Evidence based methods of facilitating extubation

Peter Davis
for
Kristin Ferguson, Calum Roberts and Brett Manley
The Royal Women's Hospital,
Melbourne, Australia

Why bother?

- For us (and perhaps parents)*
  - Extubation in common
  - Failed extubation is stressful
- For babies
  - Prolonged extubation is harmful???
    - Stressful
    - Increased risk of sepsis/pneumonia
    - Damage to the airway

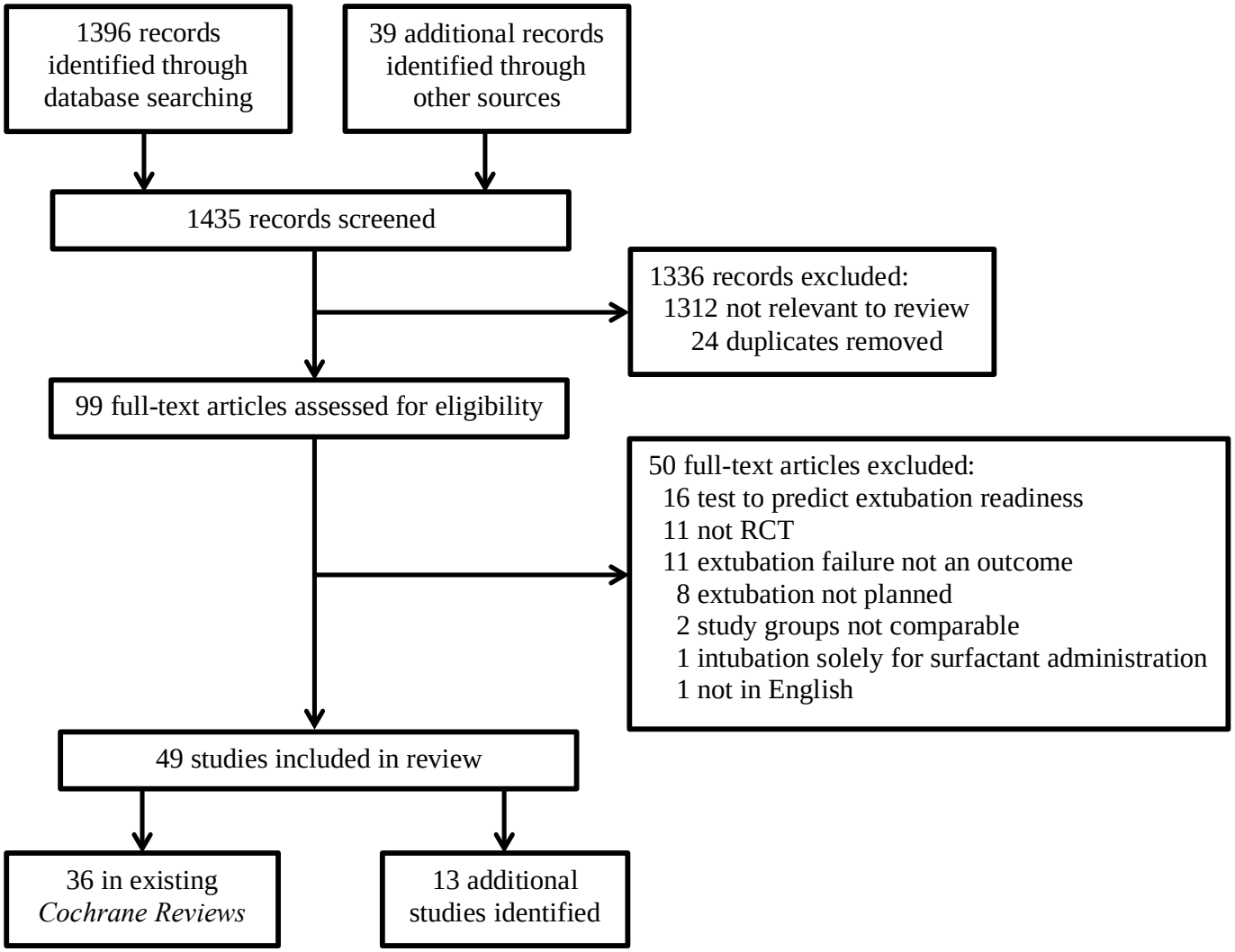
Methods

- Search of PubMed and *The Cochrane Library*
- Primary outcome: extubation failure, either
  1. Treatment failure with 7 days; OR
  2. Re-intubation within 7 days.
- Inclusion criteria:
  1. Participants were preterm infants; AND
  2. One or both primary outcomes reported.

Search strategy

- (Infant, Premature[Mesh] OR Infant, Low birth weight[Mesh] OR Infant, Newborn[Mesh]) AND (Airway Extubation[Mesh] OR Intubation, Intratracheal[Mesh] OR Ventilator Weaning[Mesh]) AND (Randomized Controlled Trial [Publication Type] OR Letter [Publication Type] OR Review [Publication Type] OR Clinical Trial [Publication Type] OR Evaluation Studies OR Comparative Study [Publication Type]).

Results


1396 records identified through database searching
39 additional records identified through other sources
1435 records screened
1336 records excluded:
1312 not relevant to review
24 duplicates removed
99 full-text articles assessed for eligibility
50 full-text articles excluded:
16 test to predict extubation readiness
11 not RCT
11 extubation failure not an outcome
8 extubation not planned
2 study groups not comparable
1 intubation solely for surfactant administration
1 not in English
49 studies included in review
36 in existing Cochrane Reviews
13 additional studies identified

Available therapies

- NCPAP
- NIPPV
- High flow nasal cannulae
- Methylxanthines
- Dexamethasone
- Doxapram
- Physiotherapy

CPAP

Rationale

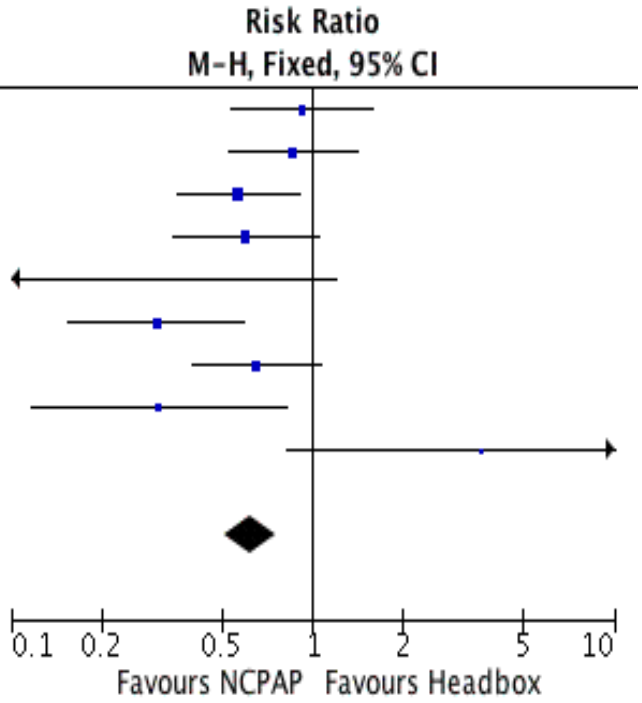
- CPAP
  - Stabilises upper airway
  - Preserves FRC
  - Reduces apnea
  - Improves oxygenation
  - Reduces work of breathing

CPAP vs. Headbox oxygen
Outcome: Extubation Failure

Study or Subgroup	NCPAP Events	NCPAP Total	Headbox Events	Headbox Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Annibale 1994	15	40	17	42	10.4%	0.93 [0.54, 1.59]
Chan 1993	19	60	22	60	13.8%	0.86 [0.52, 1.42]
Davis 1998	16	47	27	45	17.3%	0.57 [0.36, 0.90]
Dimitriou 2000	15	75	25	75	15.6%	0.60 [0.34, 1.04]
Engelke 1982	0	9	6	9	4.1%	0.08 [0.00, 1.19]
Higgins 1991	7	29	23	29	14.4%	0.30 [0.16, 0.60]
Peake 2005	16	49	24	48	15.2%	0.65 [0.40, 1.07]
So 1995	4	25	13	25	8.1%	0.31 [0.12, 0.81]
Tapia 1995	7	29	2	30	1.2%	3.62 [0.82, 16.01]
Total (95% CI)		**363**		**363**	**100.0%**	**0.62 [0.51, 0.76]**
Total events	99		159			

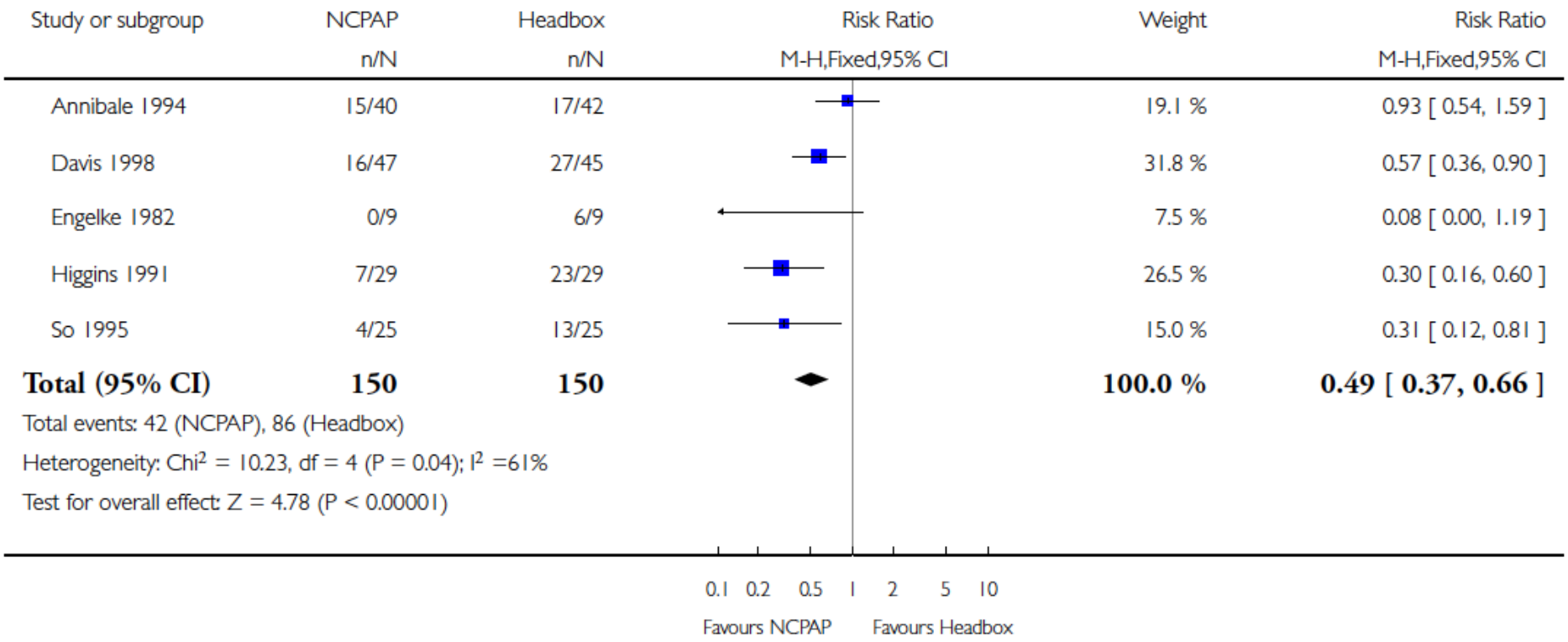
Heterogeneity: $Chi^2 = 17.93$, df = 8 (P = 0.02); $I^2 = 55\%$

Test for overall effect: Z = 4.58 (P < 0.00001)

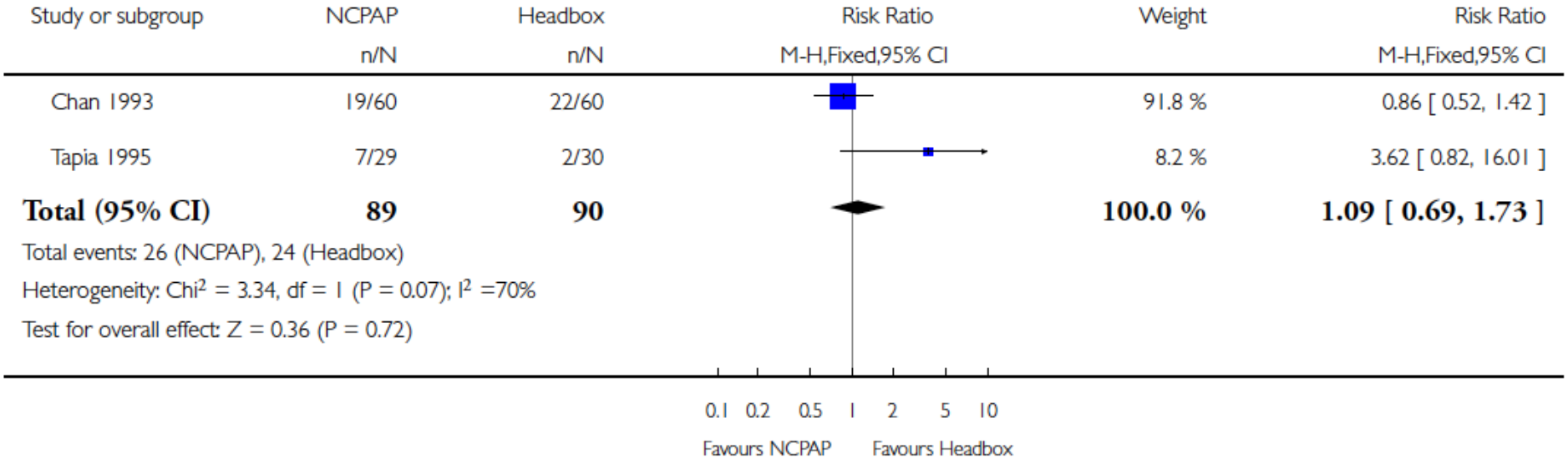


NNT = 6 (4, 10)

CPAP ≥5 cm water



CPAP <5 cm water



CPAP pressure source

- Bubbly bottle vs Ventilator: no difference (Yadav, 2012)
  - n=32
- Variable flow vs Ventilator: no difference (Stefanescu, 2003)
  - n=162
- Variable flow vs Bubbly bottle: no difference (Gupta, 2009)
  - n=140

CPAP level

- 7-9 cm better than 4-6 cm (Buzzella, 2014)
  - N=93
  - 24% vs 43% failure [borderline RR 0.56 (0.30, 1.04)]
  - 30% vs 51% reintubation [RR 0.62 (0.51, 0.76)]
  - No pneumothoraces within 96 hrs

CPAP interface

- Double prongs are better than single prongs (Davis, 2001)
  - N=87
  - RR 0.43 (0.24, 0.78)
- Nasal masks may be better than bi-nasal prongs (Keiran, 2012)
  - N=63
  - 3 days: RR 0.40 (0.16, 0.98)
  - 7 days: RR 0.81 (0.51, 1.29)

My best guess

- CPAP is better than supplemental oxygen alone
- Pressures should be at least 5 cm water (?higher)
- Bubbly bottle is probably as good as any other pressure generator
- Short double prongs or nasal masks are the most appropriate interface

NIPPV

NIPPV

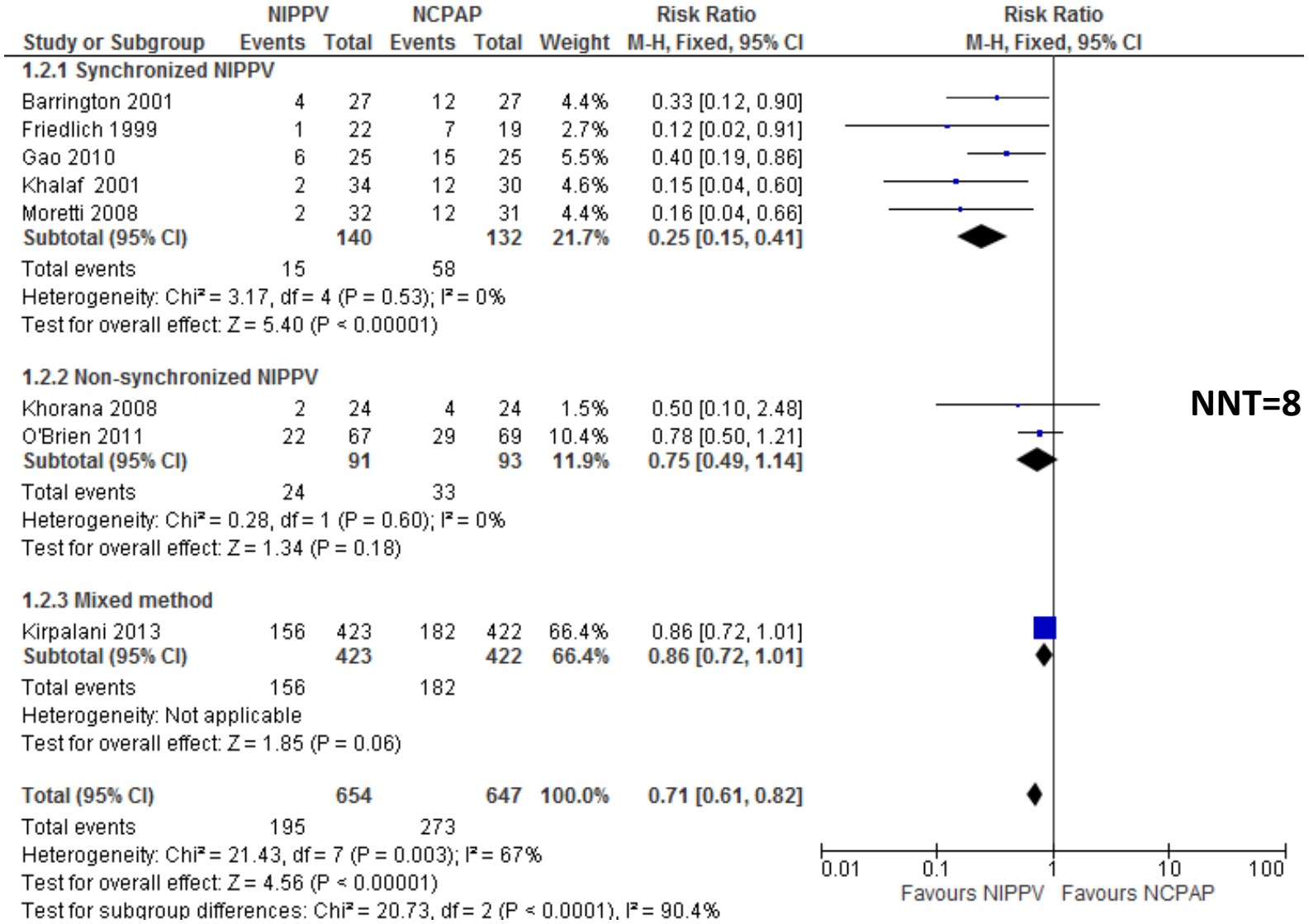
- Intermittent inflations superimposed on a background of CPAP
- Widely used since 1980s
- Questions about gastric perforation
- Impact of synchronisation (Infant Star/Graseby Capsule)

NIPPV

- Terminology
  - Cycling
  - CPAP+BUR= back up rate
  - SNIPPV = synchronised NIPPV
  - NV = nasal ventilation
  - N-SIMV = nasal synchronised IMV
  - N-IMV = nasal IMV
  - N-BiPAP = nasal bipap
  - NI-PSV = non-invasive pressure support ventilation
- Types
  - Synchronised or non-synchronised
  - High pressure or low pressure

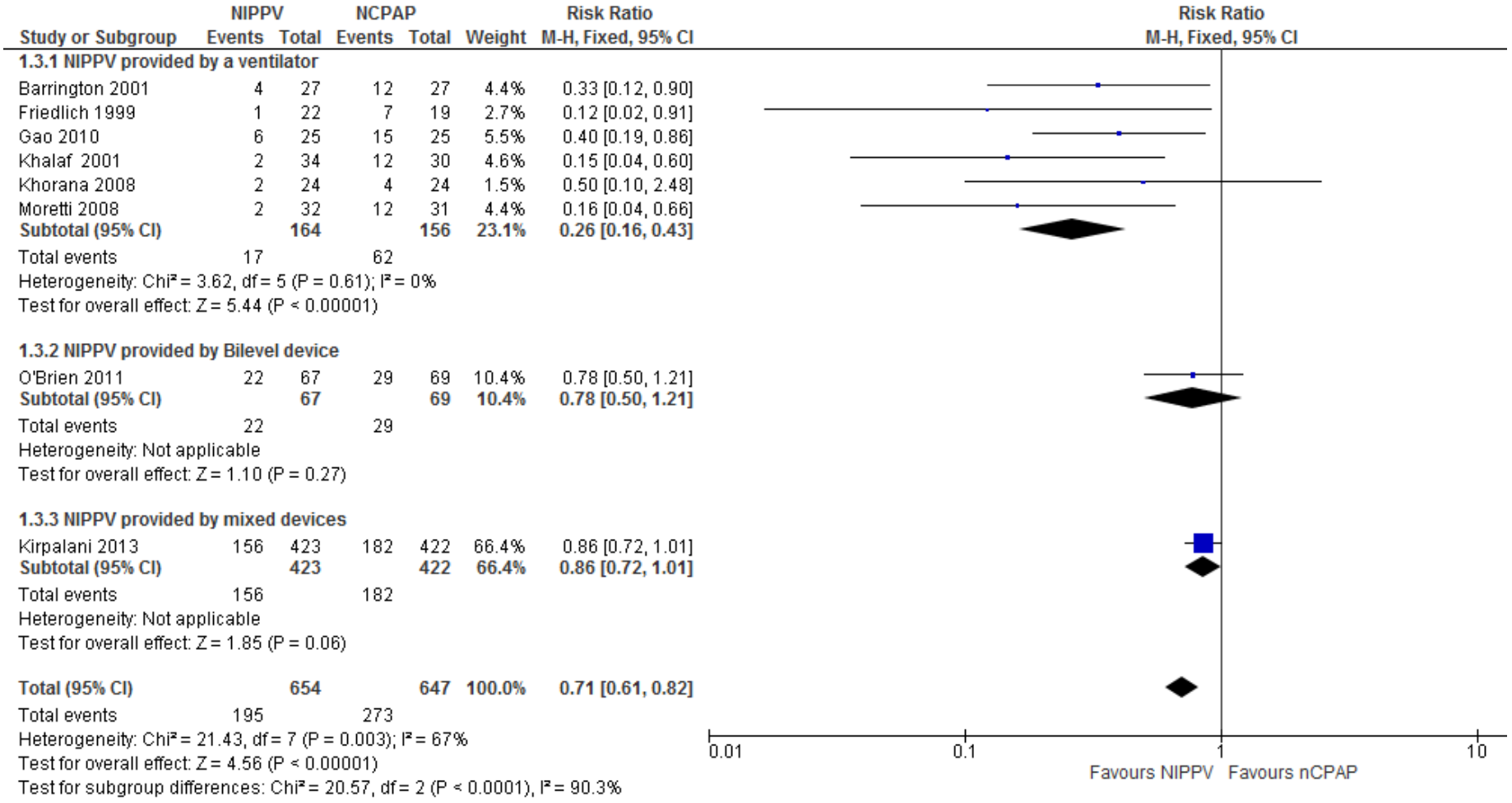
CPAP vs NIPPV

Respiratory failure post-extubation (by synchronisation)

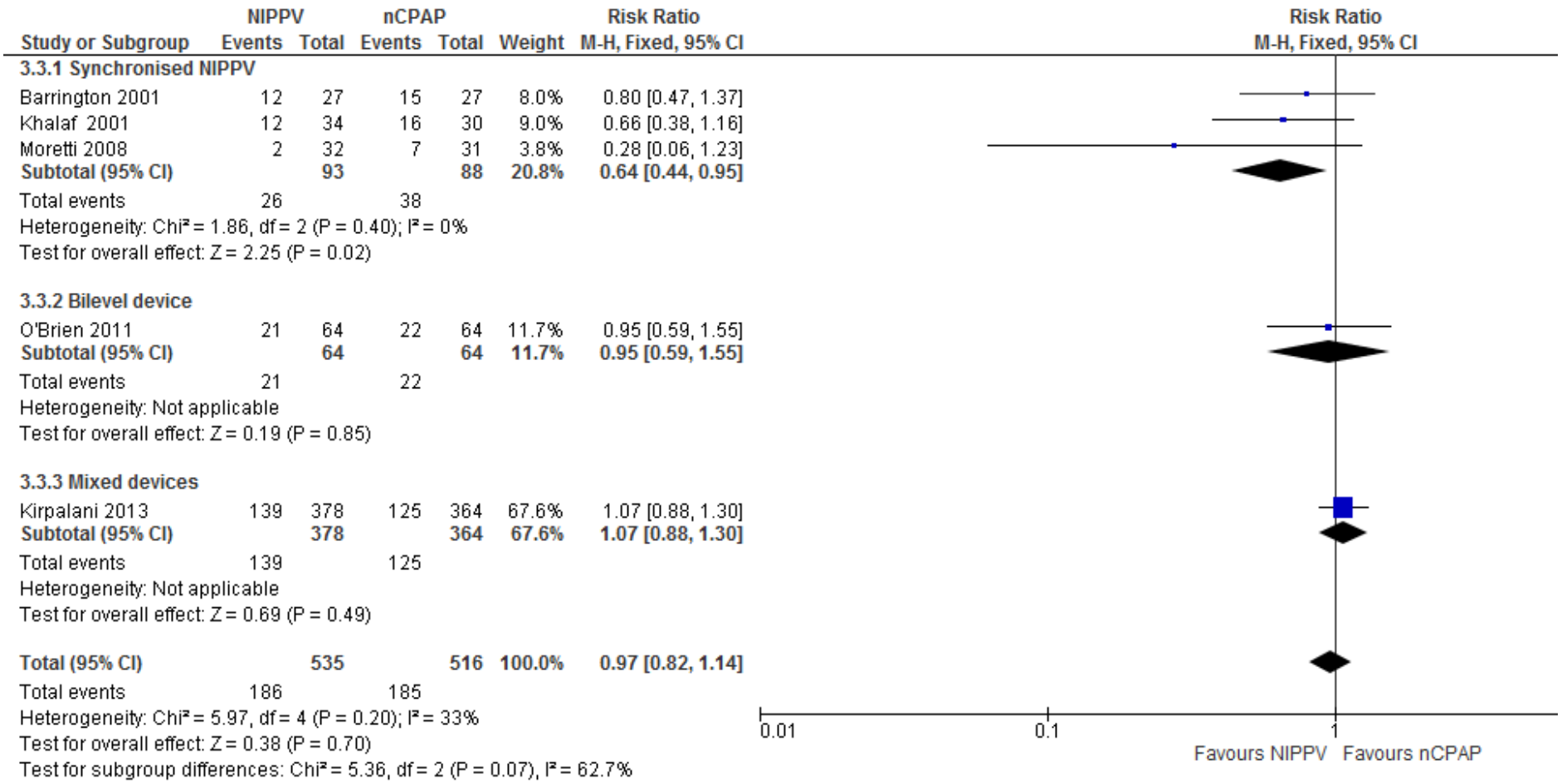


NNT=8 (6, 14)

Respiratory failure post-extubation
(by device)



BPD

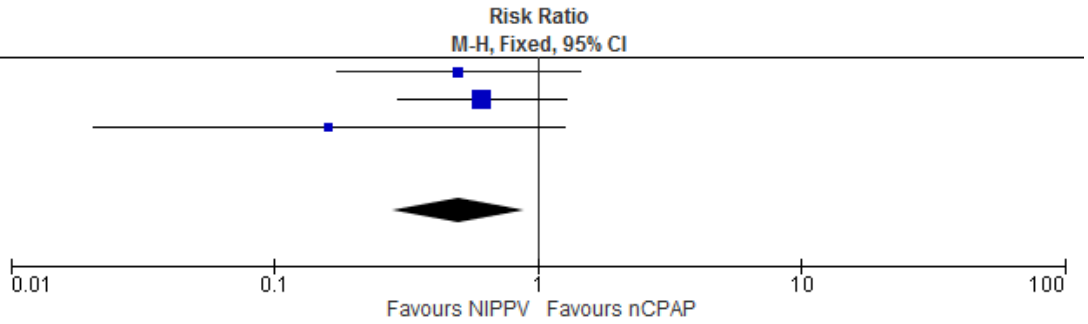

NIPPV
nCPAP
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
3.3.1 Synchronised NIPPV
Barrington 2001 12 27 15 27 8.0% 0.80 [0.47, 1.37]
Khalaf 2001 12 34 16 30 9.0% 0.66 [0.38, 1.16]
Moretti 2008 2 32 7 31 3.8% 0.28 [0.06, 1.23]
Subtotal (95% CI) 93 88 20.8% 0.64 [0.44, 0.95]
Total events 26 38
Heterogeneity: Chi² = 1.86, df = 2 (P = 0.40); I² = 0%
Test for overall effect: Z = 2.25 (P = 0.02)
3.3.2 Bilevel device
O'Brien 2011 21 64 22 64 11.7% 0.95 [0.59, 1.55]
Subtotal (95% CI) 64 64 11.7% 0.95 [0.59, 1.55]
Total events 21 22
Heterogeneity: Not applicable
Test for overall effect: Z = 0.19 (P = 0.85)
3.3.3 Mixed devices
Kirpalani 2013 139 378 125 364 67.6% 1.07 [0.88, 1.30]
Subtotal (95% CI) 378 364 67.6% 1.07 [0.88, 1.30]
Total events 139 125
Heterogeneity: Not applicable
Test for overall effect: Z = 0.69 (P = 0.49)
Total (95% CI) 535 516 100.0% 0.97 [0.82, 1.14]
Total events 186 185
Heterogeneity: Chi² = 5.97, df = 4 (P = 0.20); I² = 33%
Test for overall effect: Z = 0.38 (P = 0.70)
Test for subgroup differences: Chi² = 5.36, df = 2 (P = 0.07), I² = 62.7%
0.01
0.1
1
Favours NIPPV
Favours nCPAP

Pneumothorax

Study or Subgroup	NIPPV Events	NIPPV Total	nCPAP Events	nCPAP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gao 2010	4	25	8	25	25.0%	0.50 [0.17, 1.45]
Kirpalani 2013	11	424	18	426	56.0%	0.61 [0.29, 1.28]
Moretti 2008	1	32	6	31	19.0%	0.16 [0.02, 1.26]
O'Brien 2011	0	67	0	69		Not estimable
Total (95% CI)		**548**		**551**	**100.0%**	**0.50 [0.28, 0.89]**
Total events	16		32			

Heterogeneity: Chi² = 1.46, df = 2 (P = 0.48); I² = 0%

Test for overall effect: Z = 2.37 (P = 0.02)



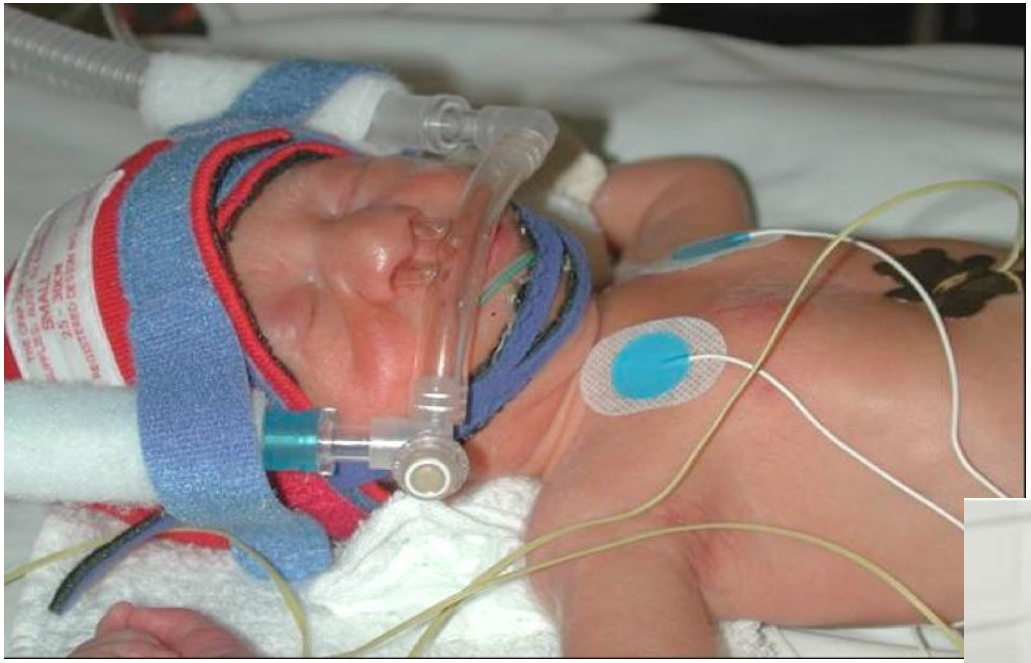
My response to the current evidence

- NIPPV may offer advantages over CPAP
- Synchronisation and the device/pressure used may be important
- NIPPV does not appear to be associated with increased side effects
- The best combination of settings for NIPPV needs to be established in future trials

HIGH FLOW NASAL CANNULAE (HF)

High flow nasal cannulae

- Alternative to NCPAP
- Widespread use before evidence
- Popular with parents, nursing staff
- Less nasal trauma, more comfortable



CPAP

HFNC

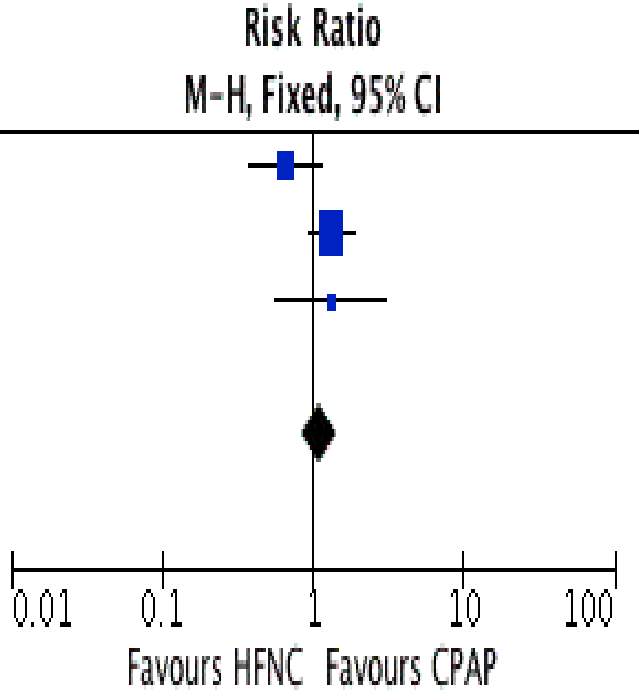
HF vs CPAP

Outcome: Failure within 7 days

Study or Subgroup	HFNC Events	HFNC Total	CPAP Events	CPAP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Collins 2013	15	67	22	65	31.9%	0.66 [0.38, 1.16]
Manley 2013	52	152	39	151	55.8%	1.32 [0.93, 1.88]
Yoder 2013	11	107	9	116	12.3%	1.33 [0.57, 3.07]
Total (95% CI)		**326**		**332**	**100.0%**	**1.11 [0.84, 1.47]**
Total events	78		70			

Heterogeneity: $Chi^2 = 4.43$, $df = 2$ ($P = 0.11$); $I^2 = 55\%$

Test for overall effect: $Z = 0.76$ ($P = 0.45$)



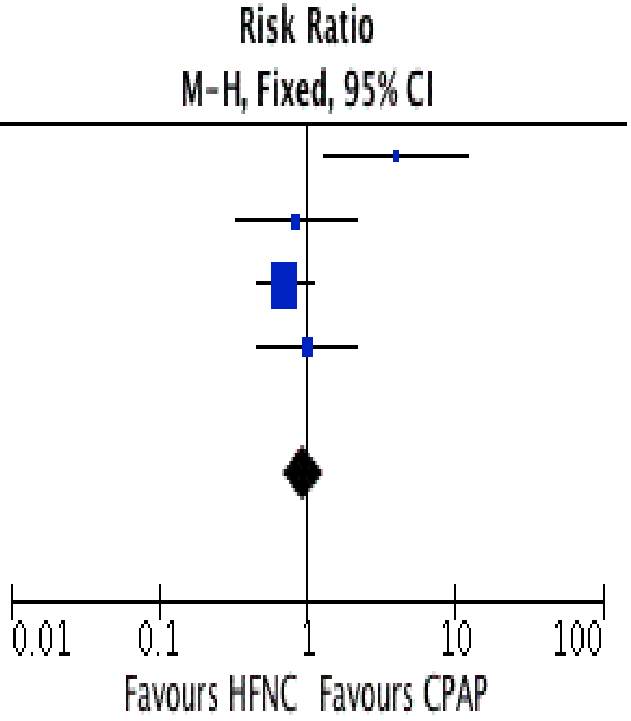
HF vs CPAP

Outcome: Re-intubation within 7 days

Study or Subgroup	HFNC Events	HFNC Total	CPAP Events	CPAP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Campbell 2006	12	20	3	20	4.9%	4.00 [1.33, 12.05]
Collins 2013	7	67	8	65	13.4%	0.85 [0.33, 2.21]
Manley 2013	27	152	38	151	62.7%	0.71 [0.46, 1.09]
Yoder 2013	11	107	12	116	19.0%	0.99 [0.46, 2.16]
Total (95% CI)		**346**		**352**	**100.0%**	**0.94 [0.68, 1.31]**
Total events	57		61			

Heterogeneity: $Chi^2 = 8.33$, df = 3 (P = 0.04); $I^2 = 64\%$

Test for overall effect: Z = 0.36 (P = 0.72)



High-Flow Nasal Cannulae as **P**ost-**E**xtubation **R**espiratory **S**upport in **P**remature Infants: **A** **C**PAP **E**quivalent?

A multicenter, randomized, non-inferiority trial

NEJM 2013

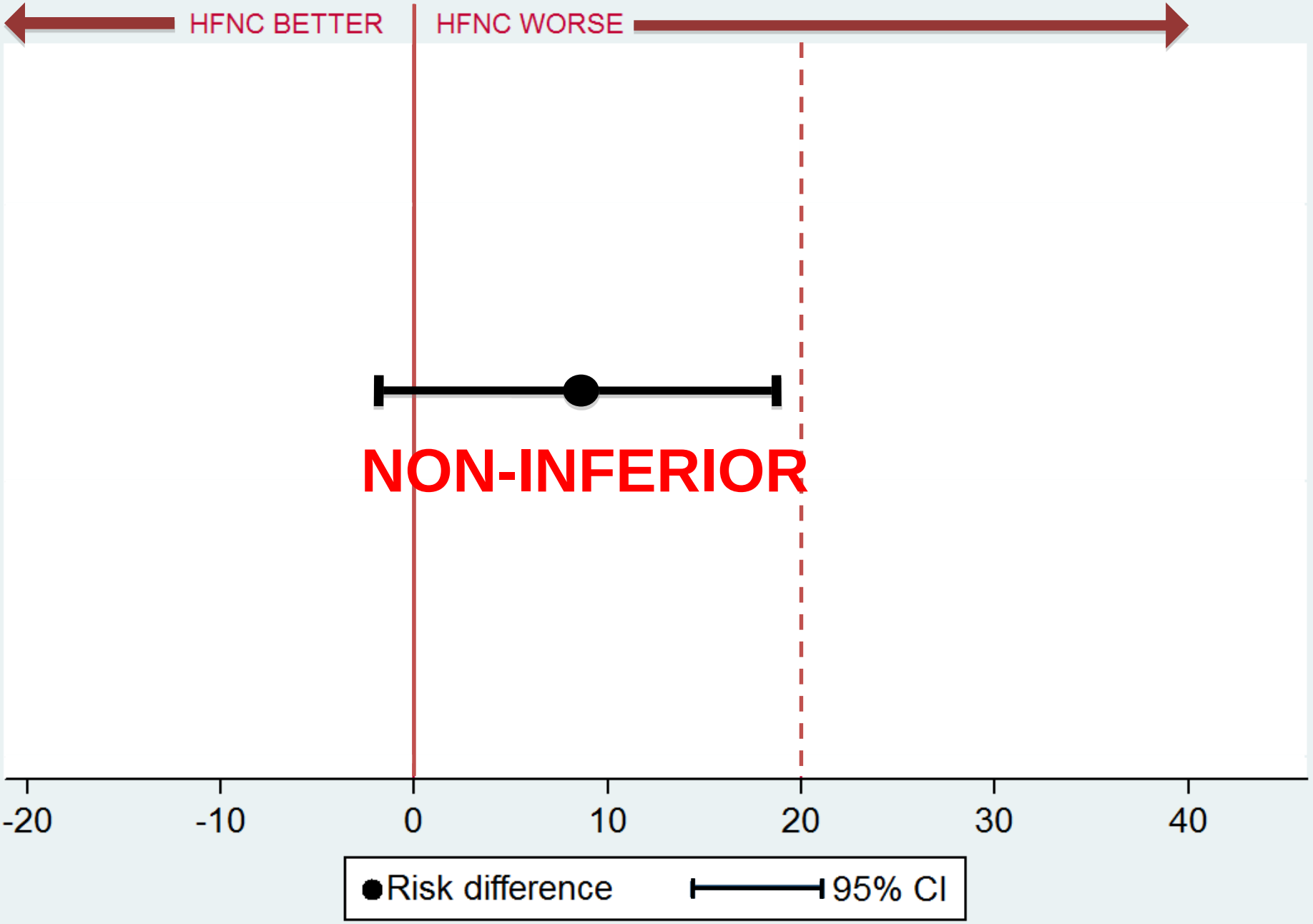
PRIMARY OUTCOME (N=303)

FAILURE OF THE ASSIGNED TREATMENT WITHIN 7 DAYS

HFNC	NCPAP
52/152	39/151
34%	26%

Risk difference 8%

95% CI (-2, 19) %


HFNC BETTER
HFNC WORSE
NON-INFERIOR
-20
-10
0
10
20
30
40
Risk difference
95% CI

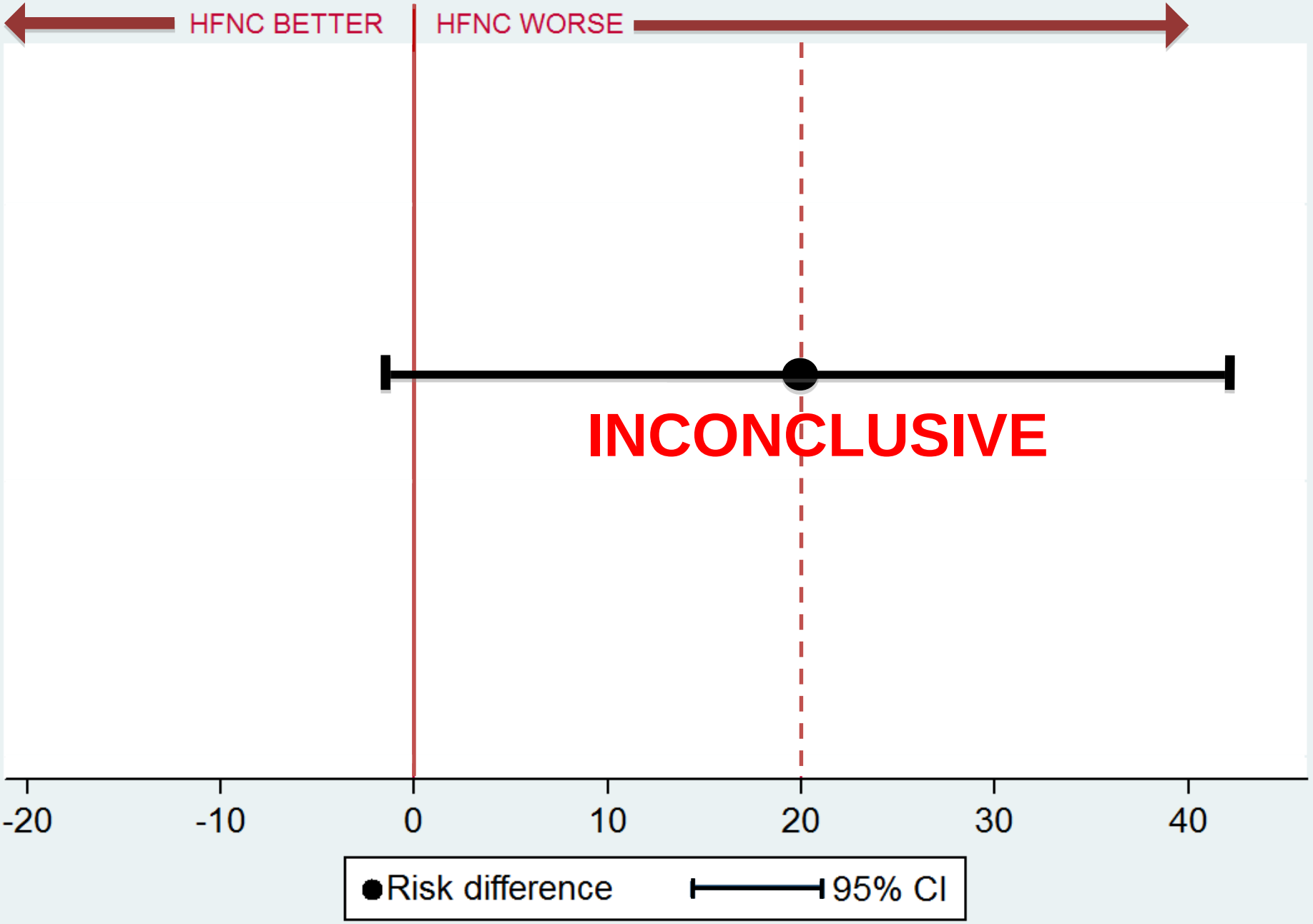
<26 WEEKS' GA (N=63)

FAILURE OF THE ASSIGNED TREATMENT WITHIN 7 DAYS

HFNC	NCPAP
26/32	19/31
81%	61%

Risk difference 20%

95% CI (-2, 42) %


HFNC BETTER
HFNC WORSE
INCONCLUSIVE
-20
-10
0
10
20
30
40
Risk difference
95% CI

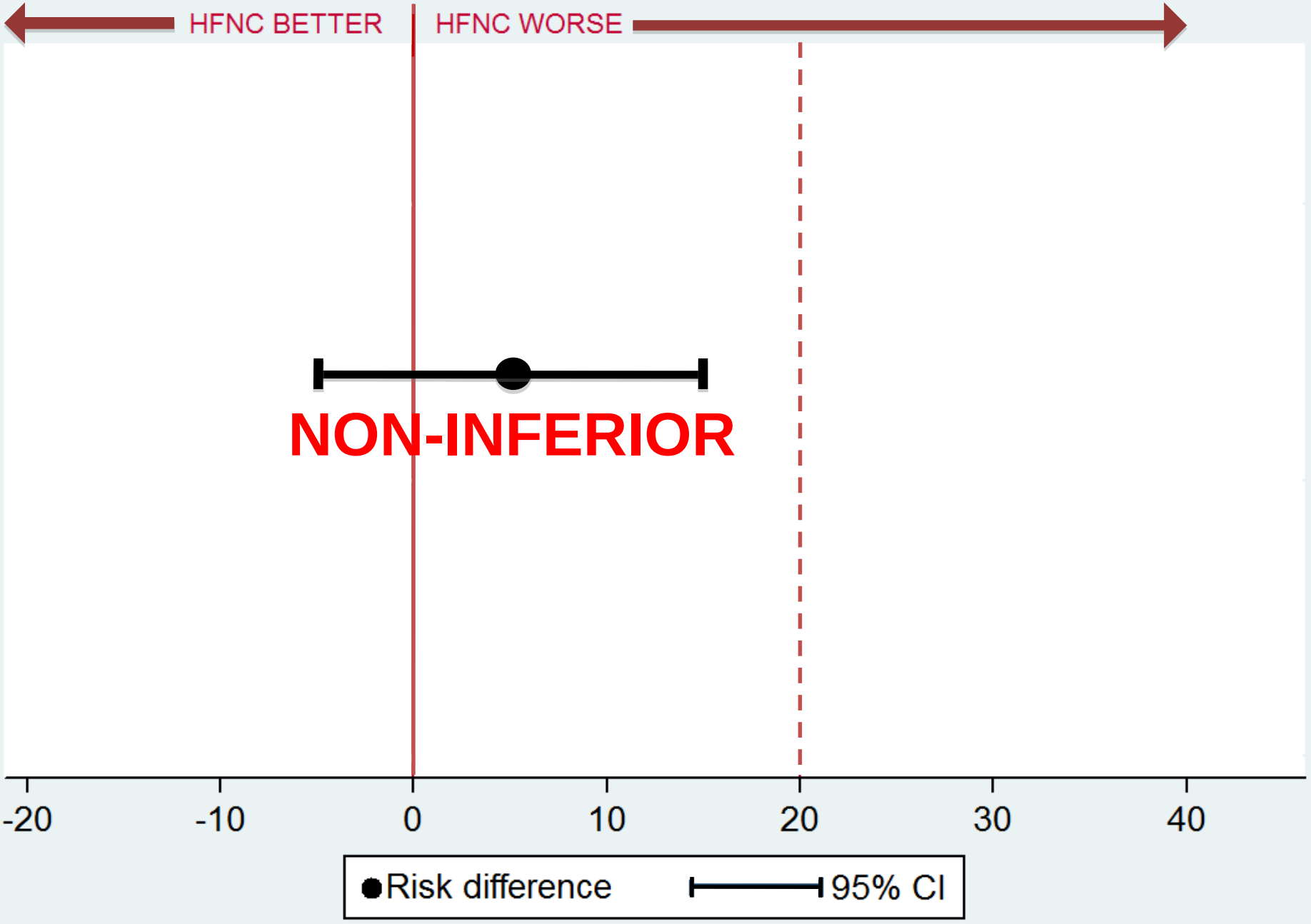
≥26 WEEKS' GA (N=240)

FAILURE OF THE ASSIGNED TREATMENT WITHIN 7 DAYS

HFNC	NCPAP
26/120	20/120
22%	17%

Risk difference 5%

95% CI (-5, 15) %


HFNC BETTER
HFNC WORSE
NON-INFERIOR
-20
-10
0
10
20
30
40
Risk difference
95% CI

SECONDARY OUTCOMES:

RE-INTUBATION WITHIN 7 DAYS

HFNC	NCPAP
27/152	38/151
18%	25%

Risk difference -7%

95% CI (-17, 2) %

SECONDARY OUTCOMES:

RE-INTUBATION WITHIN 7 DAYS

HFNC	NCPAP
27/152	38/151
18%	25%

HALF OF INFANTS IN WHOM HFNC FAILED WERE ‘RESCUED’ BY NCPAP

My response

- HF is non-inferior to NCPAP as post-extubation support in very preterm infants
- HF is feasible, but should be used with caution in infants born <26 weeks' GA
- HFNC is not associated with any increased risk of morbidity, and caused less nasal trauma than NCPAP
- CPAP remains a useful backup for HF

METHYLXANTHINES

Methylxanthines

- Central stimulants – adenosine antagonists
- Near universal usage before evidence of safety
- Caffeine preferable to theophylline/aminophylline
  - Wider therapeutic margin
  - Once a day dosage

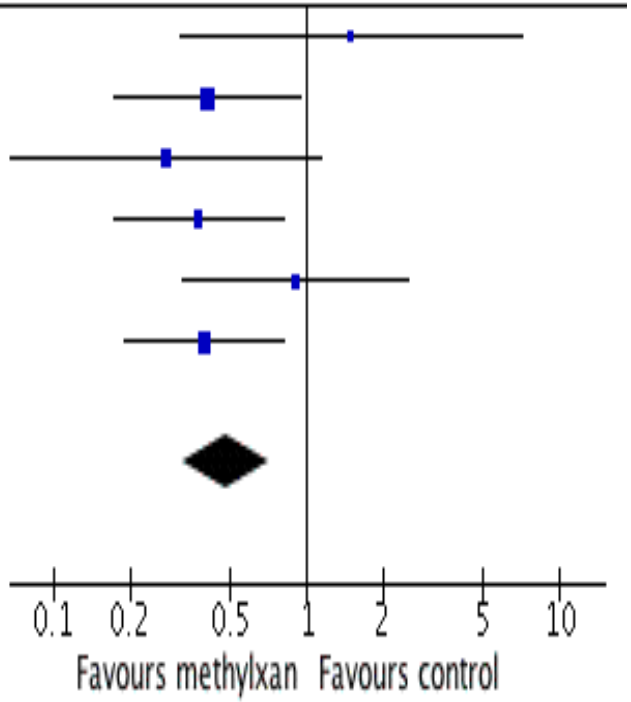
Methylxanthines vs placebo

Outcome: Extubation failure

Study or Subgroup	Methylxanthine Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barrington 1993	3	10	2	10	4.1%	1.50 [0.32, 7.14]
Durand 1987	5	23	15	28	28.0%	0.41 [0.17, 0.95]
Greenough 1985	2	18	8	20	15.7%	0.28 [0.07, 1.14]
Muro 1992	4	12	6	6	17.5%	0.37 [0.17, 0.81]
Pearlman 1991	8	31	4	14	11.4%	0.90 [0.33, 2.51]
Viscardi 1985	5	14	10	11	23.2%	0.39 [0.19, 0.81]
Total (95% CI)		**108**		**89**	**100.0%**	**0.48 [0.32, 0.71]**
Total events	27		45			

Heterogeneity: $Chi^2 = 4.95$, $df = 5$ ($P = 0.42$); $I^2 = 0\%$

Test for overall effect: $Z = 3.69$ ($P = 0.0002$)



NNT 4 (2, 7)

CAP Trial

- 2006 infants
  - 500-1250g
  - ≤10days old
  - “Candidates for methylxanthine therapy”

Intervention

- Caffeine or placebo

Loading dose:

20 mg/kg of caffeine citrate

Maintenance dose:

5-10 mg/kg every 24 hours

Caffeine reduces duration of respiratory support*

	Caffeine	Placebo	P value
Intubation	29.1	30.0	<0.001
Any positive pressure	31.0	32.0	<0.001
Supplemental oxygen	33.6	35.1	<0.001

*median postmenstrual age (weeks) of last support

N Engl J Med 2006; 354:2112-21

Other neonatal outcomes

	Caffeine	Placebo	OR (95%CI)
BPD	36%	47%	0.6 (0.5-0.8)
PDA	30%	40%	0.6 (0.5-0.8)
PDA ligation	5%	12%	0.3 (0.2-0.5)

Death or Disability

Caffeine	Placebo
377 of 937	431 of 932
40%	46%

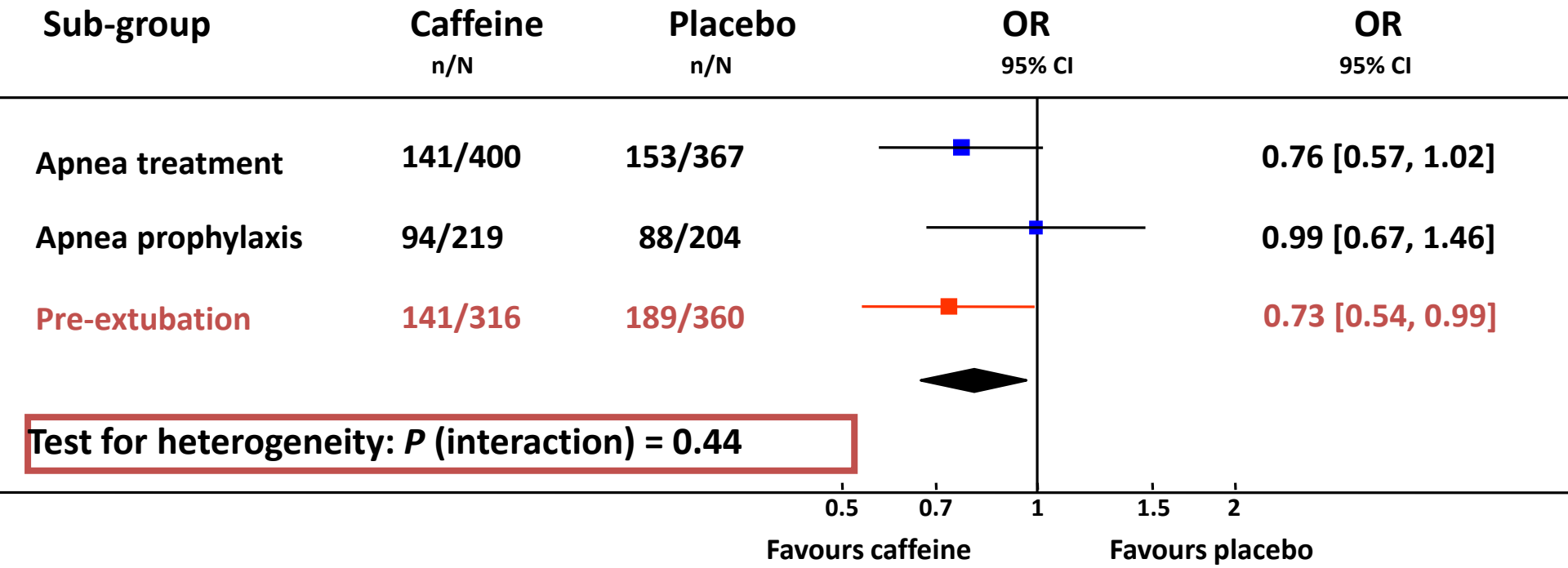
Adjusted OR = 0.77 (0.64-0.93)

NNT = 16

Conclusion

- Caffeine improves survival without neurodevelopmental disability in VLBW infants at 18-21 months

Death or major disability by main indication



My response to the evidence

- Caffeine is a safe and effective method of facilitating extubation
  - in the doses and for the indications used in the CAP trial

Other interventions

Treatment	Efficacy	Safety
Dexamethasone	✓ For prolonged or repeated intubations	???
Doxapram	?	?
Physiotherapy	? ✓	???

My strategy

- HF: for babies >26 weeks, have a plan B
- CPAP: for babies ≤26 weeks and plan B
  - I start at 7cm water
- NIPPV: before re-intubation (plan C)
- Caffeine: before extubation for babies<30 weeks' GA in CAP dosages