

Evidence based methods of facilitating extubation

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Why bother?

- For parents (and us)
 - Extubation is an important milestone
 - Failed extubation is stressful
 - and is associated with poor short- and long-term outcomes
- For babies
 - Prolonged intubation is harmful???
 - Stressful
 - Increased risk of sepsis/pneumonia
 - Damage to the airway

Available therapies

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

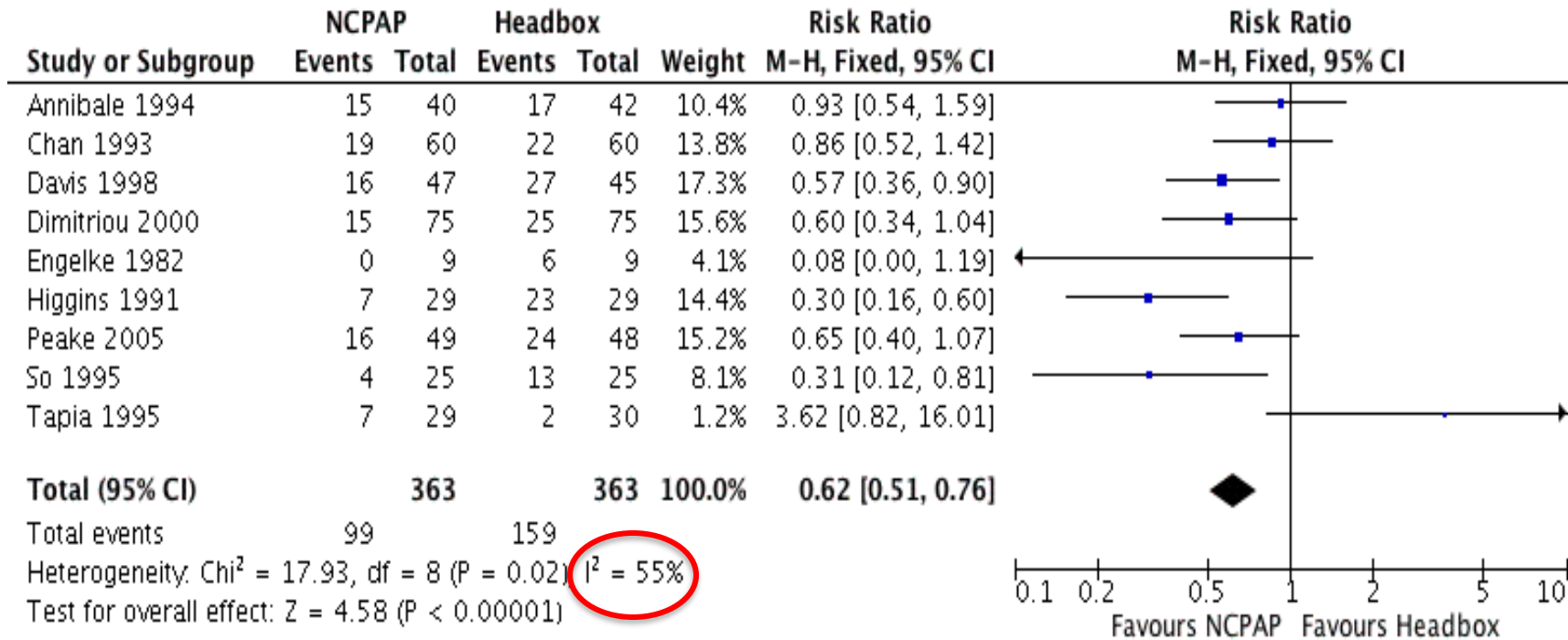
CPAP

Rationale

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

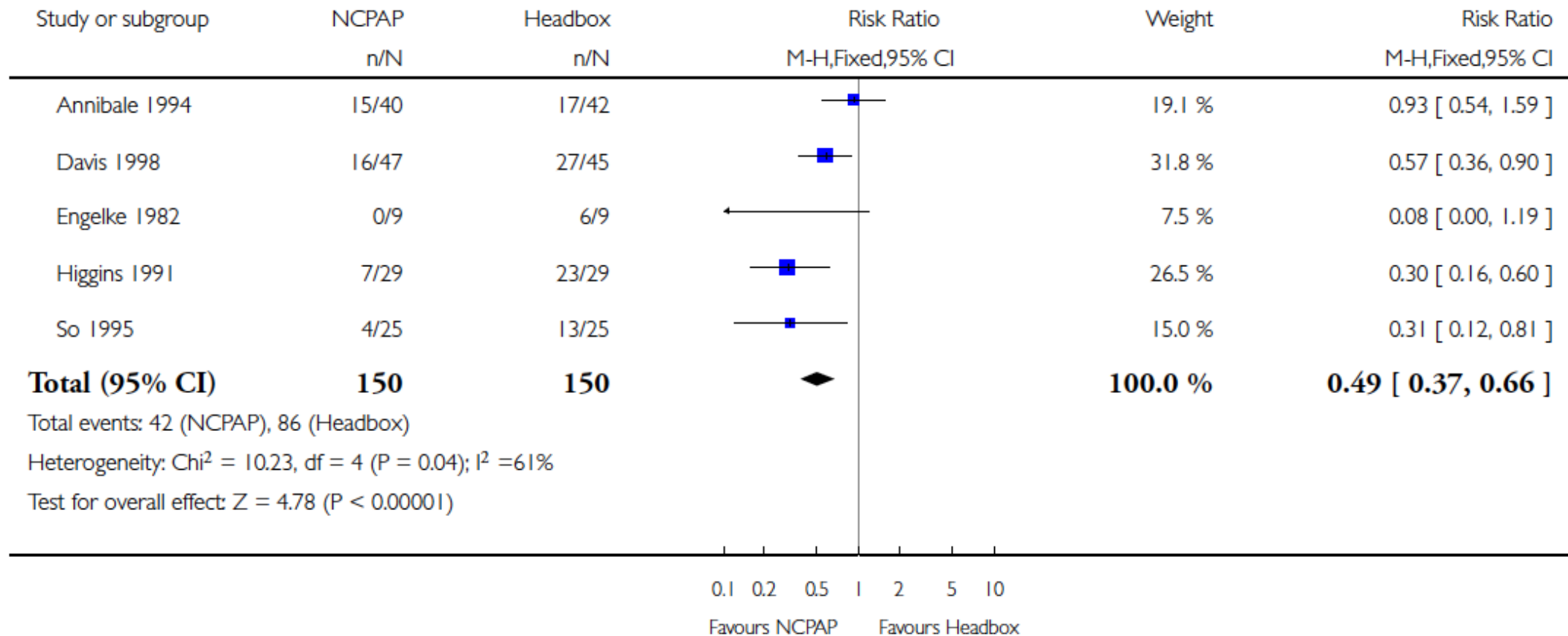
CPAP vs. Headbox oxygen

Outcome: Extubation Failure

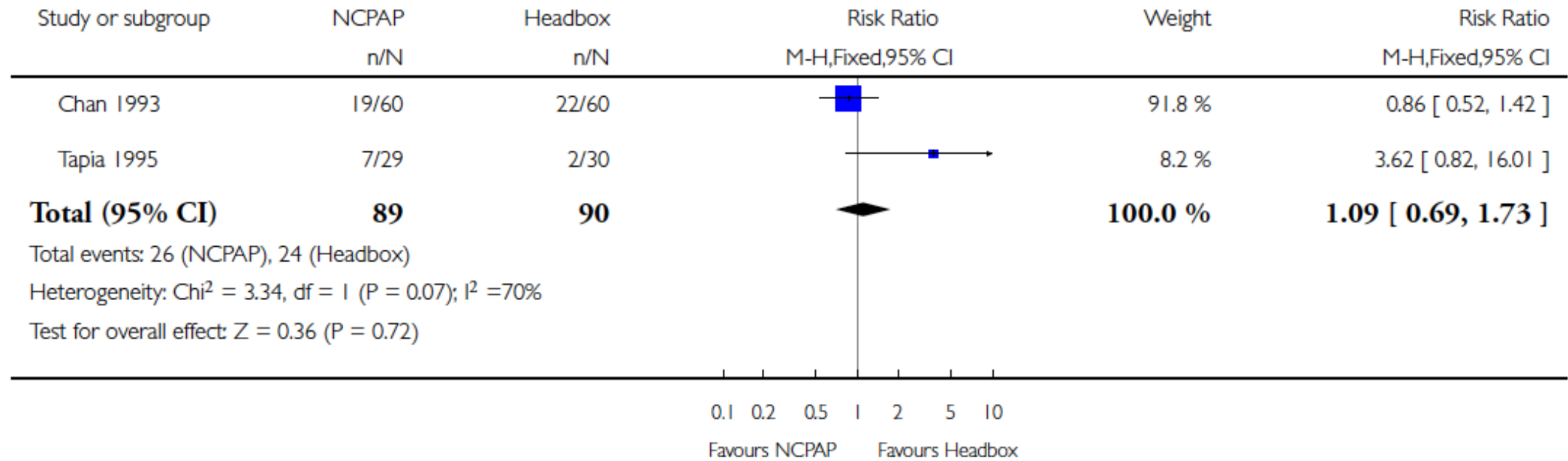


NNT = 6 (4, 10)

CPAP ≥ 5 cm water



CPAP <5 cm water



A Randomized Controlled Trial of Two Nasal Continuous Positive Airway Pressure Levels after Extubation in Preterm Infants

Bridget Buzzella, MD, Nelson Claure, MSc, PhD, Carmen D'Ugard, RRT, and Eduardo Bancalari, MD

<http://dx.doi.org/10.1016/j.jpeds.2013.08.040>

Which CPAP level?

- 7-9 cm better than 4-6 cm
 - 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

My interpretation

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



Cochrane
Library

Cochrane Database of Systematic Reviews

Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) for preterm neonates after extubation (Review)

Lemyre B, Deguise MO, Benson P, Kirpalani H, De Paoli AG, Davis PG

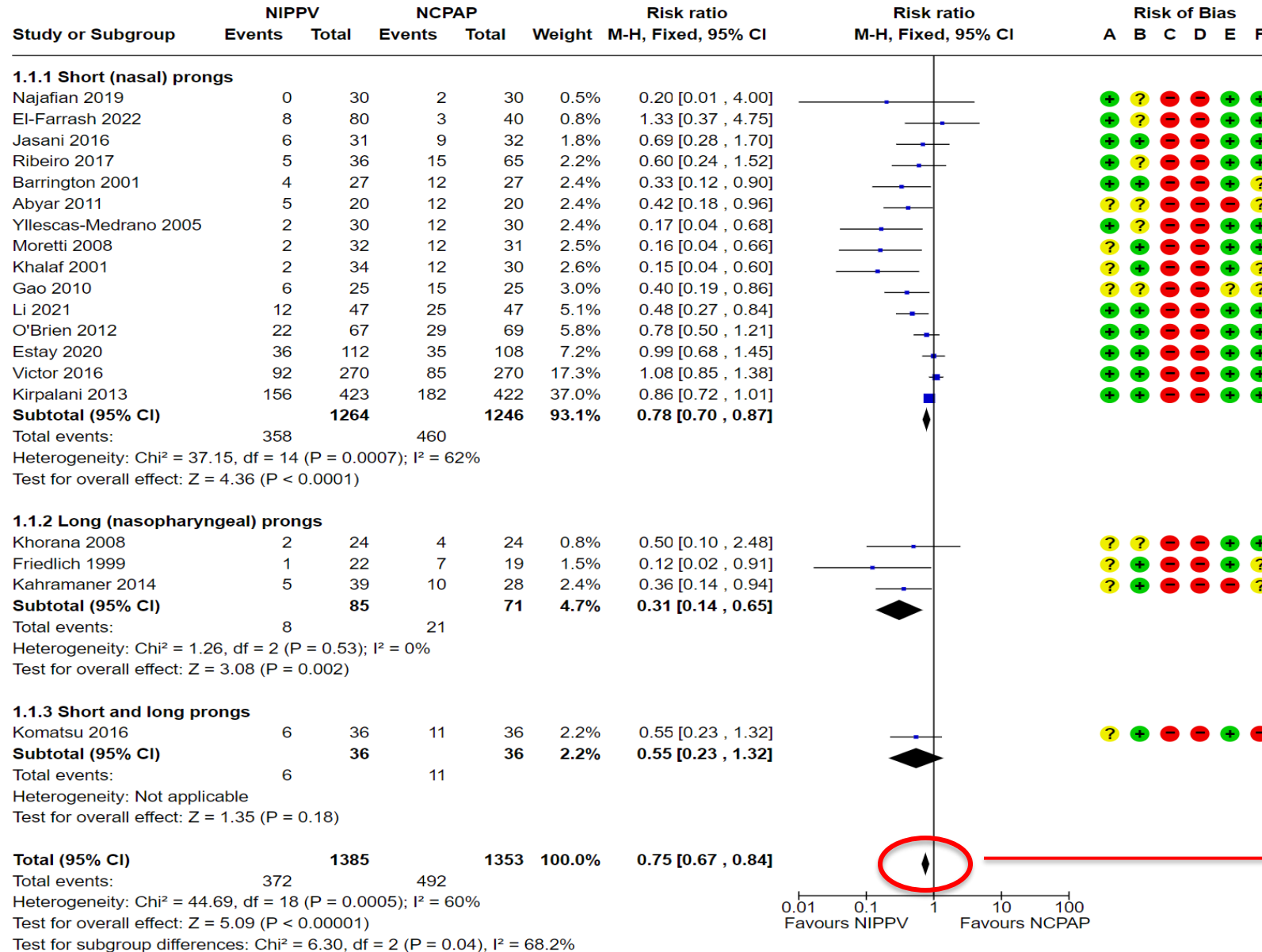
Cochrane Database of Systematic Reviews 2023, Issue 7. Art. No.: CD003212.

DOI: [10.1002/14651858.CD003212.pub4](https://doi.org/10.1002/14651858.CD003212.pub4).

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 vs CPAP: Respiratory failure postextubation



RR 0.75 (0.67 to 0.84)
RD -0.09 (-0.12 to -0.06)
NNTB 11 (8 to 17)
I² = 68.2%
19 trials, 2738 infants;
moderate-certainty
evidence

Conclusions

- Little data for infants <28 weeks' gestation
- Pulmonary air leaks were potentially *reduced* in the NIPPV group
- No effect on other clinically relevant outcomes
 - Gastrointestinal perforation
 - NEC
 - BPD
 - Mortality
- Ventilator-generated NIPPV appears superior to bi-level devices:
 - reduces respiratory failure post-extubation and need for reintubation
- Synchronisation used to deliver NIPPV *may* be important; more data required

Where to from here?

- NAVA is worth evaluation as a triggering mechanism
- The best settings for NIPPV (rate, pressure, I-time) need 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



nHF: Mechanisms of action

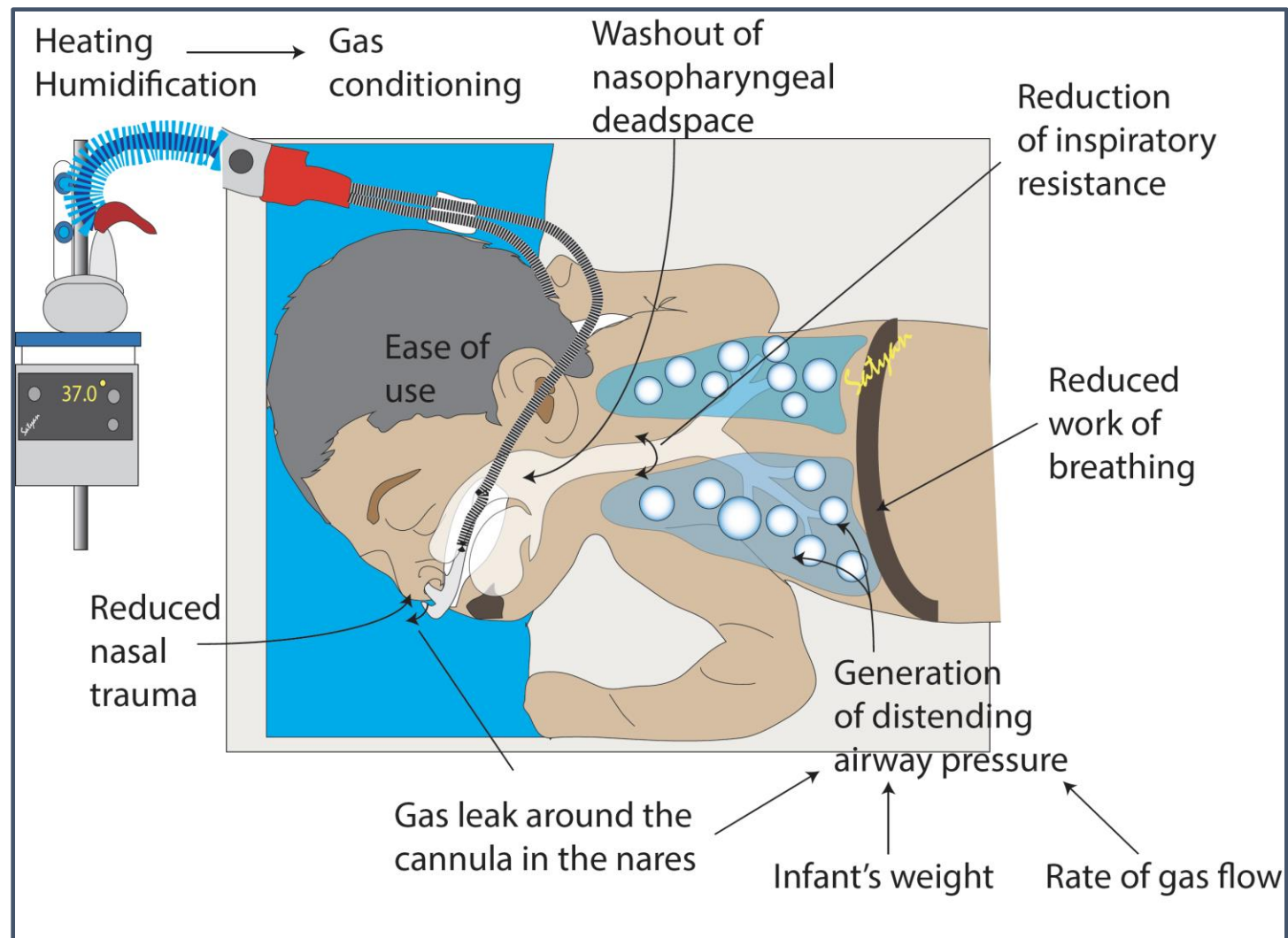


Figure courtesy Dr Satyan Lakshminrusimha, University of Buffalo



The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

High-Flow Nasal Cannulae in Very Preterm Infants after Extubation

Brett J. Manley, M.B., B.S., Louise S. Owen, M.D., Lex W. Doyle, M.D.,
Chad C. Andersen, M.B., B.S., David W. Cartwright, M.B., B.S.,
Margo A. Pritchard, Ph.D., Susan M. Donath, M.A., and Peter G. Davis, M.D.

N ENGL J MED 369;15 NEJM.ORG OCTOBER 10, 2013

PRIMARY OUTCOME (N=303)

FAILURE OF THE ASSIGNED TREATMENT WITHIN 7 DAYS

HFNC

52/152

34%

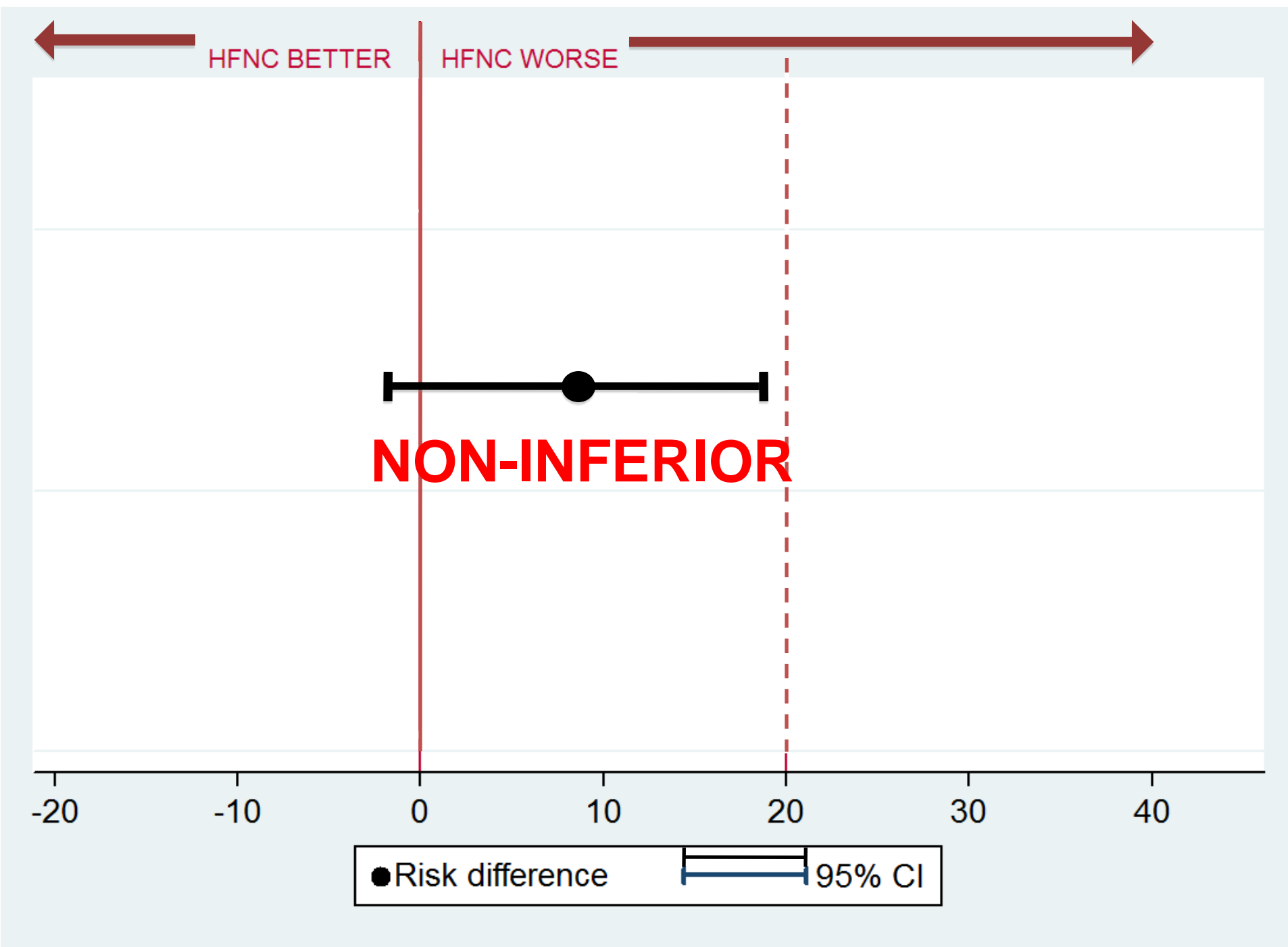
NCPAP

39/151

26%

Risk difference 8%

95% CI (-2, 19) %



<26 WEEKS' GA (N=63)

FAILURE OF THE ASSIGNED TREATMENT WITHIN 7 DAYS

HFNC

26/32

81%

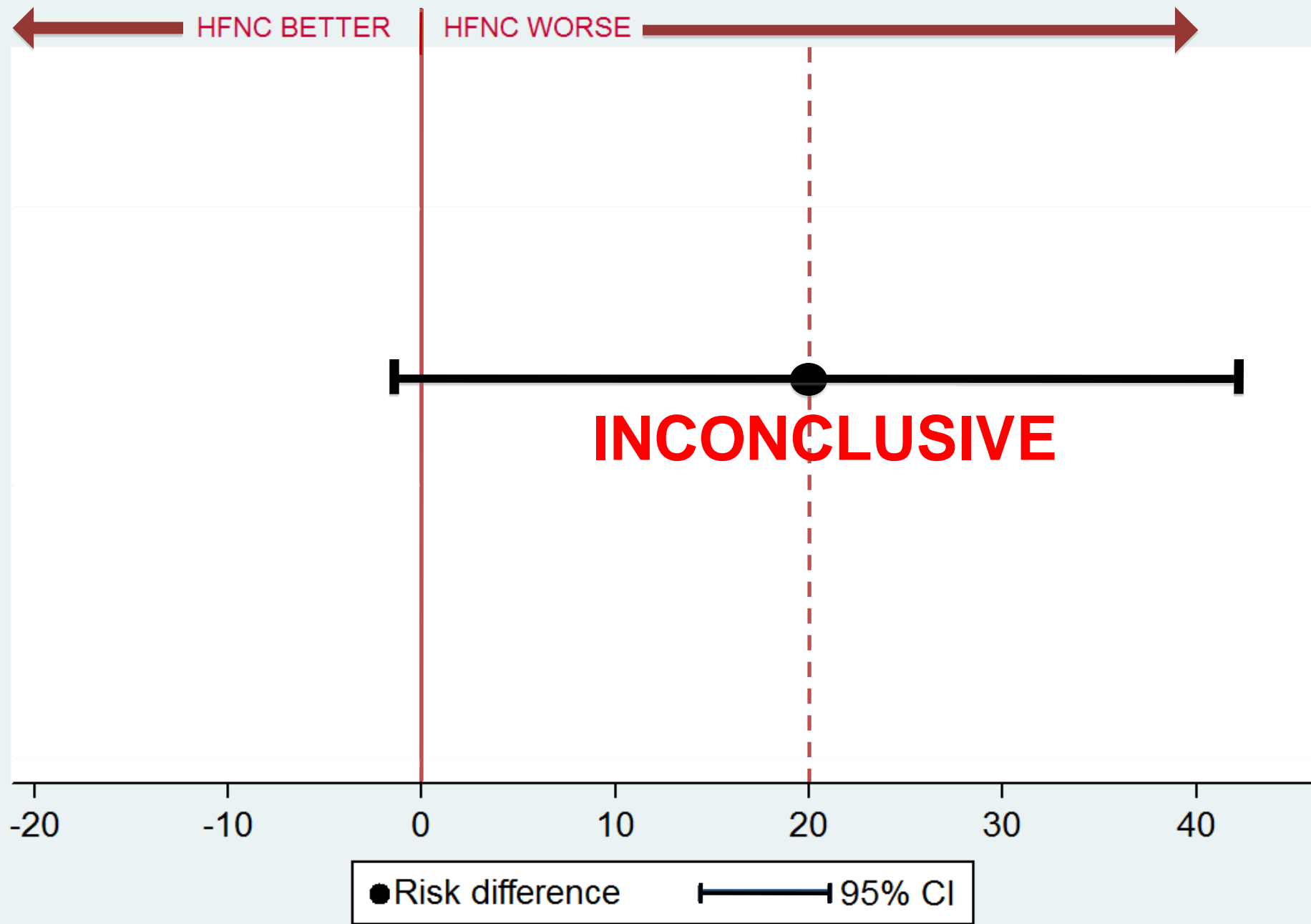
NCPAP

19/31

61%

Risk difference 20%

95% CI (-2, 42) %



≥ 26 WEEKS' GA (N=240)

FAILURE OF THE ASSIGNED TREATMENT WITHIN 7 DAYS

HFNC

26/120

22%

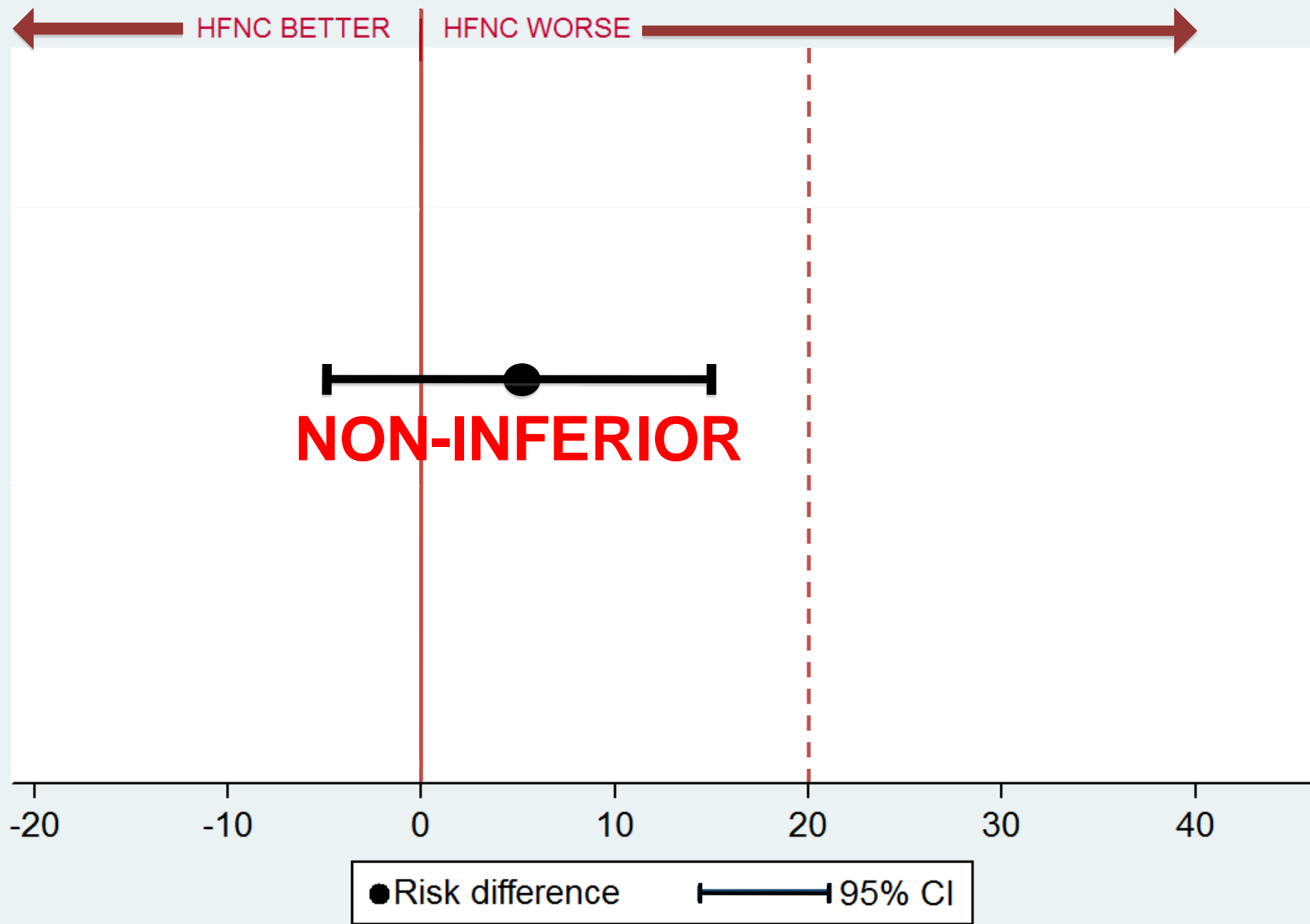
NCPAP

20/120

17%

Risk difference 5%

95% CI (-5, 15) %



SECONDARY OUTCOMES:
RE-INTUBATION WITHIN 7 DAYS

HFNC
27/152
18%

NCPAP
38/151
25%

Risk difference -7%

95% CI (-17, 2) %

SECONDARY OUTCOMES:
RE-INTUBATION WITHIN 7 DAYS

HFNC
27/152
18%

NCPAP
38/151
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 <28 weeks' GA
- HFNC is not associated with any increased risk of morbidity, and caused less nasal trauma than NCPAP
- CPAP remains an important backup if HF is used

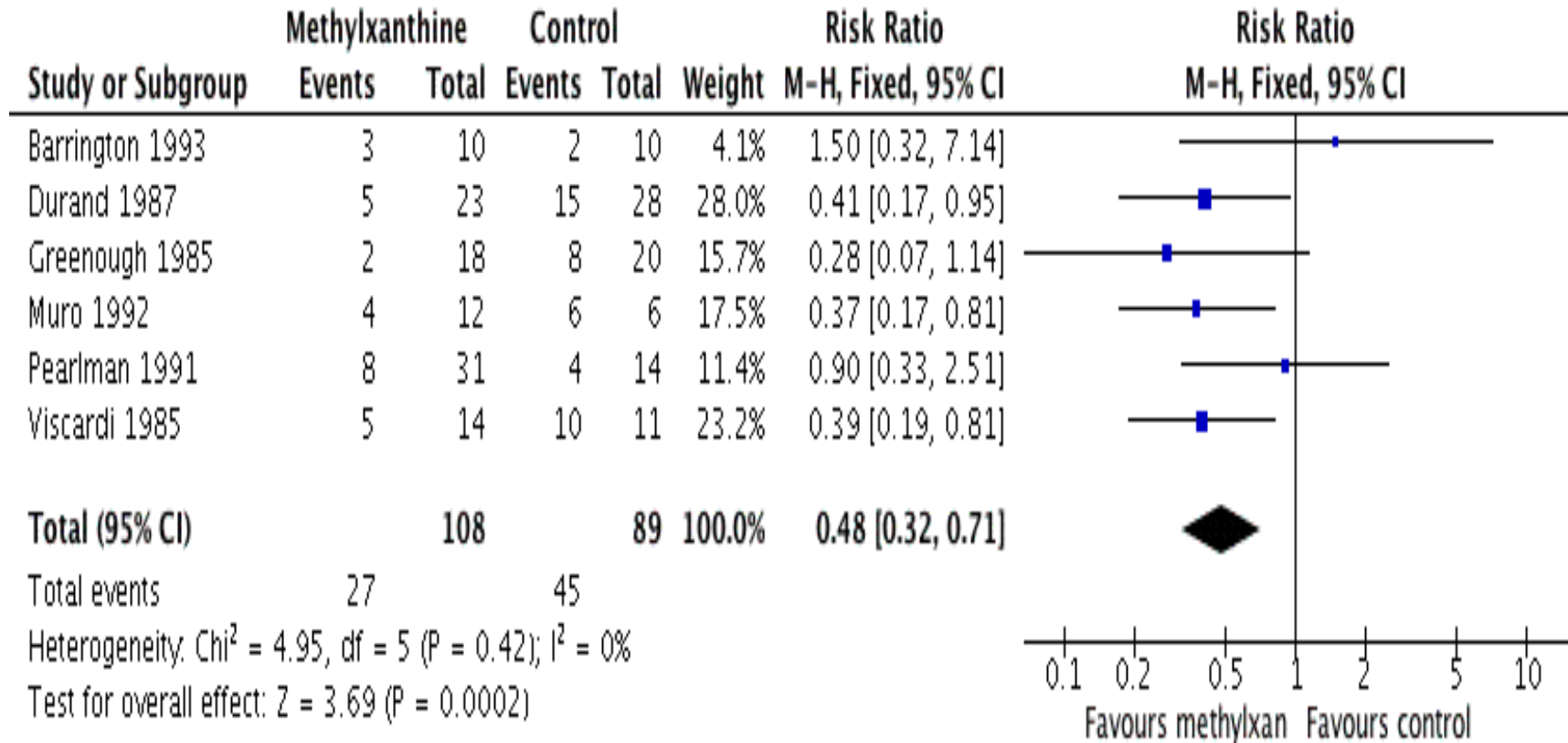
METHYLYXANTHINES

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



NNT 4 (2, 7)



CAP Trial

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

The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

Caffeine Therapy for Apnea of Prematurity

Barbara Schmidt, M.D., Robin S. Roberts, M.Sc., Peter Davis, M.D.,
Lex W. Doyle, M.D., Keith J. Barrington, M.D., Arne Ohlsson, M.D.,
Alfonso Solimano, M.D., and Win Tin, M.D.,
for the Caffeine for Apnea of Prematurity Trial Group*

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

377 of 937

40%

Placebo

431 of 932

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



Cochrane
Library

Cochrane Database of Systematic Reviews

Caffeine dosing regimens in preterm infants with or at risk for apnea of prematurity (Review)

Bruschettini M, Brattström P, Russo C, Onland W, Davis PG, Soll R

Cochrane Database of Systematic Reviews 2023, Issue 4. Art. No.: CD013873.
DOI: [10.1002/14651858.CD013873.pub2](https://doi.org/10.1002/14651858.CD013873.pub2).

Conclusions

- High-dose caffeine strategies in preterm infants may have little or no effect on **mortality**
- High-dose caffeine strategies probably reduce the rate of **bronchopulmonary dysplasia**
- We are very uncertain whether high-dose caffeine strategies effect **major neurodevelopmental disability, duration of hospital stay or seizures**



Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

Seminars in Fetal and Neonatal Medicine

journal homepage: www.elsevier.com/locate/siny



Pharmacokinetics, pharmacodynamics and metabolism of caffeine in newborns

Jacob V. Aranda^{a,b,*}, Kay D. Beharry^{a,c}



Words of wisdom from Jack Aranda

- Standard doses of caffeine citrate (20 mg/kg loading and 5–10 mg/ kg/day maintenance) exert their action on respiratory control through interaction with adenosine receptors.
- **Higher than standard doses will result in plasma concentrations at which the pharmacologic actions of caffeine become more complex and worrisome.**
- Plasma caffeine monitoring is not necessary for standard dosing regimens but may be useful when caffeine exceeds standard doses.

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
- We need trials with similar numbers to CAP to answer questions around different doses and indications

Higher versus lower nCPAP for extubation of extremely preterm infants



Higher versus lower nCPAP for extubation of extremely preterm infants



Higher versus lower nasal continuous positive airway pressure for extubation of extremely preterm infants in Australia (ÉCLAT): a multicentre, randomised, superiority trial

[Anna M Kidman, MNS](#) • [Brett J Manley, PhD](#) • [Rosemarie A Boland, PhD](#) • [Atul Malhotra, PhD](#) • [Susan M Donath, MA](#) • [Friederike Beker, DMed](#) • [Prof Peter G Davis, MD](#) • [Risha Bhatia, PhD](#)   • [Show less](#)

Published: October 26, 2023 • DOI: [https://doi.org/10.1016/S2352-4642\(23\)00235-3](https://doi.org/10.1016/S2352-4642(23)00235-3) •



Population

- Intubated infants < 28 weeks at birth

Intervention

- Extubation to nCPAP 10 cmH₂O

Comparison

- Extubation to nCPAP 7 cmH₂O

Outcome

- Extubation failure within 7 days

Randomisation

```
graph TD; A[Randomisation] --> B[Higher nCPAP<br/>10 cm H2O]; B --> C[Range for first 24 hours:<br/>9 -11 cm H2O<br/>Max pressure for first 7 days:<br/>11 cm H2O];
```

Higher nCPAP
10 cm H₂O

Range for first 24 hours:
9 -11 cm H₂O
Max pressure for first 7 days:
11 cm H₂O

Randomisation

```
graph TD; A[Randomisation] --> B[Higher nCPAP<br/>10 cm H2O]; A --> C[Standard nCPAP<br/>7 cm H2O]; B --> D["Range for first 24 hours:<br/>9 -11 cm H2O<br/>Max pressure for first 7 days:<br/>11 cm H2O"]; C --> E["Range for first 24 hours:<br/>6 - 8 cm H2O<br/>Max pressure for first 7 days:<br/>8 cm H2O"];
```

Higher nCPAP
10 cm H₂O

Range for first 24 hours:
9 -11 cm H₂O
Max pressure for first 7 days:
11 cm H₂O

Standard nCPAP
7 cm H₂O

Range for first 24 hours:
6 - 8 cm H₂O
Max pressure for first 7 days:
8 cm H₂O

Failure criteria

Receiving the maximum CPAP level (11 cm H₂O/ 8 cm H₂O)

and having at least one of:

- FiO₂ requirement >0.20 above the pre-extubation FiO₂
- ≥ 2 apnoeic episodes within a 24-hour period requiring IPPV, or; ≥ 6 apnoeic events requiring stimulation in a 6-hour period
- Respiratory acidosis with pH <7.2 & CO₂ >60 mmHg
- Urgent intubation for an acute deterioration



Results

Demographics

Higher nCPAP

Standard nCPAP

10 cm H₂O

7 cm H₂O

(n = 69)

(n = 69)

Antenatal glucocorticoids (any)

93%

96%

Caesarean section

57%

70%

Mean gestation (weeks)

25.7

25.7

Birth weight

790g

764g

*138 of planned 186 infant (74%) recruited due to COVID

Pre-extubation

Higher nCPAP

10 cm H₂O

(n = 69)

Standard nCPAP

7 cm H₂O

(n = 69)

Median days at extubation

4

4

pCO₂ (mm Hg)

46.6

44.8

FiO₂

21%

21%

Mean airway pressure (cm H₂O)

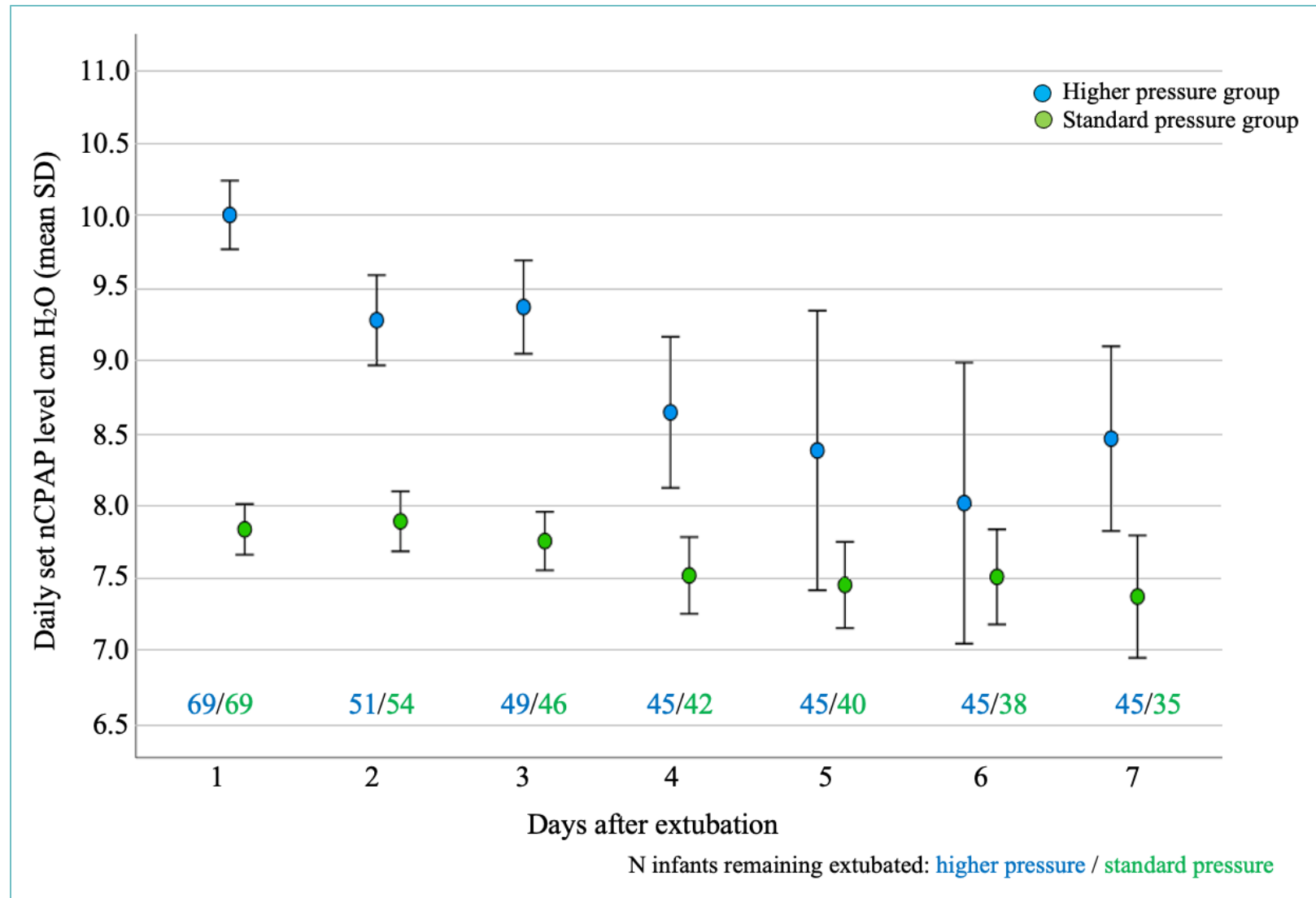
8

8

Conventional ventilation

96%

90%



Primary outcome: Failure of extubation

Higher
nCPAP 10 cmH₂O
35%

Standard
nCPAP 7 cmH₂O
57%

Risk Difference: 22% (4%, 38%)

Number needed to treat: 5 (3, 27)

Serious adverse events during primary outcome period

| | Higher nCPAP 10 cm H ₂ O (n = 69) | Standard nCPAP 7 cm H ₂ O (n = 69) |
|------------------------------------|--|---|
| Pneumothorax | 1% | 1% |
| Pulmonary interstitial emphysema | 0 | 0 |
| Spontaneous intestinal perforation | 3% | 1% |
| Death | 3% | 1% |

Conclusions

Extubation to higher nCPAP of 10 cm H₂O compared with standard nCPAP 7 cm H₂O reduced extubation failure (NNT 5) with no significant increase in adverse events

My strategy

- HF: for babies >28 weeks, have a plan B
- CPAP: for babies ≤ 28 weeks and plan B
 - I start at 7-8 but go to 11cm water if required
- NIPPV: before re-intubation (plan C)
- Caffeine: before extubation for babies <30 weeks' GA in CAP dosages