

## Postnatal Corticosteroids – Is there a baby who might benefit?

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## Postnatal Systemic Corticosteroids

### Risks vs Benefits

Short-term

Long-term

## Postnatal Systemic Corticosteroids

- Respiratory Morbidity
- Mortality vs Morbidity
- DART study?



## Respiratory Morbidity

### Postnatal Corticosteroids (PCS) in the late 1990s

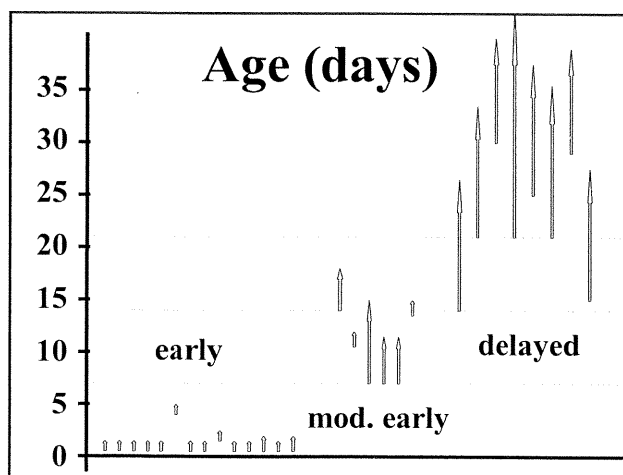
- increasingly prescribed
- clinical effect within 48-72 hours
- reduce ventilator dependence
- reduce BPD

## Respiratory Morbidity

Cochrane Library

Initially 3 reviews of postnatal  
corticosteroids

- early (<96 hours)
- moderately early (7-14 days)
- delayed (>3 weeks)



# Respiratory Morbidity

Cochrane Library

two reviews of postnatal corticosteroids

- early (<8 days)
- late (>7 days)

# Respiratory Morbidity

Three reviews of postnatal corticosteroids

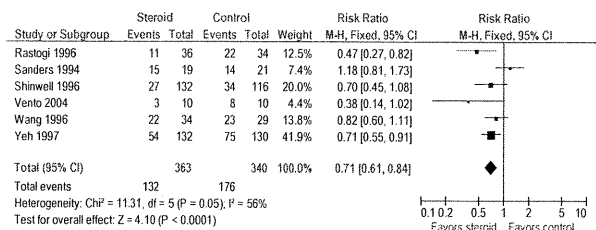
- hydrocortisone (all early) (Neonatology 2010;98:111-117)
- early Dex (<8 days) (Neonatology 2010;98:217-24)
- late Dex (>7 days) (Neonatology 2010;98:289-96)

## Three reviews

Review	N studies	N subjects
Hydrocortisone (all early)	8	880
Early Dex (<8 days)	20	2860
Late Dex (>7 days)	19	1345

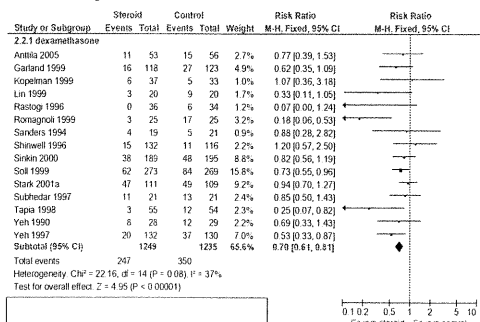
# Respiratory Morbidity

Early Dex – failure to extubate by day 7



# Respiratory Morbidity

Early Dex – BPD at 36 weeks



# Early Dexamethasone

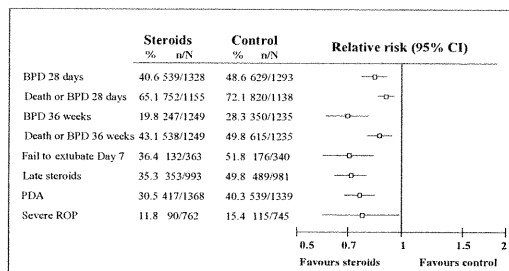
Mortality

28 days RR 1.06, 95% CI 0.90, 1.24  
Latest age RR 1.02, 95% CI 0.90, 1.17

(Neonatology 2010;98:217-24)

## Early Dexamethasone

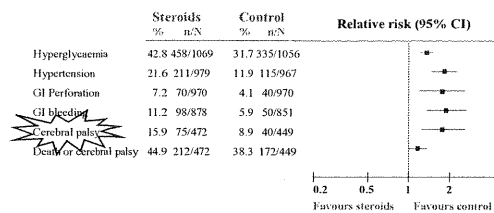
### Benefits



(Neonatology 2010;98:217-24)

## Early Dexamethasone

### Harms



(Neonatology 2010;98:217-24)

## Early Dexamethasone

### Conclusions

Benefits do not outweigh risks  
Not recommended for routine practice

(Neonatology 2010;98:217-24)

## Late Dexamethasone

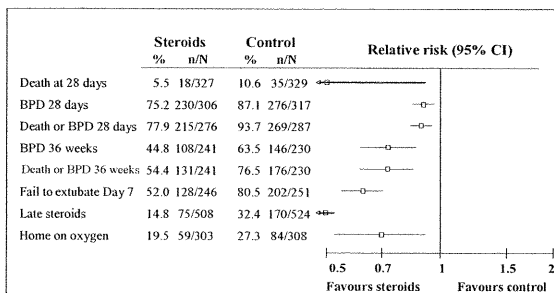
### Mortality

28 days RR 0.49, 95% CI 0.28, 0.85  
Latest age RR 0.87, 95% CI 0.67, 1.13

(Neonatology 2010;98:289-96)

## Late Dexamethasone

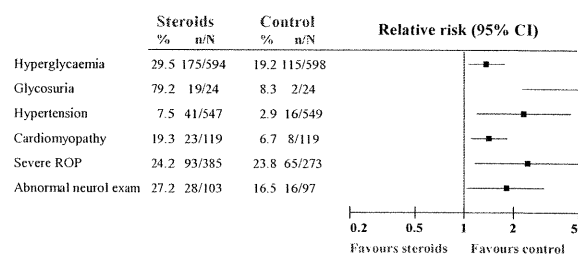
### Benefits



(Neonatology 2010;98:289-96)

## Late Dexamethasone

### Harms



(Neonatology 2010;98:289-96)

## Late Dexamethasone

### Cerebral palsy

Cerebral palsy RR 1.22, 95% CI 0.84, 1.77

Death or CP RR 0.98, 95% CI 0.80, 1.21

(Neonatology 2010;98:289-96)

## Late Dexamethasone

### Conclusions

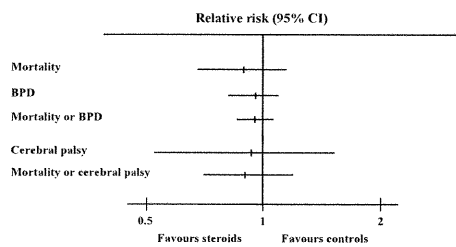
Benefits may not outweigh potential harms

Reserve for ventilator dependent babies

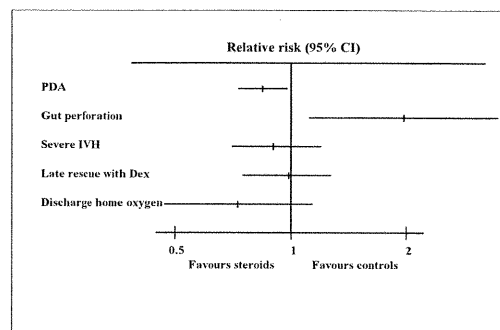
Minimise dose

(Neonatology 2010;98:289-96)

## Hydrocortisone - early



## Hydrocortisone - early



## Early Hydrocortisone

### Conclusions

Few effects in doses used

Not recommended to prevent BPD

(Neonatology 2010;98:289-96)

## Late Hydrocortisone

### Conclusions

No trials in chronically ventilator dependent infants

(Neonatology 2010;98:289-96)

## **Respiratory Morbidity**

### **- Conclusions**

Cochrane Library/other reviews

- reduce ventilator dependence
- reduce chronic lung disease

## **Respiratory Morbidity**

### **- Conclusions**

Short-term Risks

- hypertension
- hyperglycaemia
- cardiomyopathy
- intestinal haemorrhage
- intestinal perforation
- poor growth

## **Respiratory Morbidity**

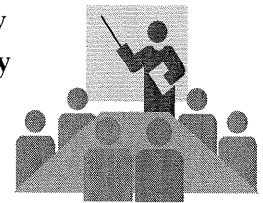
### **- Conclusions**

Long-term Risks

Increases cerebral palsy  
? Effect on mortality

## **Postnatal Systemic Corticosteroids**

- Respiratory Morbidity
- Mortality vs Morbidity
- DART study?

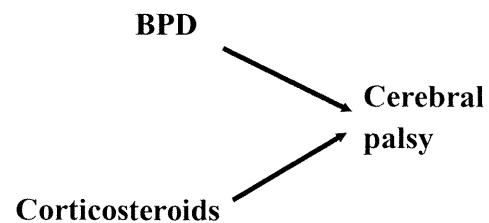


## **Competing risks**

Mortality vs Morbidity

1. Both are possible outcomes when considering treatment
2. Can't have neurosensory disability if don't survive!

## **Competing risks**



### **RCTs of postnatal corticosteroids**

**Interpretation difficult**

**Selection criteria**

- different baseline risk
- time and dose of steroids
- rate of open-label drug (“contamination rate”)

### **RCTs of postnatal corticosteroids**

**Follow-up**

- age of survivors
- follow-up rate
- assessed by experts

### **Aim**

**To review data on long-term effects of systemic corticosteroids**

(Pediatrics 2005; 115:655-66)

### **Eligibility**

• RCTs

- treatment or prevention of BPD
- Systemic postnatal corticosteroids
- Long-term mortality and morbidity data (cerebral palsy)

### **Data from RCTs**

1. BPD in control group (oxygen at 36 weeks)
2. Mortality at latest age
3. Cerebral palsy

### **Analyses**

- Meta-analysis
- Meta-regression
- Rate of combined outcome death or CP vs risk of BPD in control group

# Results

21 RCTs

9 "early"

12 "late"

1791 infants randomised

# Results

Dose DEX 3.4 mg/kg

Contamination 33%

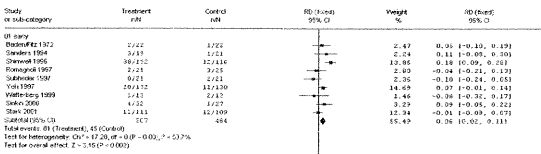
BPD 49%

Age follow-up < 2 years - 38%

Follow-up rate < 90% - 29%

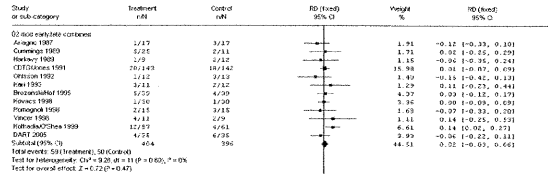
# Cerebral Palsy

Review: RCTs steroids with outcome data. ERD versus (with DART added)  
Comparison: 02 early steroids - randomised analysis combined  
Outcome: 01 CP in randomised



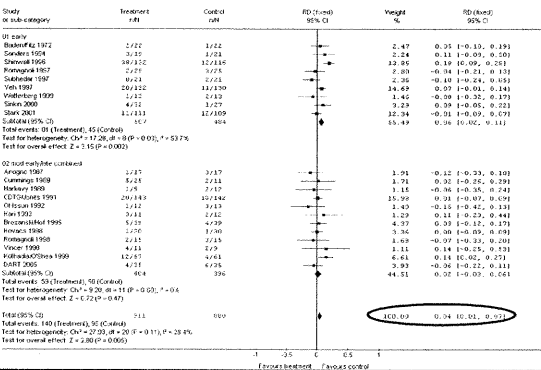
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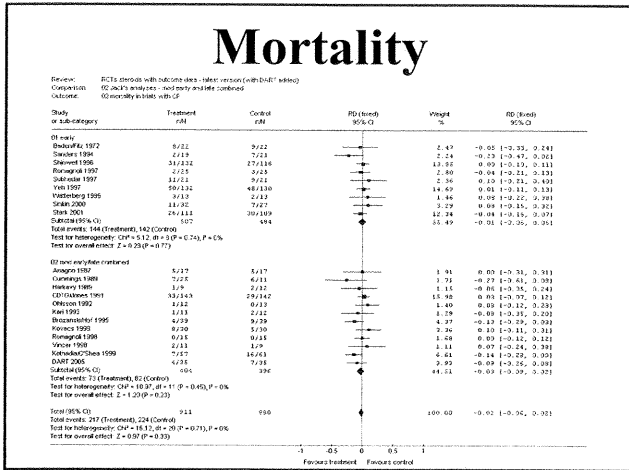
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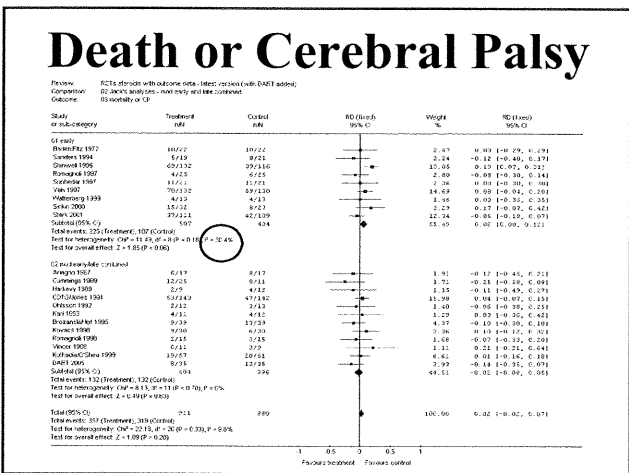
# Cerebral Palsy

Group	Steroids	Controls	ERD (95% CI)
Early	16.0%	9.3%	6% (2%, 11%); P=0.002
Later	14.6%	12.6%	2% (-3%, 6%); P=0.47
Total	15.4%	10.8%	4% (1%, 7%); P=0.005



## Mortality

Group	Steroids	Controls	ERD (95% CI)
Early	28.4%	29.3%	-1% (-6%, 5%); P=0.77
Later	18.1%	20.7%	-3% (-9%, 2%); P=0.23
Total	23.8%	25.5%	-2% (-6%, 2%); P=0.33



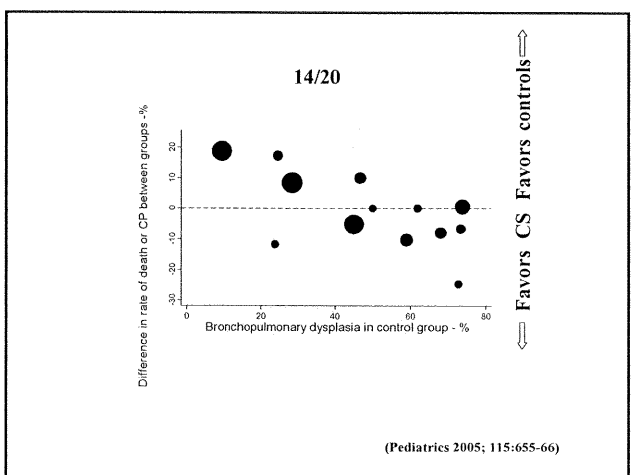
## Death or Cerebral Palsy

Group	Steroids	Controls	ERD (95% CI)
Early	44.4%	38.6%	6% (0%, 12%); P=0.06
Later	32.7%	33.3%	-2% (-8%, 5%); P=0.63
Total	39.2%	36.2%	2% (-2%, 7%); P=0.28

## Metaregression

Perhaps infants in 'early' studies had different baseline risk to infants in 'later' studies.

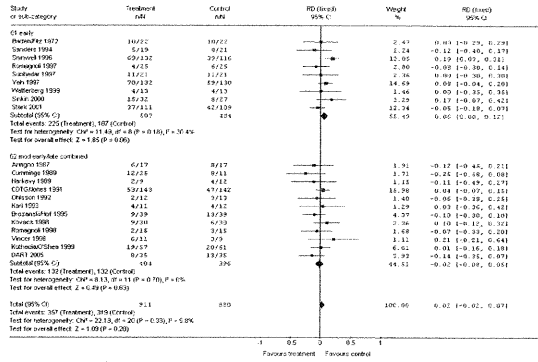
Regress difference in rate of death or CP (y-axis) against risk of BPD in control group (x-axis)



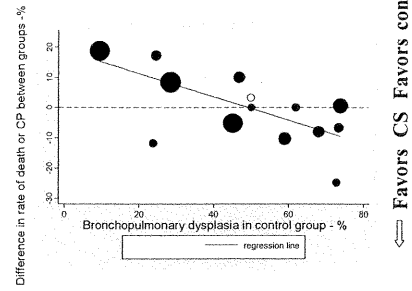


# Death or Cerebral Palsy

Review: RCTs (studies with outcome data, latest version (with DART added))  
 Comparison: 02: corticosteroids - most likely vs late control  
 Outcome: 03: mortality or CP

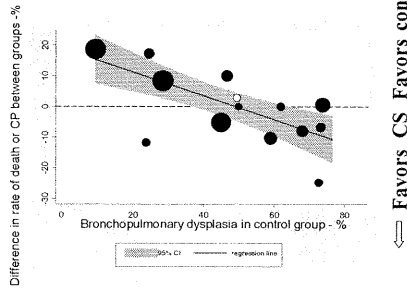


## Fit regression line



(Pediatrics 2005; 115:655-66)

$$y = 18.989 - 0.386x \quad x = 49.2\% \text{ when } y = 0$$



(Pediatrics 2005; 115:655-66)

# Mortality vs Morbidity - Conclusions (1)

Adverse long-term effects of corticosteroids mostly in RCTs starting in first week of life

Effect of postnatal corticosteroids on death + cerebral palsy varies with risk of BPD

# Mortality vs Morbidity - Conclusions (2)

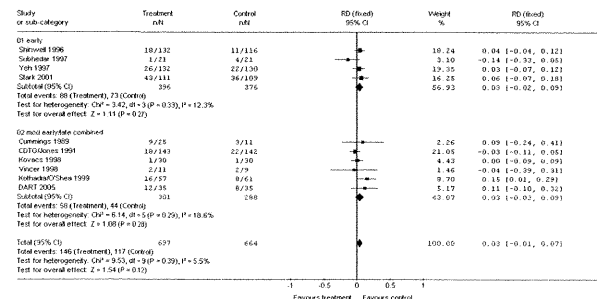
Return to the high rates of postnatal corticosteroids of the late 1990s?

No!

- effect on function?

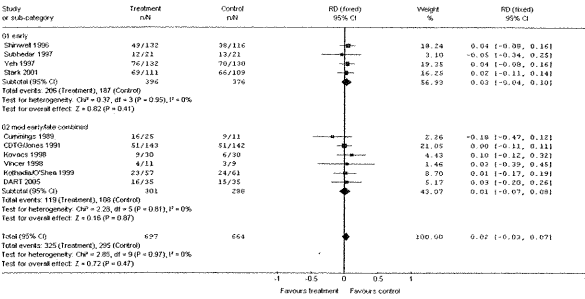
# Major Disability

Review: RCTs (studies with outcome data, latest version (with DART added))  
 Comparison: 02: corticosteroids - most likely vs late control  
 Outcome: 05: major disability (handicapped)



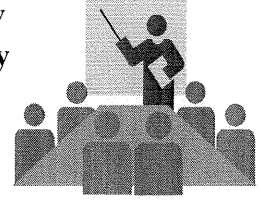
# Death or Major Disability

Review: RCTs steroids with outcome data; latest version (with DART added)  
 Comparison: 02: dact's analyses - mod early and late combined  
 Outcome: 02: mortality or major disability



# Postnatal Systemic Corticosteroids

- Respiratory Morbidity
- Mortality vs Morbidity
- DART study?



# Aims



Does low-dose dexamethasone reduce ventilator dependence without adversely affecting survival free of major disability?

# Eligibility



- Birthweight < 1000 g, or gestational age < 28 weeks
- age 7+ days
- ventilator dependent
- clinicians consider steroids

# Exclusions



- few
- major chromosomal anomaly
  - structural defect of CNS (not CVH or PVL)

# Allocation

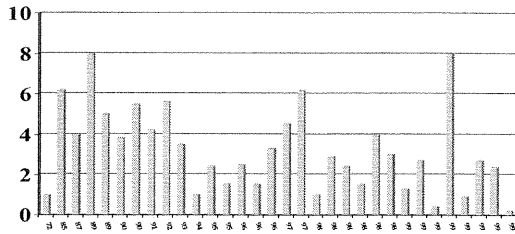


Randomized  
 Within centres  
 Blocks of size 4 to 8

## Dose?



Dexamethasone equivalent mg/kg/total



## Dexamethasone



Dose

Days 1-3 0.15 mg/kg/day

Days 4-6 0.10 mg/kg/day

Days 7-8 0.05 mg/kg/day

Days 9-10 0.02 mg/kg/day

total 0.89 mg/kg

Sulphite-free

## Outcomes

### - Short-term



Survival

Duration of intubation, O<sub>2</sub>

FiO<sub>2</sub> @ 36 weeks = BPD

Growth

Complications - gut, BP, glucose

## Outcomes

### - Long-term



Two years of age

• Cerebral palsy

• Blindness

• Deafness

• Developmental delay

(Bayley MDI - DQ)

## Sample size



Survival free of major disability

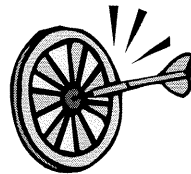
- Victoria 1991-92 - 56%

- Estimated 60%

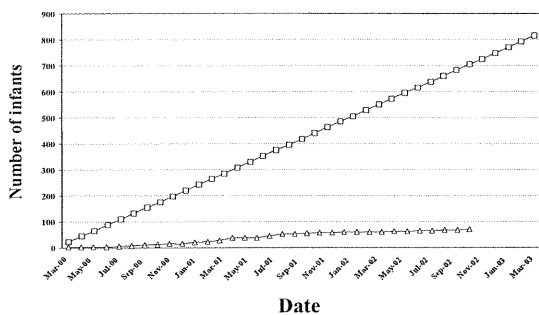
- Absolute difference 10%

- n = 407 each group, 814 total

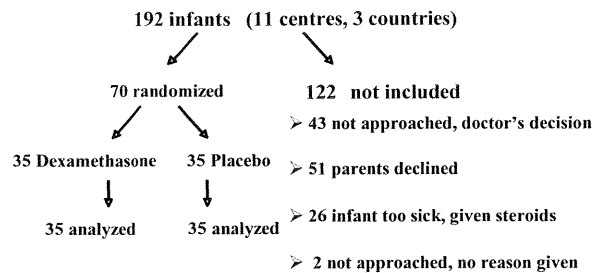
## What Happened?



## DART recruitment



## DART study



## DART study

Study ceased recruitment October 2002

N=70

Other aspects of the study continued

- Short-term outcomes
- Long-term outcomes

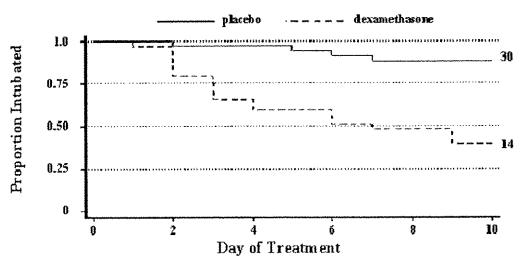
## DART study

	DEX	Control
Birthweight – g	652	700
Gestational age – weeks	24	25
Postnatal age – days	23	22
Inspired oxygen concentration %	47	45
Mean airway pressure – cm H <sub>2</sub> O	10	10

## DART study

### Extubation

Figure 1. Survival curve of time to extubation



## DART study

	Dex	placebo
Failure to extubate	40%	89%
Death	11%	20%
BPD	80%	83%
Death or BPD	86%	91%

# DART study

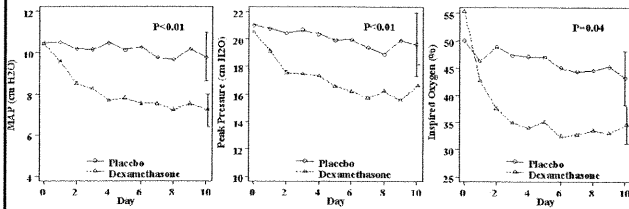


## Ventilation and Oxygen

MAP

Peak

FiO<sub>2</sub>



# DART study



- no differences in growth, blood pressure, or blood glucose
- no gastrointestinal haemorrhage or perforation
- 1 infant cardiac hypertrophy control

# DART study



## Short-term conclusions

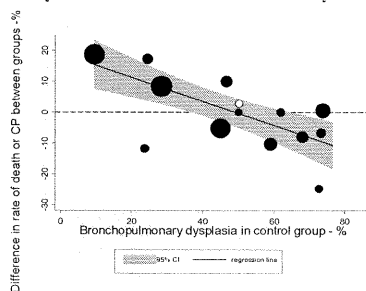
- low dose dexamethasone to chronically ventilator-dependent infants facilitates extubation and improves lung function
- no acute complications
- long term effects?

# Long-term Incomplete



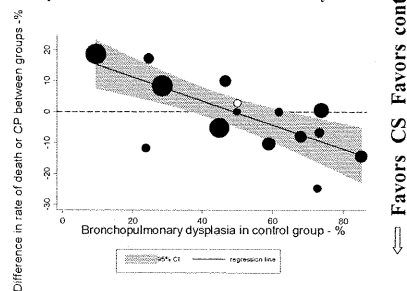
	Dex	placebo
Death	11%	20%
Assessed	28/31	26/28
Cerebral palsy	11%	17%
Death or CP	23%	37%
RD death or CP	-14% (-35%, 7%)	

$$y = 18.989 - 0.386x \quad x = 49.2\% \text{ when } y = 0$$



Pediatrics 2005; 115:655-66

$$y = 19.003 - 0.385x \quad x = 49.4\% \text{ when } y = 0$$



## **DART study**



### **Long-term conclusions**

- **From DART study alone - inconclusive**
- **Collectively - Low dose dexamethasone to chronically ventilator-dependent infants at high risk for BPD may reduce the combined rate of death or cerebral palsy**
- **Overall evidence still not conclusive**