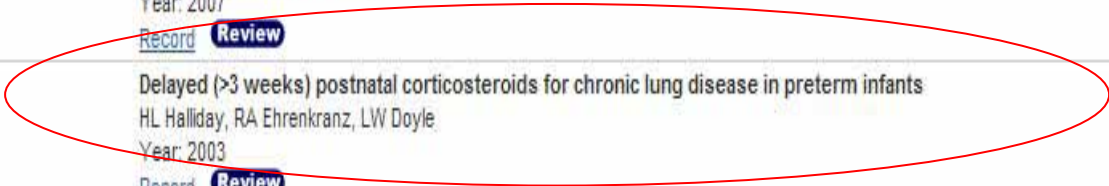
Delayed (>3 weeks) postnatal corticosteroids for chronic lung disease in preterm infants
HL Halliday, RA Ehrenkranz, LW Doyle
Year: 2003

[Record](#) [Review](#)



Alpha-1 proteinase inhibitor (a1PI) for preventing chronic lung disease in preterm infants
P Shah, A Ohlsson

Key word: Dexamethasone, preterm, chronic lung disease, adverse outcome



Delayed (>3 weeks) postnatal corticosteroids for chronic lung disease in preterm infants (Review)

Halliday HL, Ehrenkranz RA, Doyle LW

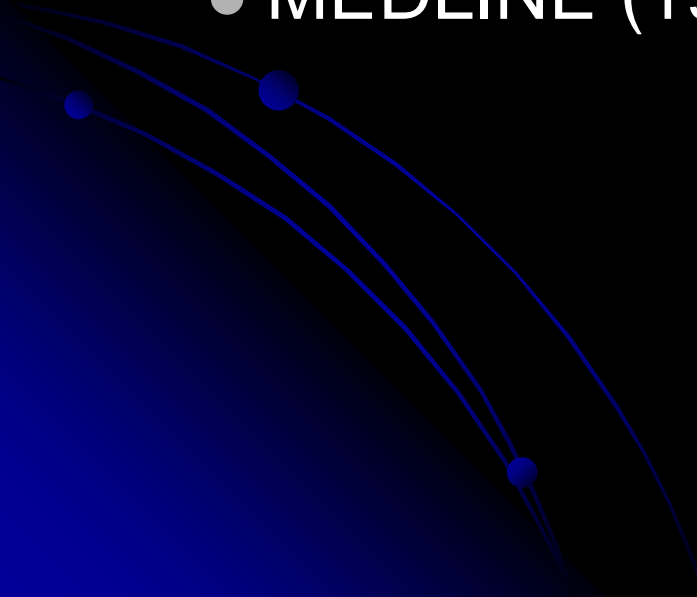
This record should be cited as:

Halliday HL, Ehrenkranz RA, Doyle LW. Delayed (>3 weeks) postnatal corticosteroids for chronic lung disease in preterm infants. *Cochrane Database of Systematic Reviews* 2003, Issue 1. Art. No.: CD001145. DOI: 10.1002/14651858.CD001145.

This version first published online: 20 January 2003 in Issue 1, 2003.

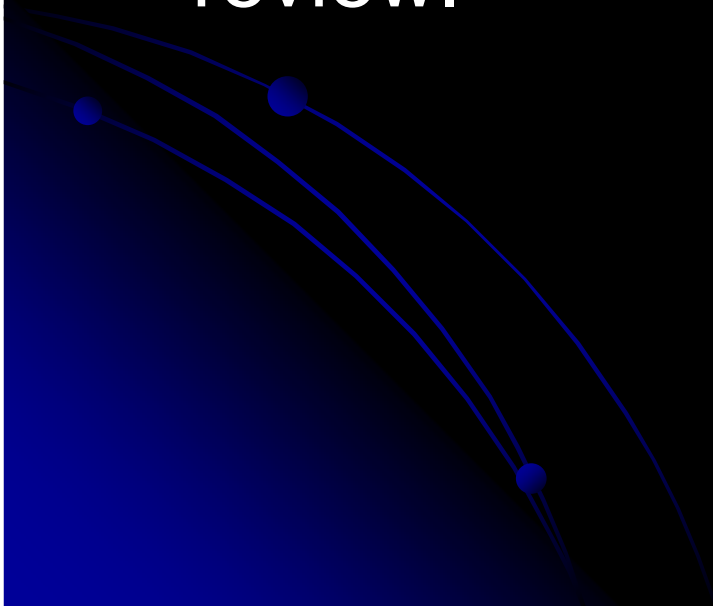
Date of most recent substantive amendment: 11 November 2002

Search strategy

- Randomised controlled trials of postnatal corticosteroid therapy were sought from
 - Oxford Database of Perinatal Trials
 - Cochrane Controlled Trials Register
 - MEDLINE (1966 - October 2002)
- 

Selection criteria

- **Randomised controlled trials** of postnatal corticosteroid treatment initiated at predominantly **> 3 weeks of age in preterm** infants with **CLD** were selected for this review.



Appraising

Grade of Recommendation	Level of Evidence	Therapy
[A]	1a	Systemic review of RCTs
	1b	Single RCT
	1c	'All-or-none'
[B]	2a	Systemic review of cohort studies
	2b	Cohort study or poor RCT
	2c	'Outcomes' research
	3a	Systemic review of case-control studies
	3b	Case-control study
[C]	4	Case series
[D]	5	Expert opinion, physiology, bench research

Evidence-Based Medicine: How to Practice and Teach EBM. 2nd ed. David L. Sackett, Sharon E. Straus, W. Scott Richardson, William Rosenberg, R. Brian Haynes. Churchill Livingstone. 2000, p173-177

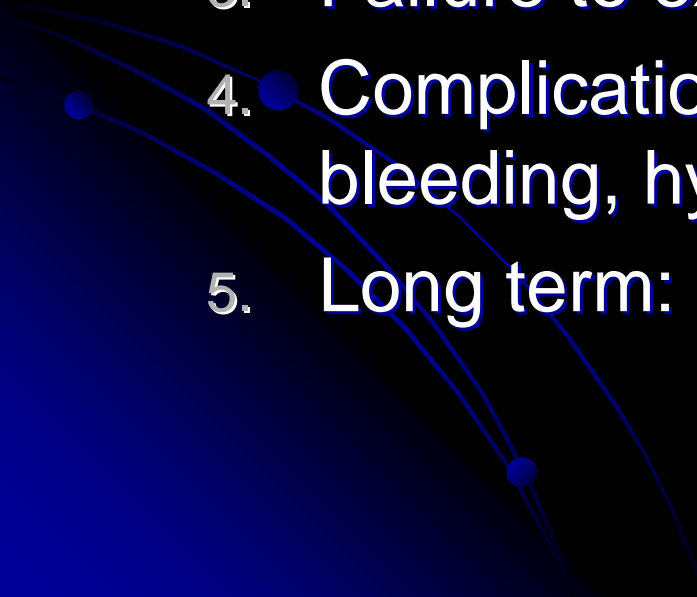
The Evidence Pyramid



Description of studies

- Nine trials qualified for inclusion in this review
- Enrolled preterm babies who were oxygen or ventilator dependent beyond 3 weeks of age
- Dexamethasone was used in an initial dose of 0.5~1 mg/kg/day with duration of therapy varying between 3 days and up to 3 weeks.

Data collection and analysis

- Evaluating clinical outcomes including
 1. Mortality
 2. Chronic lung disease severity (need for home oxygen, late rescue with steroid)
 3. Failure to extubate
 4. ● Complication in hospitalization (infection, GI bleeding, hypertension.....)
 5. Long term: ROP, neuro-development
- 

Characteristics of included studies

Study	Ariagno 1987
Methods	Random allocation by pharmacist <u>Blinding of randomisation: yes. Blinding of intervention: yes . Complete follow-up: yes for outcomes measured within the first year, no for later outcomes. Blinding of outcome: yes.</u>
Participants	<u>34 preterm infants < 1501 g birthweight, ventilator dependent and no weaning from mechanical ventilation at 3 weeks. CXR changes</u>
Interventions	<u>Two regimens were used in this study : a 10 day or a 7 day. 10 d- intravenous dexamethasone 1 mg/kg/d for 4 d followed by 0.5 mg/kg/d for 6 d, 7 d - 1 mg/kg/d for 3 d then 0.5 mg/kg/d for 4 d. Of the 17 dexamethasone treated infants, 4 received the 10-day protocol and 13 the 7-day protocol. Saline placebos were used during the respective treatment periods.</u>
Outcomes	<u>Pulmonary function tests, failure to extubate, mortality, hyperglycaemia, hypertension, infection, gastrointestinal bleeding, NEC, mortality, time to extubation, rate of weight gain and head growth, need for home oxygen, duration of oxygen, ROP and CP.</u>
Notes	The results in the abstract have been updated with complete data provided by the investigators in September 2000.
Allocation concealment	A – Adequate

Study	Avery 1985
Methods	Random allocation by opening sealed envelopes. Stratified by birthweight and sequential analysis. Blinding of randomisation: yes. Blinding of intervention: unsure. Complete follow-up: yes. Blinding of outcome: uncertain.
Participants	<u>16 infants < 1500 g birthweight, age 2-6 weeks who had RDS but at entry radiological signs of BPD of stages 2 or 3 by Northway Classification. Exclusion for PDA, congenital heart disease, pneumonia, IV lipids within 24 hours.</u>
Interventions	<u>Intravenous dexamethasone 0.5 mg/kg/day every 12 h intravenously for 3 days, 0.3 mg/kg/day for 3 days decreased by 10% every 3 days. Placebo not administered.</u>

Characteristics of included studies (Continued)

Outcomes Pulmonary function tests, extubation within 3 days, mortality, sepsis, hypertension, hyperglycaemia and duration of hospital stay.

Notes

Allocation concealment A – Adequate

Study CDTG 1991

Methods Random allocation using unmarked vials and telephone randomisation. Stratified by clinical centre and whether or not the babies were ventilator dependent. Survivors at 3 years were followed up. 14 infants died after discharge and follow up information was available for 209 of the 212 infants (99% follow-up).

Participants 287 preterm infants from 3 weeks of age with oxygen dependency, with or without mechanical ventilation whose condition was static or deteriorating over the preceding week. Exclusion of major malformations.

Interventions Dexamethasone 0.6 mg/kg/day for 1 week intravenously or orally, with an option to give a second tapering 9 day course (0.6, 0.4, and 0.2 mg/kg/day for 3 days each). If after initial improvement relapse occurred. Matching saline placebo was given intravenously (or orally if there was no intravenous line) for one week.

Outcomes Duration of mechanical ventilation, death, sepsis, NEC, pneumothorax, blood pressure, plasma glucose, gastrointestinal bleeding, duration of O₂ and hospital stay. Cerebral palsy and blindness in survivors as assessed by questionnaires from general practitioners, health visitors and parents.

Notes Babies could be enrolled if breathing spontaneously.

Allocation concealment A – Adequate

Study Harkavy 1989

Methods Random allocation in the pharmacy using cards of random numbers. Blinding of randomisation: yes. Blinding of intervention: yes. Complete follow-up: yes. Blinding of outcome: yes.

Participants 21 preterm infants with ventilator and O₂ dependency at 30 days.

Interventions Dexamethasone 0.5 mg/kg/day every 12 hours for 2 weeks either intravenously or orally. Saline placebo given to controls.

Outcomes FiO₂, duration of oxygen, mortality, hypertension, hyperglycaemia, infection and ROP.

Notes

Allocation concealment A – Adequate

Study	Kazzi 1990
Methods	Random allocation by drawing a card in the pharmacy, stratified for birthweight (< 1000 g, 1000-1250 g and 1251-1500 g). Blinding of randomisation: yes. Blinding of intervention: yes. Complete follow-up: yes. Blinding of outcome: yes.
Participants	23 preterm infants, 3-4 weeks old who weighed < 1500 g at birth with radiological findings of BPD and needing mechanical ventilation in over 34% O ₂ : failure of medical treatment. Exclusion for PDA, pneumonia, sepsis and hypertension.
Interventions	Dexamethasone 0.5 mg/kg/day for 3 days, 0.4 mg/kg/day for 2 days, 0.25 mg/kg/day for 2 days, given by nasogastric tube as a single daily dose, then hydrocortisone every 6 h for 10 days. Infants in the control group received equal volumes of saline.
Outcomes	FiO ₂ , ventilator settings, extubation < 9 days, hyperglycaemia, sepsis, hypertension, ROP, duration of O ₂ , mechanical ventilation and hospital stay.
Notes	
Allocation concealment	A – Adequate

Study	Kothadia 1999
Methods	Random allocation within 6 strata according to birth weight (500-800 g, 801-1100 g and 1101-1500 g) and gender. Method not stated. Blinding of randomisation: probably. Blinding of intervention: probably. Complete follow-up : yes for outcomes measured within first year; no for 5-year assessments. Blinding of outcome : largely
Participants	118 preterm infants , < 1501 g age 15-25 days, ventilator dependent over 30% oxygen, no PDA, major malformation, HIV or HBV infection.
Interventions	42 day tapering course of dexamethasone or an equal volume of normal saline. Dexamethasone 0.25 mg/kg 12 hourly for 3 days, 0.15 mg/kg 12 hourly for 3 days, then a 10% reduction in dose every 3 days until a dose of 0.1 mg/kg had been given for 3 days, from which time 0.1 mg/kg qod until 42 days after entry.
Outcomes	Duration of ventilation, oxygen, hospital stay; death, oxygen at 36 weeks, grade 3 ROP, infection, hypertension and hyperglycaemia. Follow-up : Bayley MDI and PDI, cerebral palsy, abnormal neurological examination.
Notes	
Allocation concealment	B – Unclear

Study	Noble-Jamieson 1989
Methods	Random allocation, method not stated.
Participants	18 preterm infants over 4 weeks old and needing more than 30% O ₂ . Exclusion for congenital anomalies, infection, gastric erosion and NEC.
Interventions	Dexamethasone 0.5 mg/kg/day for 7 days either orally or intravenously, 0.25 mg/kg/day for 7 days, 0.1 mg/kg/day for 7 days. Saline placebo given to controls.
Outcomes	FiO ₂ , duration of oxygen, leucocytosis, cranial ultrasound scan.
Notes	Spontaneously breathing infants could be enrolled.
Allocation concealment	B – Unclear

Study	Ohlsson 1992
Methods	Random allocation in pharmacy using sealed envelopes. Blinding of randomisation: yes. Blinding of intervention: probably. Complete follow-up: yes. Blinding of outcome: attempted.
Participants	25 preterm infants, 21-35 days old, weighing < 1501 g birthweight and needing mechanical ventilation > 29% O ₂ . Chest radiograph consistent with CLD. Exclusion for infection, congenital anomalies, PDA, NEC, intestinal bleeding or perforation.
Interventions	Dexamethasone 0.5 mg/kg b.d. for 3 days, followed by 0.25 mg/kg b.d. for 3 days and 0.125 mg/kg b.d. for 3 days intravenously. Intravenous placebo was not permitted by Ethics Committee. Sham injection of saline was given into the bed in the control group by a Physician not involved in the respiratory care of the infant or in the study. A band aid was affixed to a possible site for intravenous infusion.
Outcomes	Extubation < 7 days, change in chest radiograph, blood pressure, full blood picture, perforation of stomach, severe ROP, death.
Notes	
Allocation concealment	A – Adequate

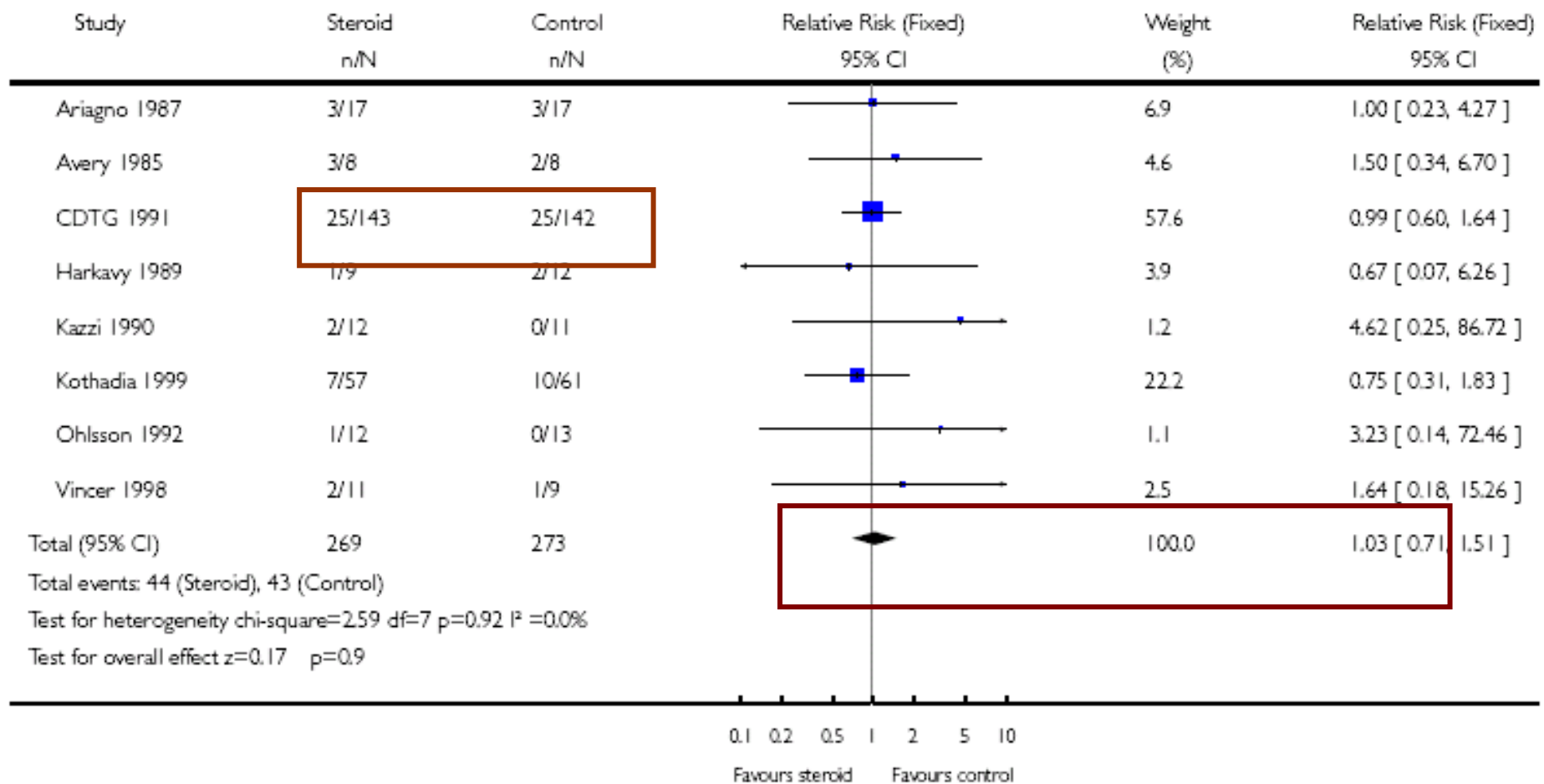
Study	Vincer 1998
Methods	Random assignment, method not stated. Blinding of randomisation : unclear. Blinding of intervention : probably. Complete follow-up : yes. Blinding of outcome measurements : yes.
Participants	20 very low birth weight infants who were ventilator dependent at 28 days postnatal age.
Interventions	Either a 6 day course of intravenous dexamethasone 0.5 mg/kg/day for 3 days followed by 0.3 mg/kg/day for the final 3 days or to receive an equal volume of saline placebo.
Outcomes	Mortality, median number of days ventilated after treatment, days of apnoeic spells, length of hospital stay, weight and head circumference at 2 years, corrected MDI, retinopathy of prematurity, cerebral palsy in survivors and blindness in survivors.
Notes	Published as an abstract only.
Allocation concealment	B – Unclear

Analysis 01.01. Comparison 01 Mortality, Outcome 01 Mortality to hospital discharge

Review: Delayed (>3 weeks) postnatal corticosteroids for chronic lung disease in preterm infants

Comparison: 01 Mortality

Outcome: 01 Mortality to hospital discharge

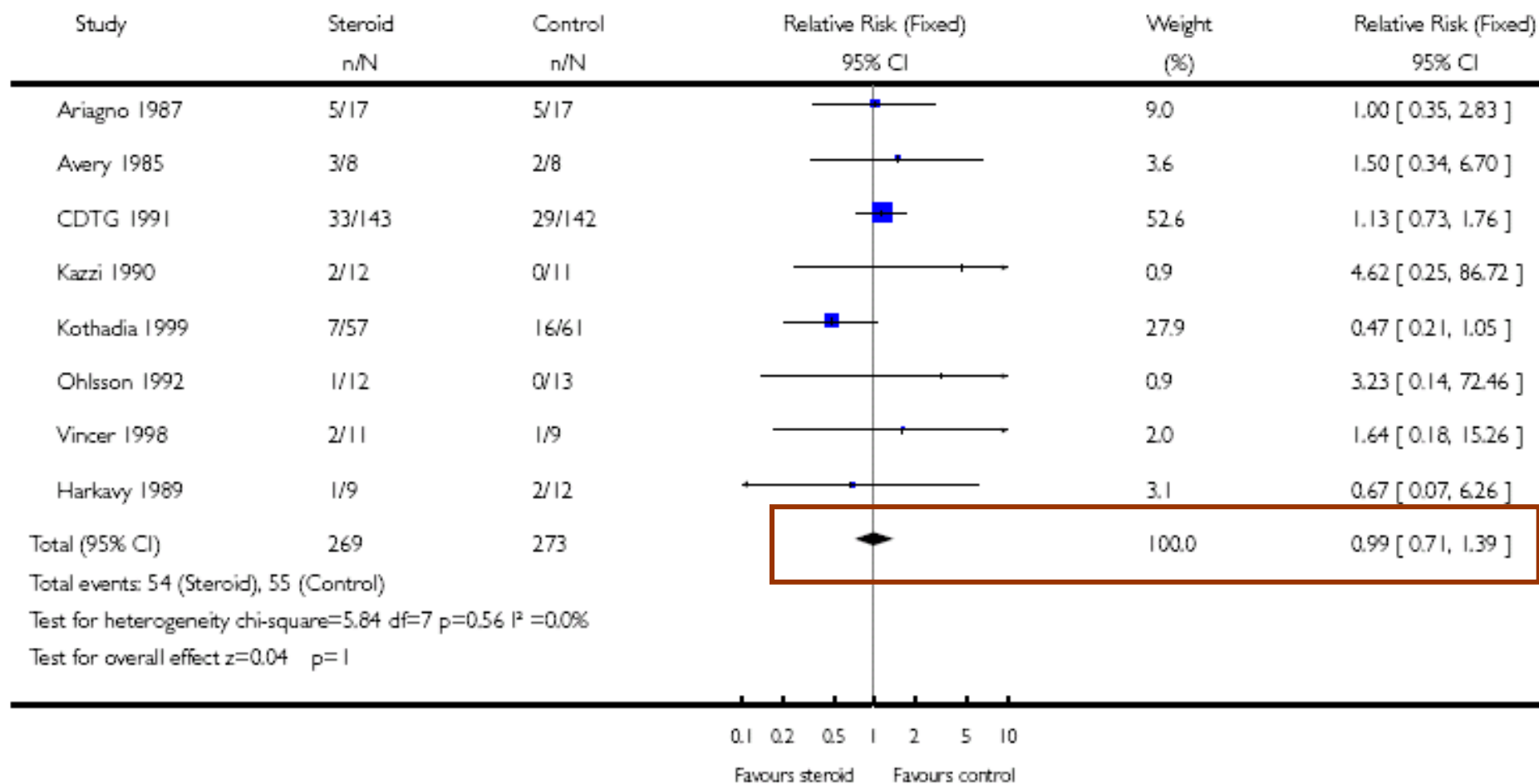


Analysis 01.02. Comparison 01 Mortality, Outcome 02 Mortality at latest reported age

Review: Delayed (>3 weeks) postnatal corticosteroids for chronic lung disease in preterm infants

Comparison: 01 Mortality

Outcome: 02 Mortality at latest reported age

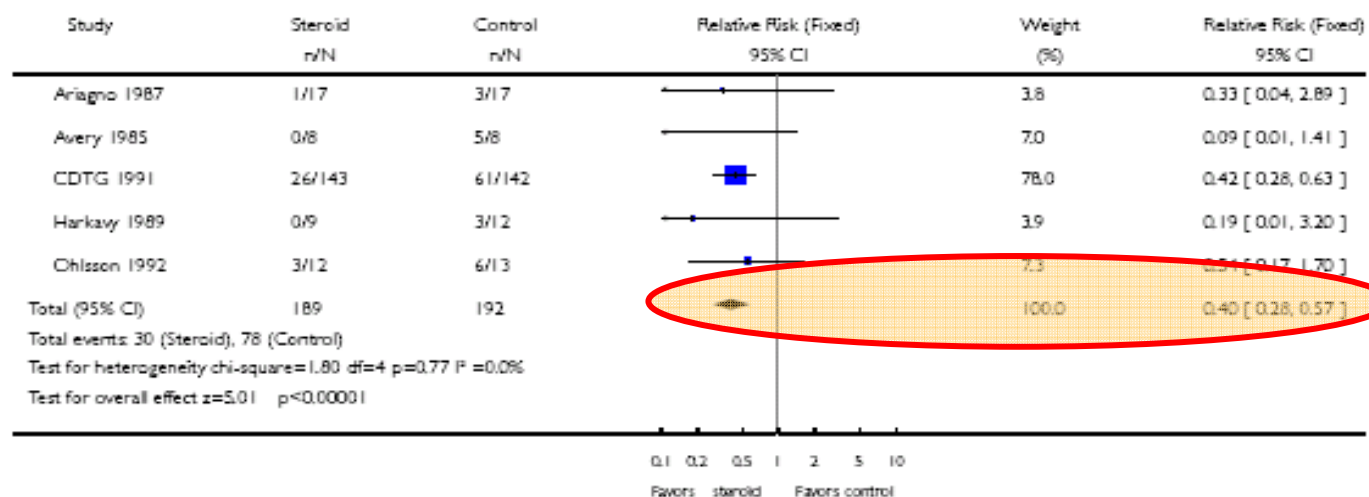


Analysis 02.02. Comparison 02 Chronic lung disease (CLD)/bronchopulmonary dysplasia (BPD), Outcome 02 Late rescue with corticosteroids

Review: Delayed (>3 weeks) postnatal corticosteroids for chronic lung disease in preterm infants

Comparison: 02 Chronic lung disease (CLD)/bronchopulmonary dysplasia (BPD)

Outcome: 02 Late rescue with corticosteroids

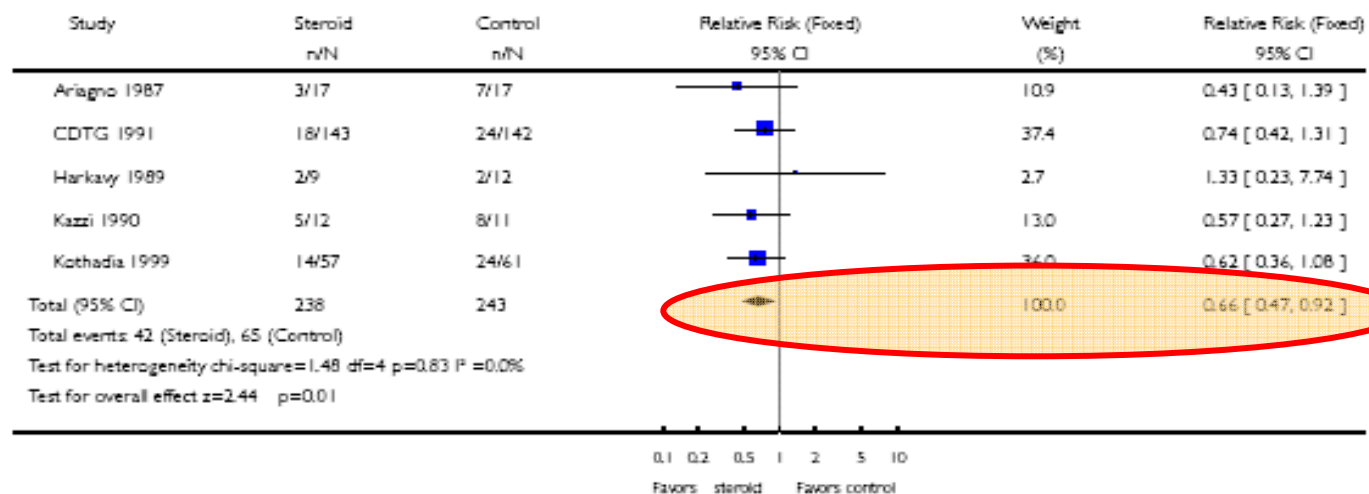


Analysis 02.03. Comparison 02 Chronic lung disease (CLD)/bronchopulmonary dysplasia (BPD), Outcome 03 Home on oxygen

Review: Delayed (>3 weeks) postnatal corticosteroids for chronic lung disease in preterm infants

Comparison: 02 Chronic lung disease (CLD)/bronchopulmonary dysplasia (BPD)

Outcome: 03 Home on oxygen

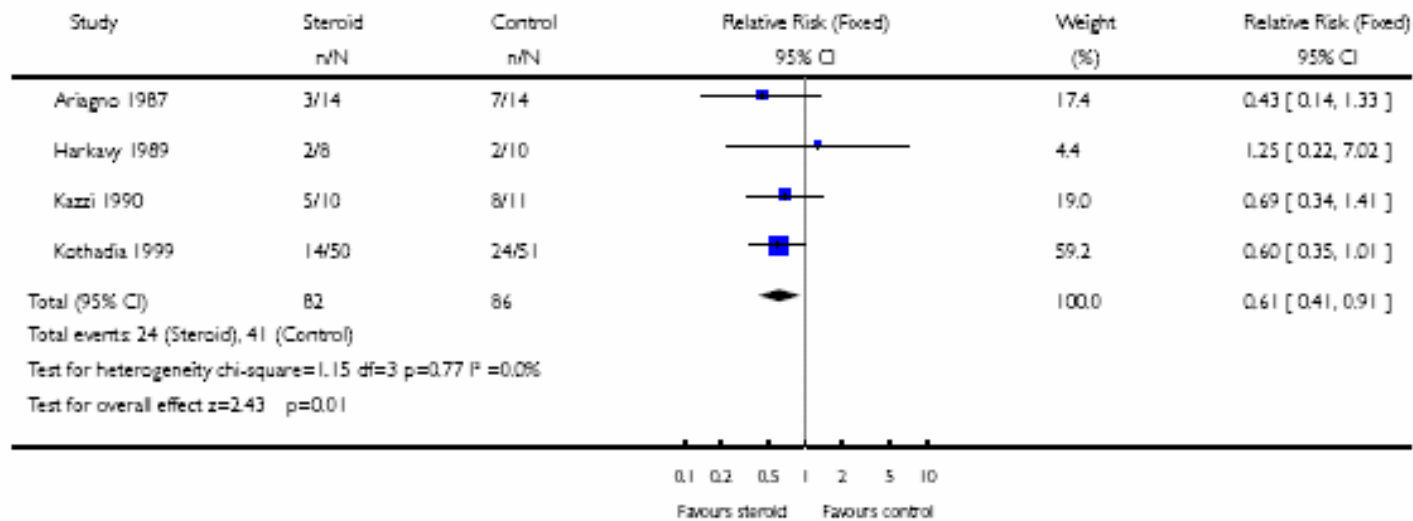


Analysis 02.04. Comparison 02 Chronic lung disease (CLD)/bronchopulmonary dysplasia (BPD), Outcome 04 Survivors discharged home on oxygen

Review: Delayed (>3 weeks) postnatal corticosteroids for chronic lung disease in preterm infants

Comparison: 02 Chronic lung disease (CLD)/bronchopulmonary dysplasia (BPD)

Outcome: 04 Survivors discharged home on oxygen

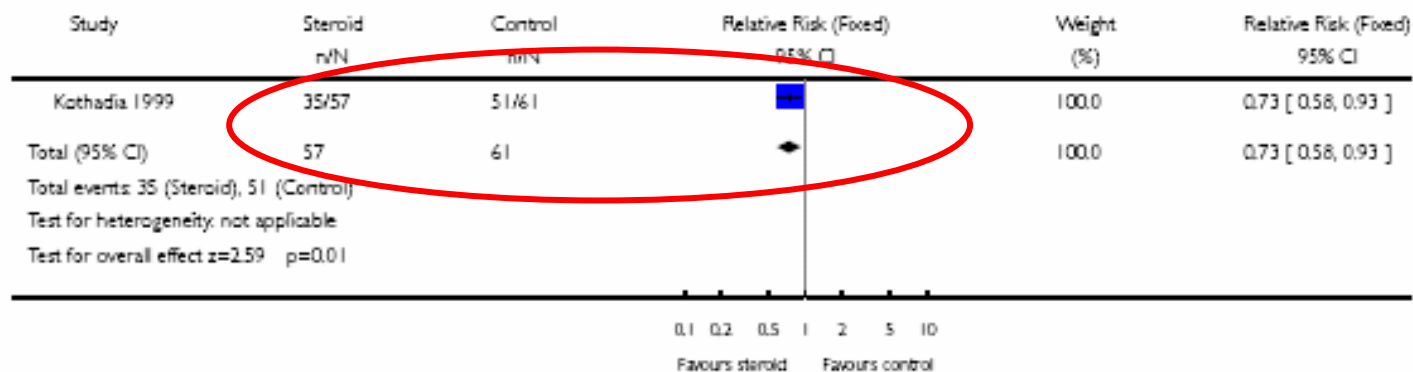


Analysis 03.01. Comparison 03 Death or CLD, Outcome 01 Death or CLD at 36 weeks

Review: Delayed (>3 weeks) postnatal corticosteroids for chronic lung disease in preterm infants

Comparison: 03 Death or CLD

Outcome: 01 Death or CLD at 36 weeks

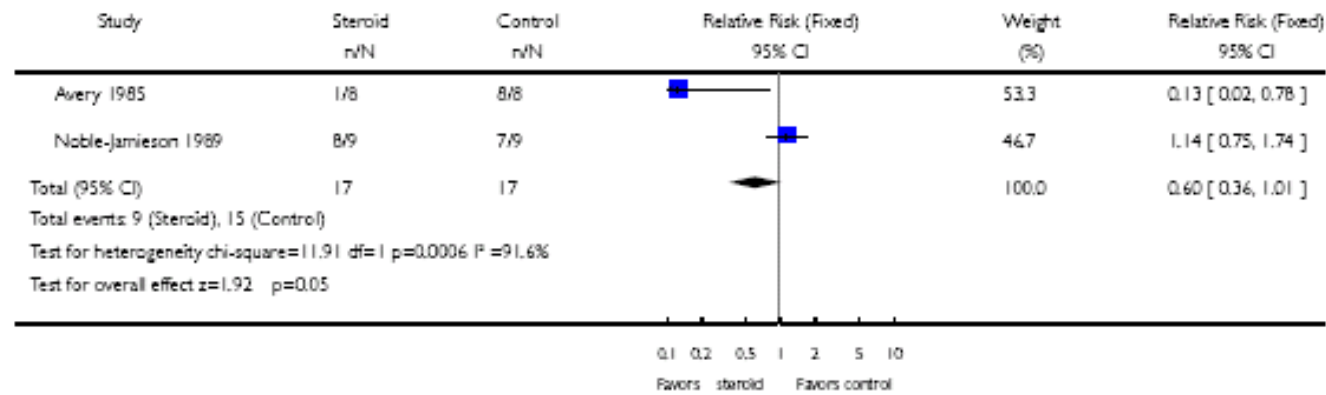


Analysis 04.01. Comparison 04 Failure to extubate, Outcome 01 Failure to extubate by 3rd day

Review: Delayed (>3 weeks) postnatal corticosteroids for chronic lung disease in preterm infants

Comparison: 04 Failure to extubate

Outcome: 01 Failure to extubate by 3rd day

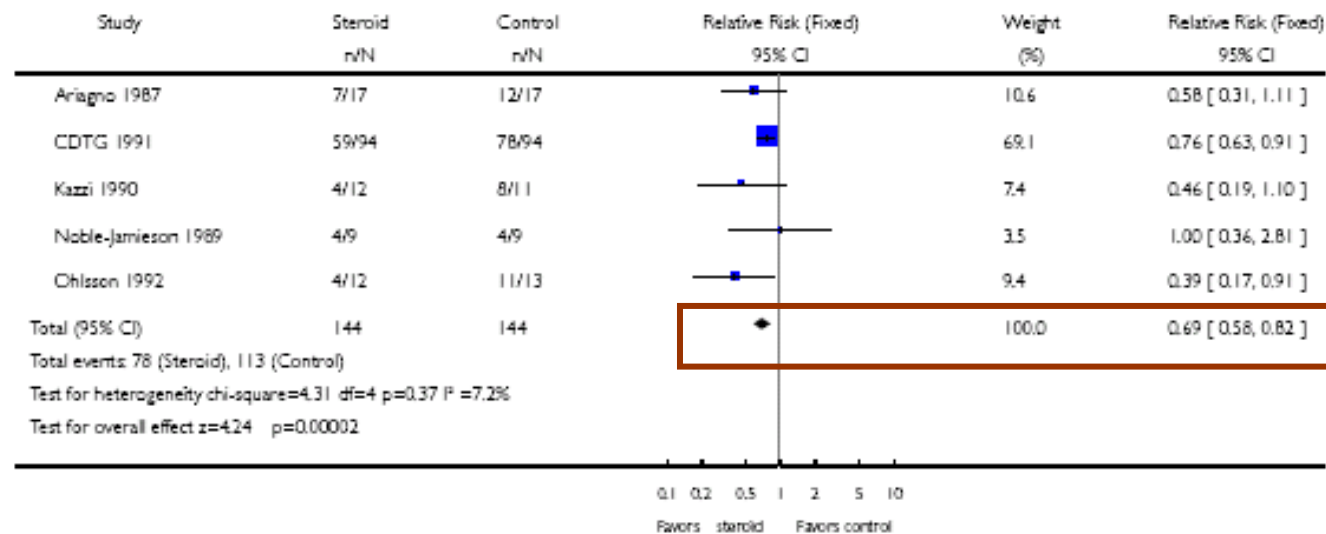


Analysis 04.02. Comparison 04 Failure to extubate, Outcome 02 Failure to extubate by 7th day

Review: Delayed (>3 weeks) postnatal corticosteroids for chronic lung disease in preterm infants

Comparison: 04 Failure to extubate

Outcome: 02 Failure to extubate by 7th day

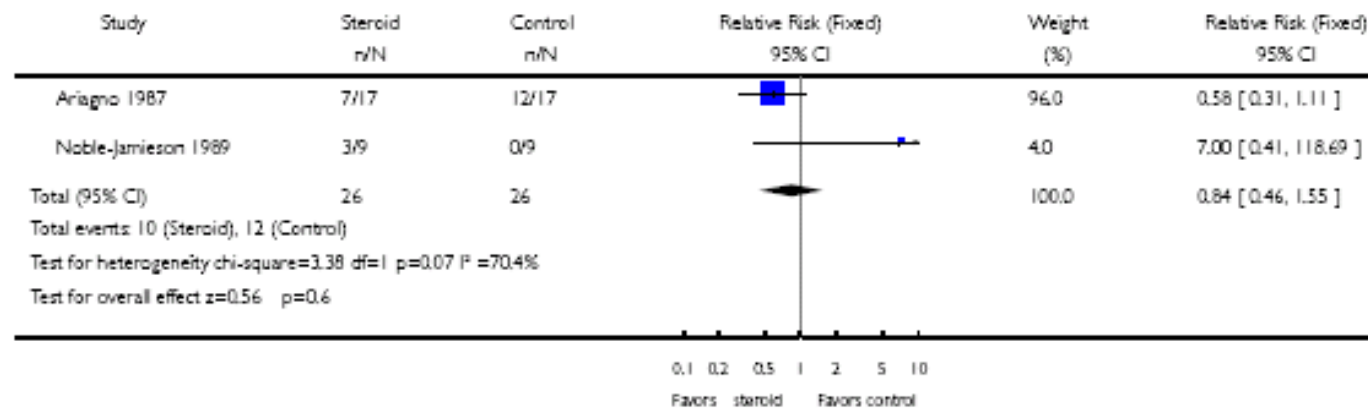


Analysis 04.03. Comparison 04 Failure to extubate, Outcome 03 Failure to extubate by 14th day

Review: Delayed (>3 weeks) postnatal corticosteroids for chronic lung disease in preterm infants

Comparison: 04 Failure to extubate

Outcome: 03 Failure to extubate by 14th day

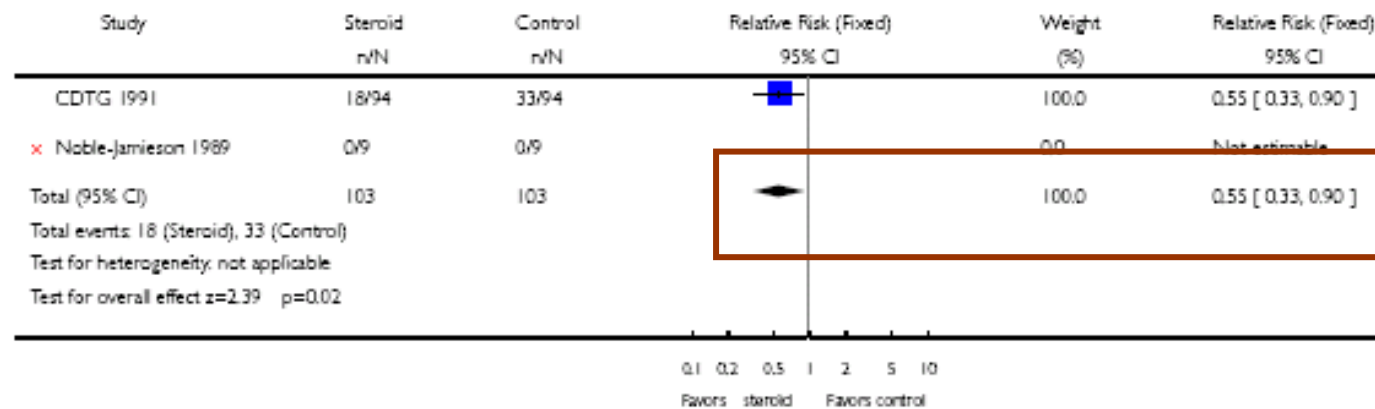


Analysis 04.04. Comparison 04 Failure to extubate, Outcome 04 Failure to extubate by 28th day

Review: Delayed (>3 weeks) postnatal corticosteroids for chronic lung disease in preterm infants

Comparison: 04 Failure to extubate

Outcome: 04 Failure to extubate by 28th day

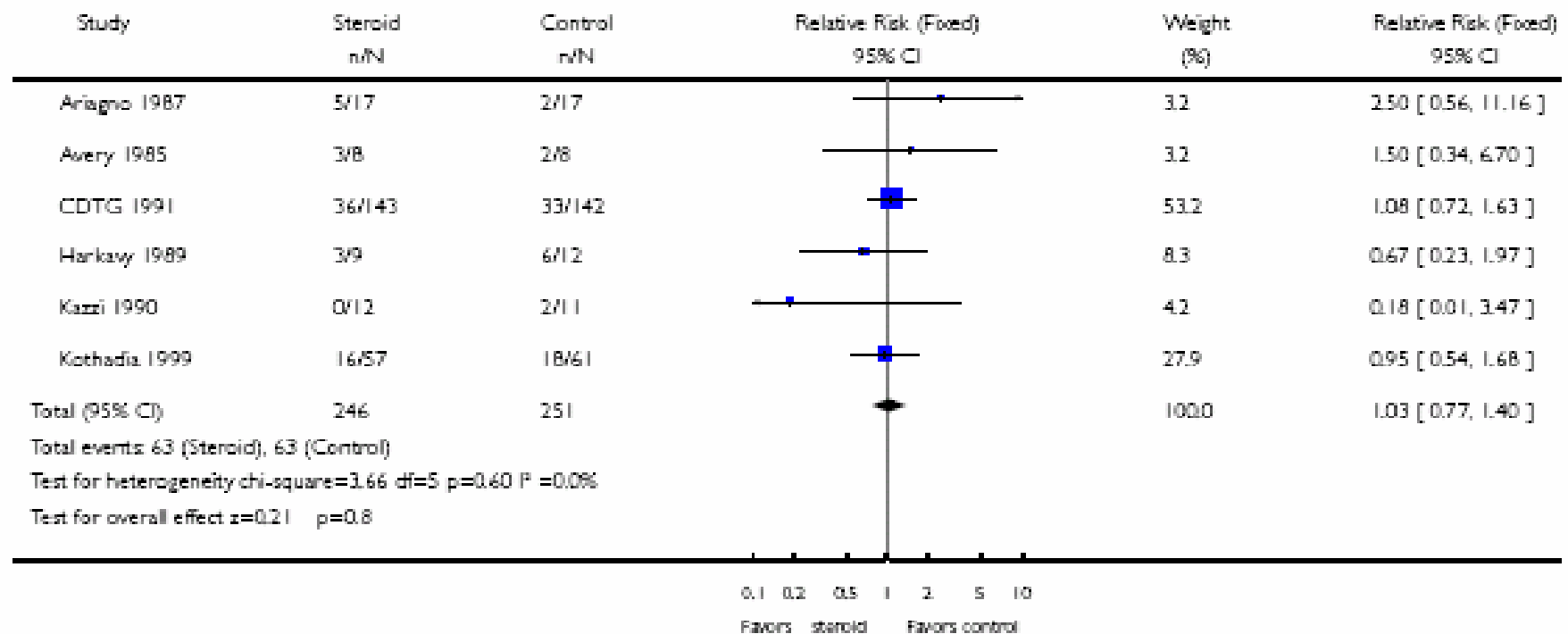


Analysis 05.01. Comparison 05 Complications during primary hospitalisation, Outcome 01 Infection

Review: Delayed (>3 weeks) postnatal corticosteroids for chronic lung disease in preterm infants

Comparison: 05 Complications during primary hospitalisation

Outcome: 01 Infection

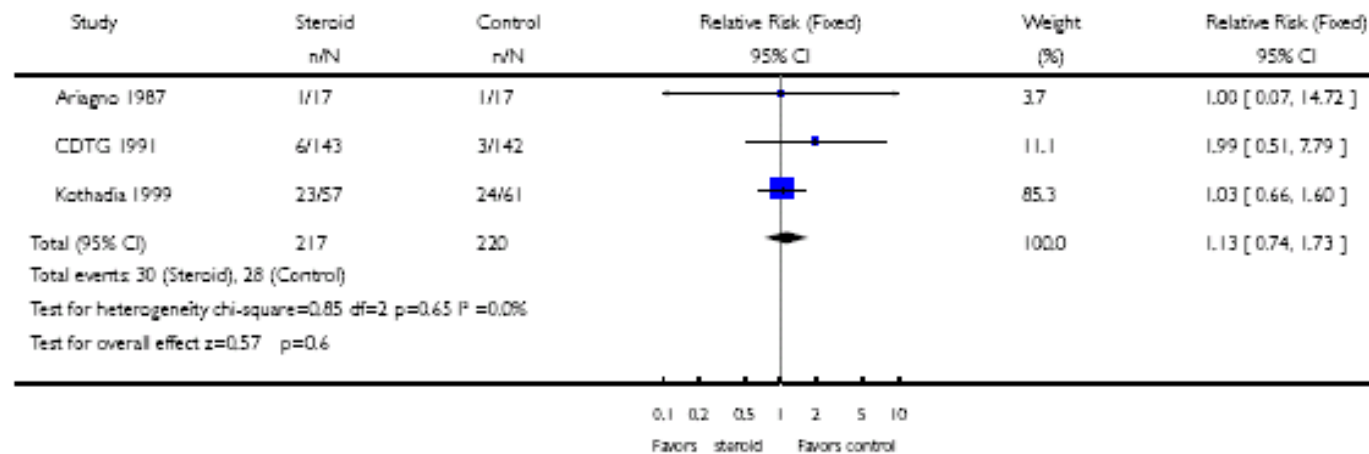


Analysis 05.07. Comparison 05 Complications during primary hospitalisation, Outcome 07 Gastrointestinal bleeding

Review: Delayed (>3 weeks) postnatal corticosteroids for chronic lung disease in preterm infants

Comparison: 05 Complications during primary hospitalisation

Outcome: 07 Gastrointestinal bleeding

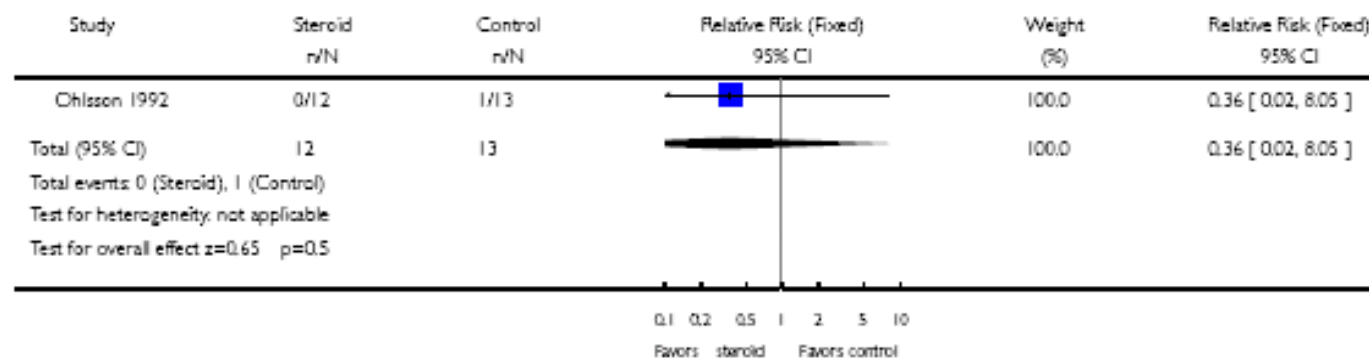


Analysis 05.08. Comparison 05 Complications during primary hospitalisation, Outcome 08 Intestinal perforation

Review: Delayed (>3 weeks) postnatal corticosteroids for chronic lung disease in preterm infants

Comparison: 05 Complications during primary hospitalisation

Outcome: 08 Intestinal perforation

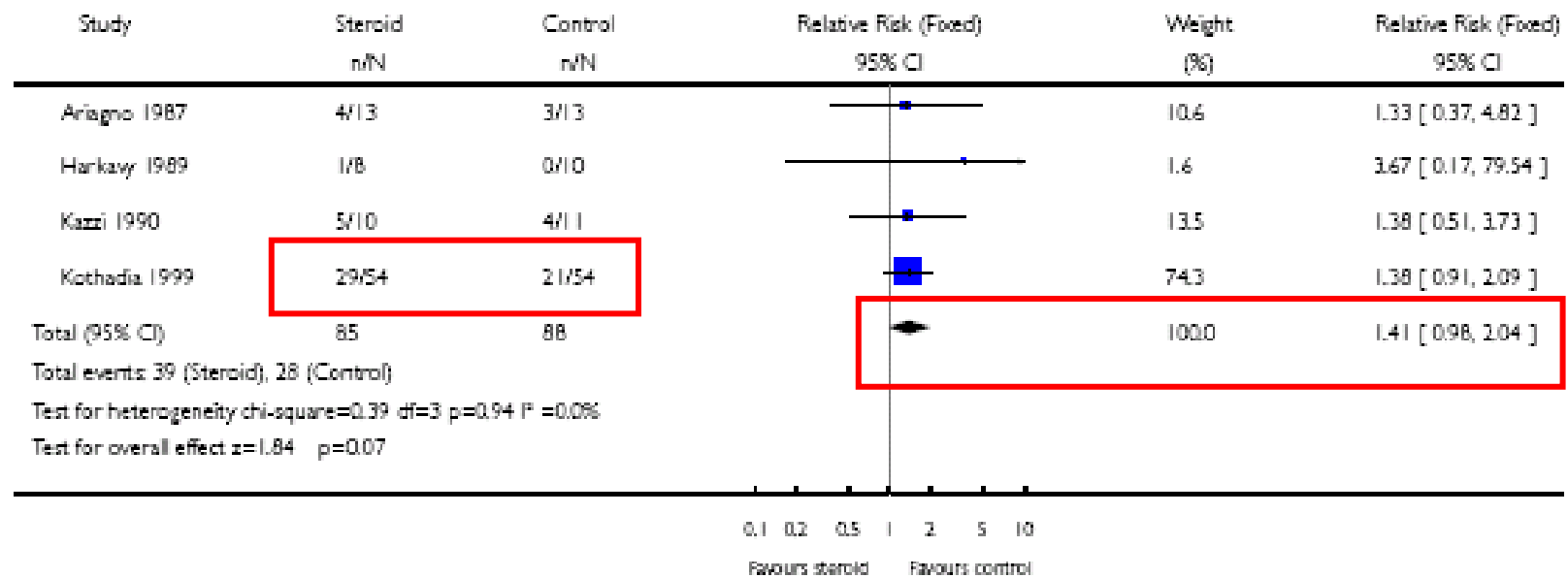


Analysis 05.10. Comparison 05 Complications during primary hospitalisation, Outcome 10 Severe ROP in survivors

Review: Delayed (>3 weeks) postnatal corticosteroids for chronic lung disease in preterm infants

Comparison: 05 Complications during primary hospitalisation

Outcome: 10 Severe ROP in survivors

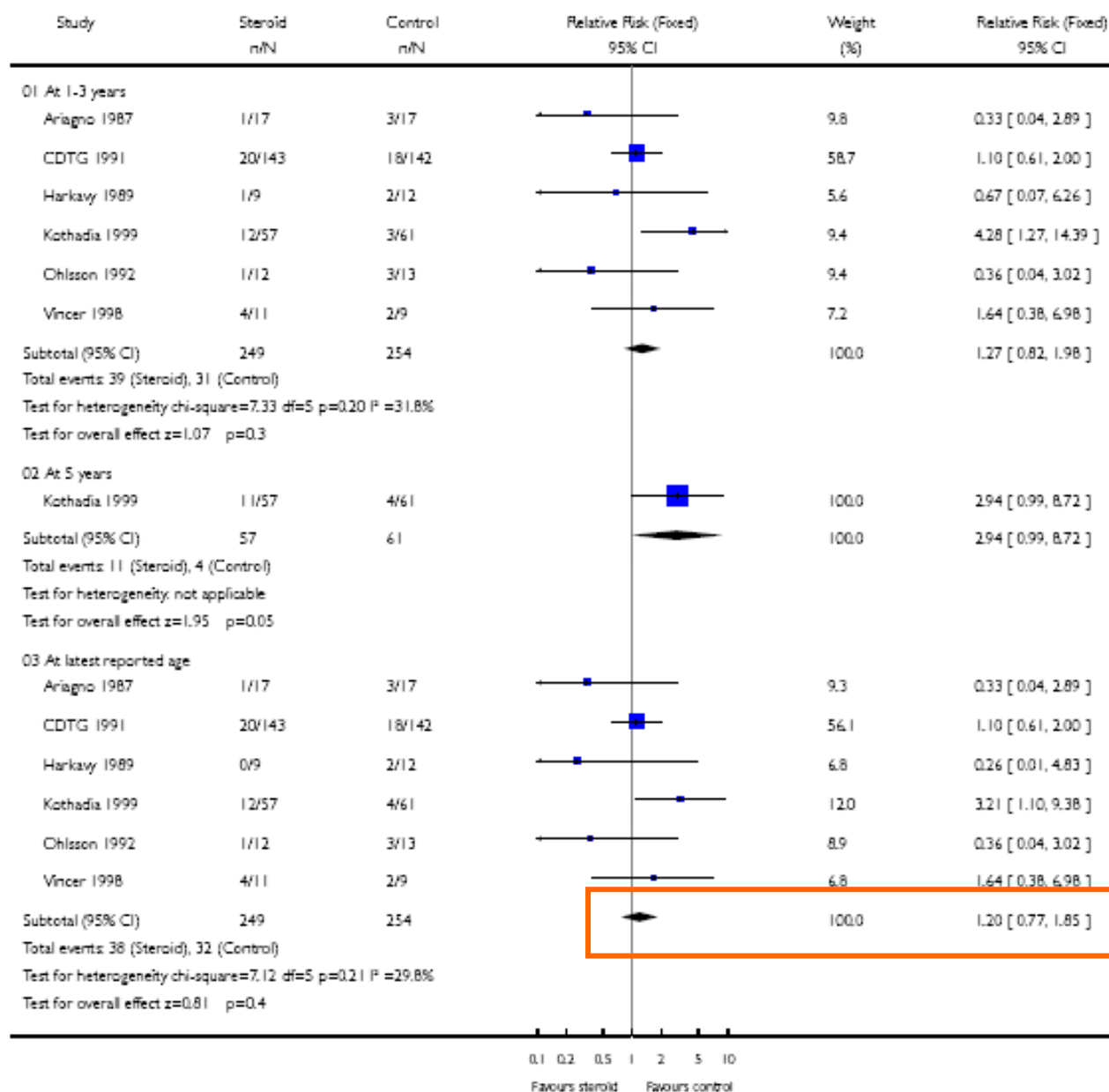


Analysis 06.09. Comparison 06 Long-term follow-up, Outcome 09 Cerebral palsy

Review: Delayed (>3 weeks) postnatal corticosteroids for chronic lung disease in preterm infants

Comparison: 06 Long-term follow-up

Outcome: 09 Cerebral palsy

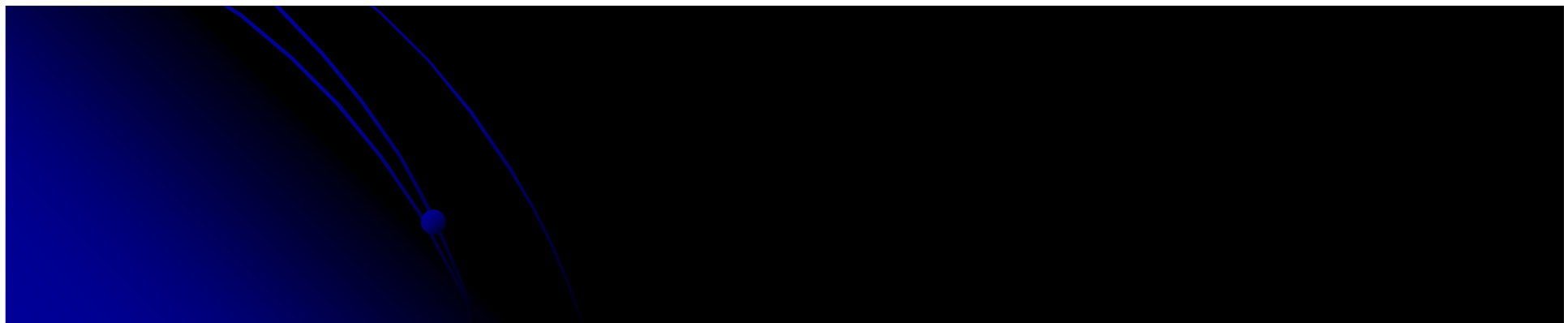
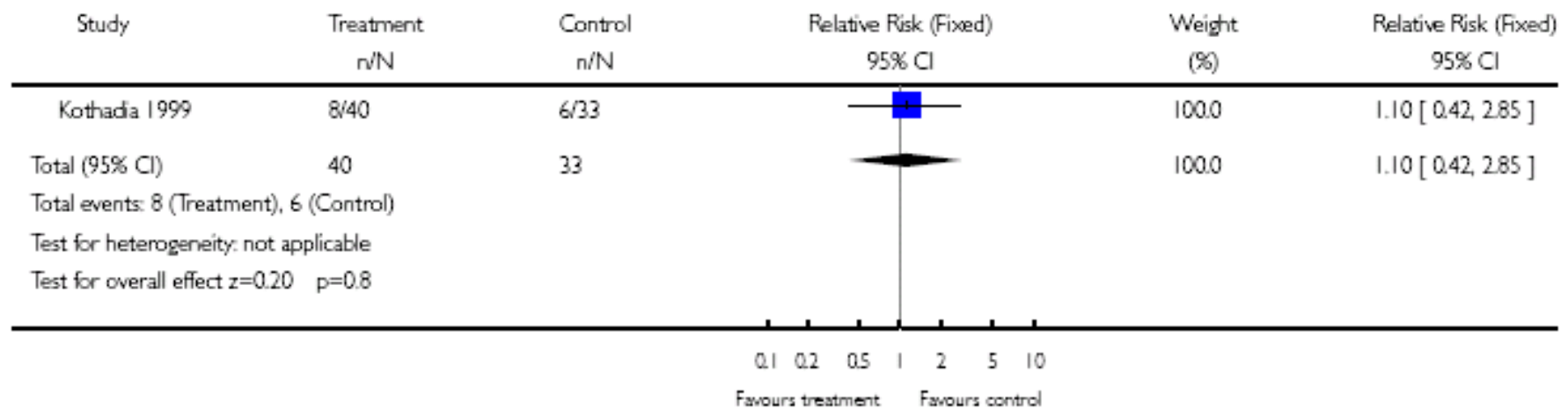


Analysis 07.05. Comparison 07 Later childhood outcomes, Outcome 05 Intellectual impairment in survivors tested at 5 years

Review: Delayed (>3 weeks) postnatal corticosteroids for chronic lung disease in preterm infants

Comparison: 07 Later childhood outcomes

Outcome: 05 Intellectual impairment in survivors tested at 5 years

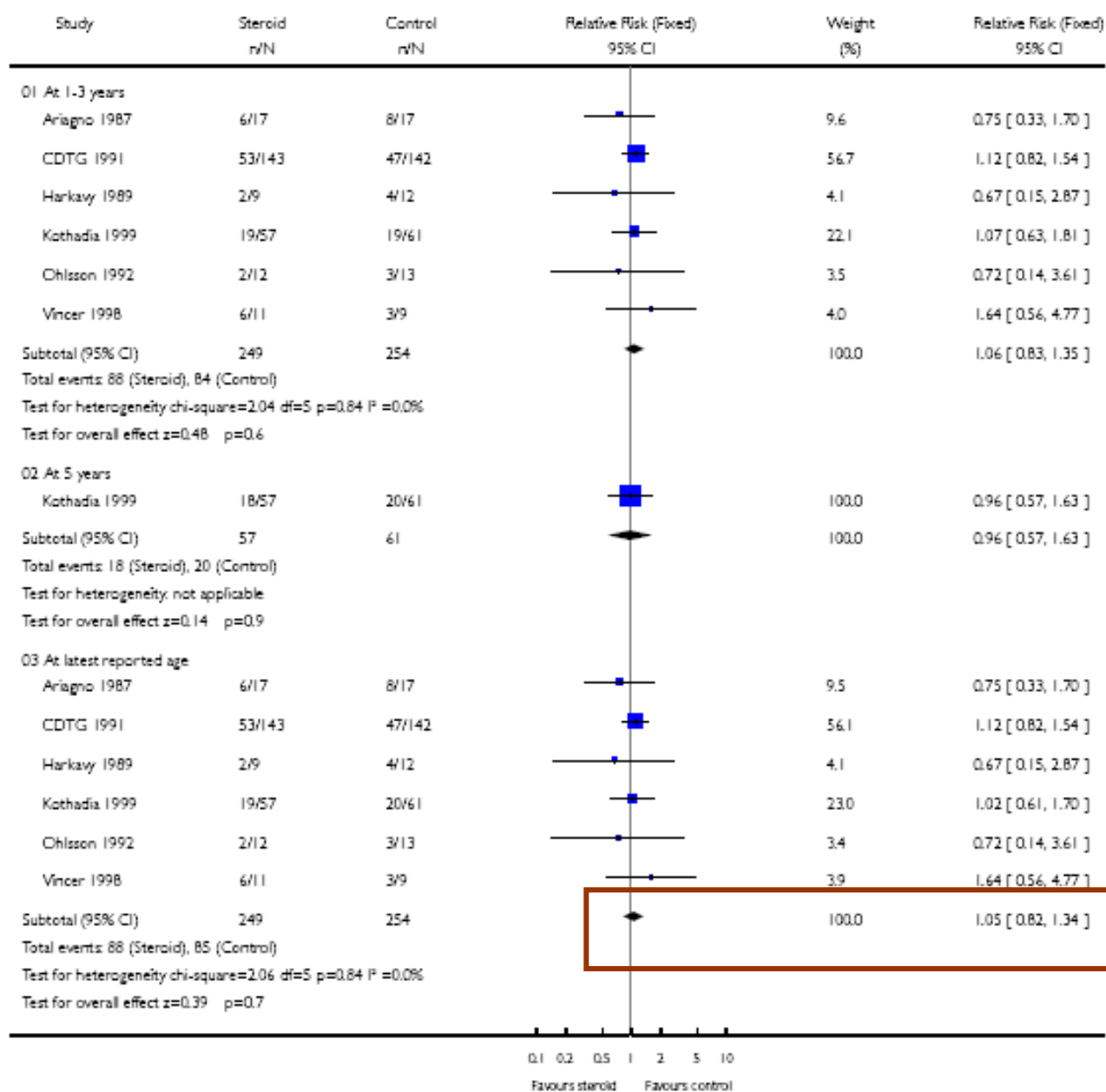


Analysis 06.11. Comparison 06 Long-term follow-up, Outcome 11 Death or cerebral palsy

Review: Delayed (>3 weeks) postnatal corticosteroids for chronic lung disease in preterm infants

Comparison: 06 Long-term follow-up

Outcome: 11 Death or cerebral palsy

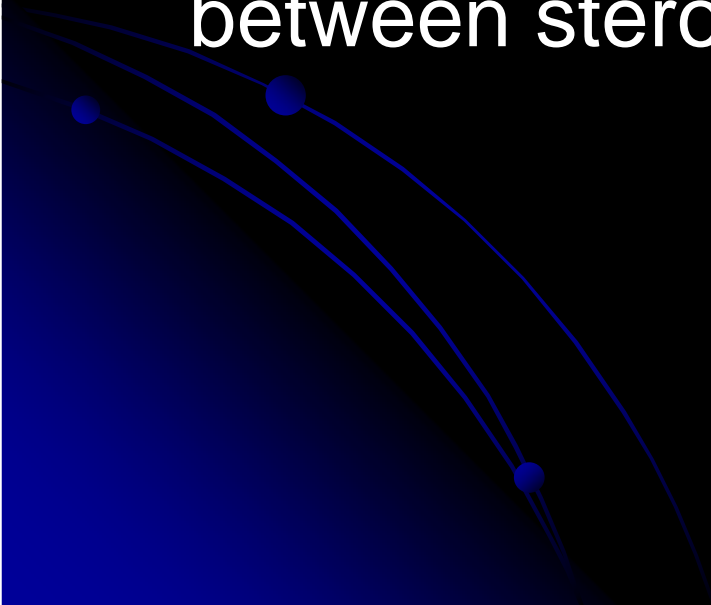


Main results

- Nine trials enrolling a total of 562 participants were eligible for this review.
- Delayed steroid treatment had **no significant effect on mortality**.
- Beneficial effects of delayed steroid treatment showed the **reductions** of :
 - failure to extubate by 7 or 28 days
 - chronic lung disease or death at 36 weeks
 - need for late rescue treatment with dexamethasone
 - discharge to home on oxygen therapy

Main results

- There was an increase in severe ROP
- The combined rate of death or cerebral palsy was not significantly different between steroid and control groups.



Implications for practice

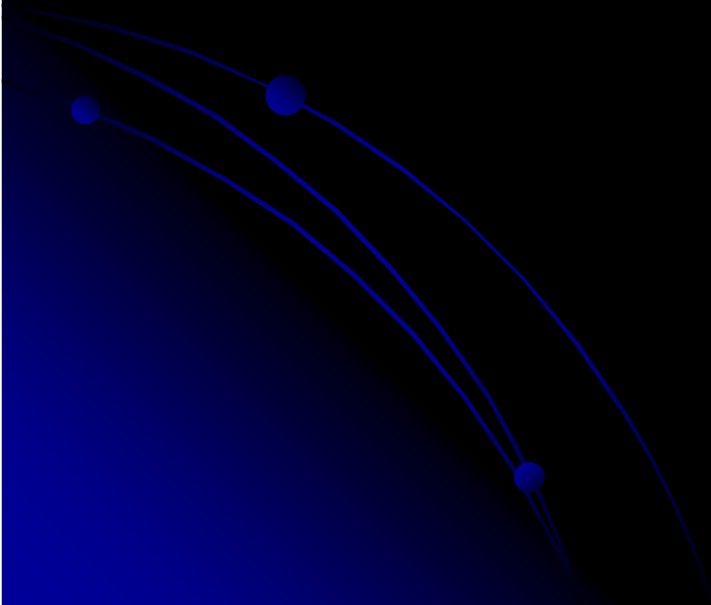
- The benefits of late corticosteroid therapy may **not** outweigh actual or potential adverse effects.
- This review of postnatal corticosteroid treatment for CLD initiated predominantly after three weeks of age suggests **that late or delayed therapy may not significantly increase the risk of adverse long-term neurodevelopmental outcomes.**

Implication in practice

- The long-term outcome is **limited** in some cases, the children have been assessed predominantly before school age, and no study has been sufficiently powered to detect important adverse **long-term neurosensory outcomes**.
- it appears prudent to **reserve the use of late corticosteroids** to infants who **cannot be weaned from mechanical ventilation**, and to minimise the dose and duration of any course of treatment

Applying on our patient

- 3+ m/o male baby under ventilator-dependent state
 - Postnatal dexamethasone use can be considered for our patient.



Auditing

- Studies are **needed to** examine the **lowest safe dose** of corticosteroid
- **More information on long-term outcome of infants is needed clearly.**
- New studies should be designed to assess the overall risks and benefits of corticosteroids, and be sufficiently powered to detect important adverse long-term **neurosensory sequelae.**

Thank you for your
attention

