

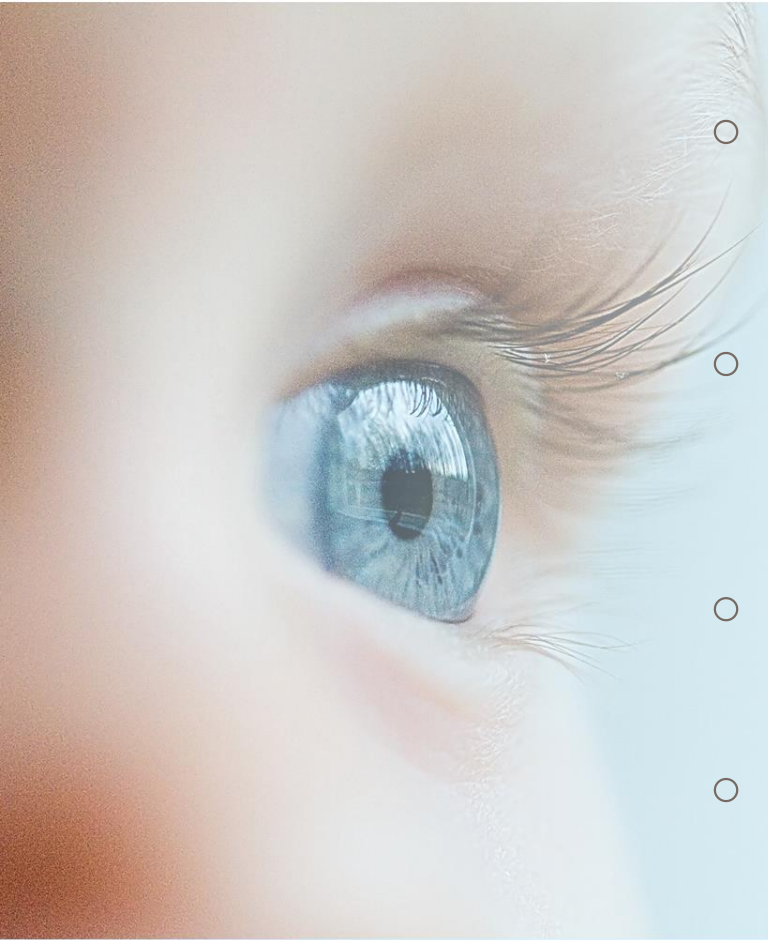
Nasal High Flow

Past, present and future

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Fisher and Paykel Healthcare

Overview

- 
- A close-up photograph of a baby's eye, showing the iris and eyelashes. The eye is looking slightly to the left. The background is a soft, out-of-focus blue and white.
- Background
 - Nasal High Flow (NHF) in the preterm infant population
 - NHF for post extubation respiratory support
 - Recap on three trials from 2013
 - NHF for primary respiratory support
 - Review two trials 'hot off the press'
 - Future directions

Background

- Nasal High Flow (NHF)
 - Open system (no seal with the nares)
 - Flow based therapy (typically 4 to 8 L/min)
 - Air and oxygen are blended to desired fraction of oxygen
 - Gas is heated and humidified

THE RESPIRATORY CARE CONTINUUM



Who is Using NHF and Why?

United States of America

Hochwald et al. *J Neonatal-Perinatal Medicine*. 2010

- 2/3 of US academic units using NHF



Australia and New Zealand

Hough et al. *J Paediatr Child Health*. 2011

Manley et al. *J Paediatr Child Health*. 2011

- 2/3 of NICUs using NHF
- Growing use in non tertiary units



United Kingdom

Ojha et al. *Acta Paediatrica*. 2013

Nath et al. *Pediatrics International*. 2010

- 80% of NICUs using NHF
- 50% of level 2 units using NHF



- Consensus from survey data:

Reduces
nasal trauma

Well
tolerated

High nursing
/caregiver
satisfaction

Easier than
CPAP

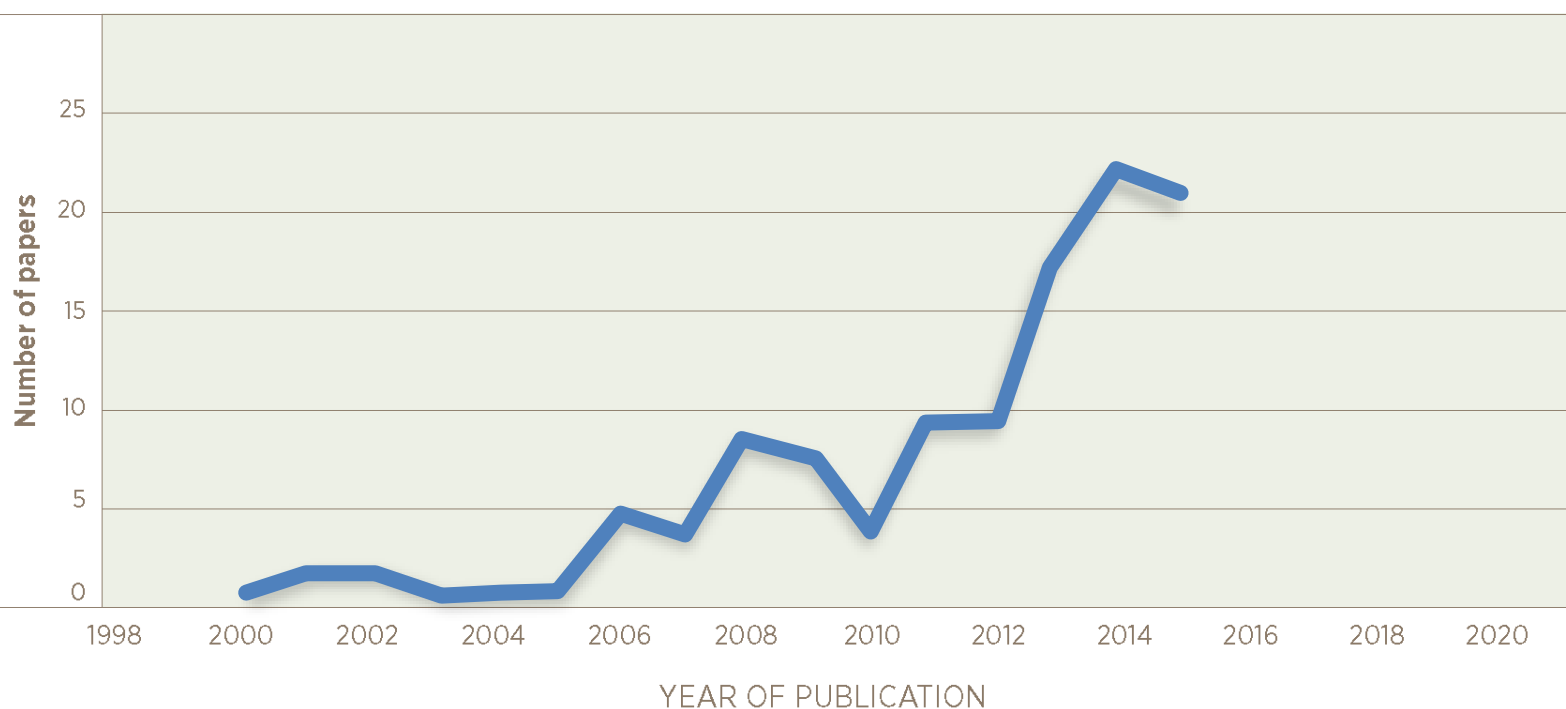
Improved
mother-infant
bonding

Alternative to
CPAP in
some
centres

Note: All surveys were conducted before RCTs were published

Growing evidence base...

Nasal high flow publications NEONATAL AND PEDIATRIC



NHF for post extubation respiratory support

Recap on three trials from 2013

Collins et al. 2013

A Randomized Controlled Trial to Compare Heated Humidified High-Flow Nasal Cannulae with Nasal Continuous Positive Airway Pressure Postextubation in Premature Infants

Collins C, Holberton J, Barfield C. et al. A Randomized controlled trial to compare heated humidified high-flow nasal cannulae with nasal continuous positive airway pressure postextubation in premature infants. J Pediatr. 2013 May;162(5):949-54

Who? What? Where?

MELBOURNE, AUSTRALIA (Collins et al.)



SAMPLE SIZE



132 infants
(< 32 weeks GA*)

RANDOMLY ASSIGNED TO NHF OR CPAP POST EXTUBATION

NHF:

- Vapotherm
- Starting flows 8 L/min



CPAP:

- Hudson bi-nasal prongs
- Starting pressure 7 – 8 cmH₂O

* GA = Gestational Age

Collins et al. 2013 Key points

- No significant difference in extubation failure within 7 days
- NHF caused less nasal trauma

Yoder et al. 2013

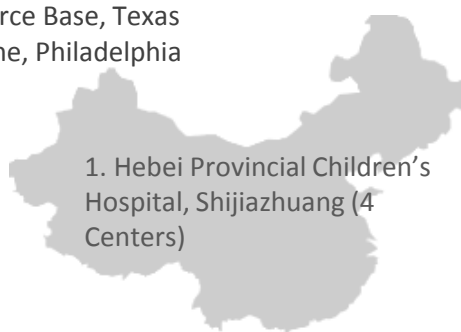
Heated, Humidified High-Flow Nasal Cannula
Versus Nasal CPAP for Respiratory Support in
Neonates

Yoder B, Stoddard R, Li M. et al. Heated, humidified high-flow nasal cannula versus basal CPAP for respiratory support in neonates. Pediatrics 2013 May;131(5)

Who? What? Where?

USA AND CHINA (Yoder et al.)

- 
1. University of Utah School of Medicine, Salt Lake City
 2. Utah Valley Regional Medical Center, Provo
 3. Wilford Hall Medical Center, Lackland Air Force Base, Texas
 4. University of Pennsylvania School of Medicine, Philadelphia

- 
1. Hebei Provincial Children's Hospital, Shijiazhuang (4 Centers)

SAMPLE SIZE



432 infants
(226 infants post extubation)
(> 28 weeks GA)

RANDOMLY ASSIGNED TO NHF OR CPAP

NHF:

- Vapotherm, Fisher and Paykel Healthcare, Comfort Flo
- Starting flows 3 – 5 L/min



CPAP:

- Bubble CPAP, Infant Flow, Ventilator
- Starting pressure 5 – 6 cmH₂O

Yoder et al. 2013 Key points

- No significant difference in extubation failure within 72 hours
- NHF caused less nasal trauma

Manley et al. 2013

High-Flow Nasal Cannulae in Very Preterm
Infants after Extubation

(HIPERSPACE – A noninferiority trial)

Manley B, Owen L, Doyle L. et al. High-flow nasal cannulae in very preterm infants after extubation.
N Engl J Med. 2013 Oct 10;369(15):1425-33

Who? What? Where?

AUSTRALIA



1. Royal Women's Hospital, Melbourne
2. The Royal Brisbane and Women's Hospital, Brisbane
3. Women's and Children's Hospital, Adelaide

SAMPLE SIZE



303 infants
(< 32 weeks GA)

RANDOMLY ASSIGNED TO NHF OR CPAP POST EXTUBATION

NHF:

- Fisher and Paykel Healthcare
- Starting flows 5 – 6 L/min



CPAP:

- Bubble CPAP
- Starting pressure 7 cmH₂O

A note about non-inferiority trials



- Most RCTs are *superiority* trials
- Non-inferiority trials assess if a new treatment (e.g. NHF) has similar efficacy to, or is no worse than, an established therapy (e.g. CPAP)
- The premise is that the new treatment has some other benefit and might be favoured over the standard treatment, even if the efficacy is the same or lower

A note about non-inferiority trials



Manley et al:

*To be considered non-inferior, NHF needed to be **no worse than CPAP** by a margin of 20%* in terms of treatment failure within 7 days*

*Based on the difference in failure rate between NHF and CPAP, including the 95% CI

Manley et al. Key points

- NHF **non inferior** to CPAP in terms of treatment failure within 7 days
- Intubation rate in the NHF group was slightly lower than in the CPAP group (non significant difference; 17.8% vs. 25.2%, $p=0.12$)
 - 'rescue CPAP' probably avoided intubation for approx. half the babies in whom NHF had failed
- NHF caused less nasal trauma

Caution for
subgroup of
infants < 26
weeks GA

Wilkinson et al. 2016



**Cochrane
Library**

Cochrane Database of Systematic Reviews

High flow nasal cannula for respiratory support in preterm infants (Review)

Wilkinson D, Andersen C, O'Donnell C. et al. Cochrane Database Syst Rev. 2016 Feb 22;2:CD006405.

Fisher & Paykel
HEALTHCARE

Wilkinson et al. 2016 Key points

- NHF vs CPAP for respiratory support after extubation (934 infants from 6 studies)
 - No difference in rates of death or chronic lung disease
 - No difference in rates of treatment failure or reintubation
 - Small reduction in rate of re intubation in infants 28 to 32 weeks' gestation with NHF
 - Small reduction in rate of pneumothorax with NHF
 - Significant reduction in nasal trauma

Note:
Relatively few
infants < 28
weeks GA
included in trials

NHF or CPAP Post Extubation?

- For infants under 26 weeks GA?
- For infants under 28 weeks GA?
- For infants between 28 and 32 weeks GA?
- For infants >32 weeks GA?

Good evidence to support the use of NHF in infants >28 weeks GA post extubation

But don't throw out your CPAP!



NHF for Primary Respiratory Support

Review two trials 'hot off the press'

Roberts et al. 2016

Nasal High-Flow Therapy for Primary Respiratory
Support in Preterm Infants

(HIPSTER)

Roberts CT, Owen LS, Manley BJ. et al. Nasal high-flow therapy for primary respiratory support in preterm infants. N Engl J Med. 2016 Sep 22;375(12):1142-51.

Aim and methods

STUDY DESIGN

International, multicenter, randomised, noninferiority trial

AIM

To determine the efficacy of Nasal High Flow (NHF) as primary respiratory support

WHO?

564 preterm infants with early respiratory distress
(gestational age, ≥ 28 weeks 0 days, to 36 weeks 6 days. No prior surfactant)

WHAT?

Infants randomised shortly after birth to receive NHF or CPAP

HOW?

Assessed therapy outcome within 72 hours of randomisation

Who? What? Where?

AUSTRALIA AND NORWAY

- 
1. **Royal Women's Hospital, Melbourne**
 2. The Royal Brisbane and Women's Hospital, Brisbane
 3. Monash Medical Centre, Melbourne
 4. Mercy Hospital for Women, Melbourne

1. Oslo University Hospital, Ullevål,
2. Akershus University Hospital, Lørenskog
3. Oslo University Hospital Rikshospitalet
4. Innlandet Hospital, Lillehammer
5. University Hospital of North Norway, Tromsø

SAMPLE SIZE



564 infants
(Recruitment stopped early)

INFANTS RANDOMLY ASSIGNED TO NHF OR CPAP

- NHF:

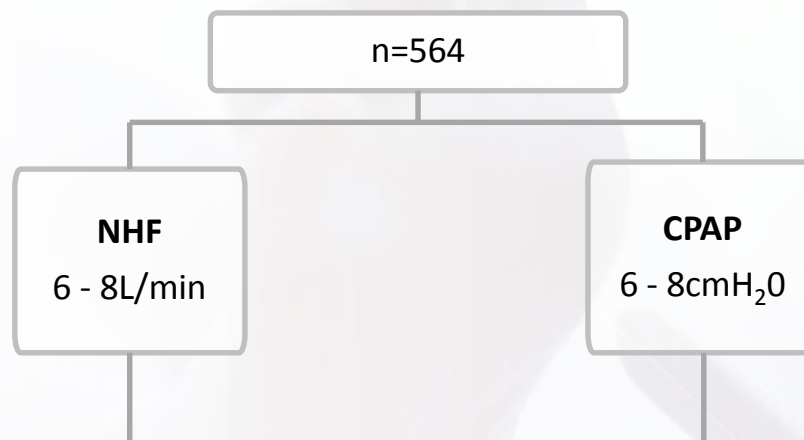
 - Optiflow In or Vapotherm
 - Starting flow 6 – 8 L/min
- 

Nasal High Flow
- 

CPAP
- CPAP:

 - Bubble or variable flow
 - Starting pressure 6 – 8 cmH₂O

Aim and methods

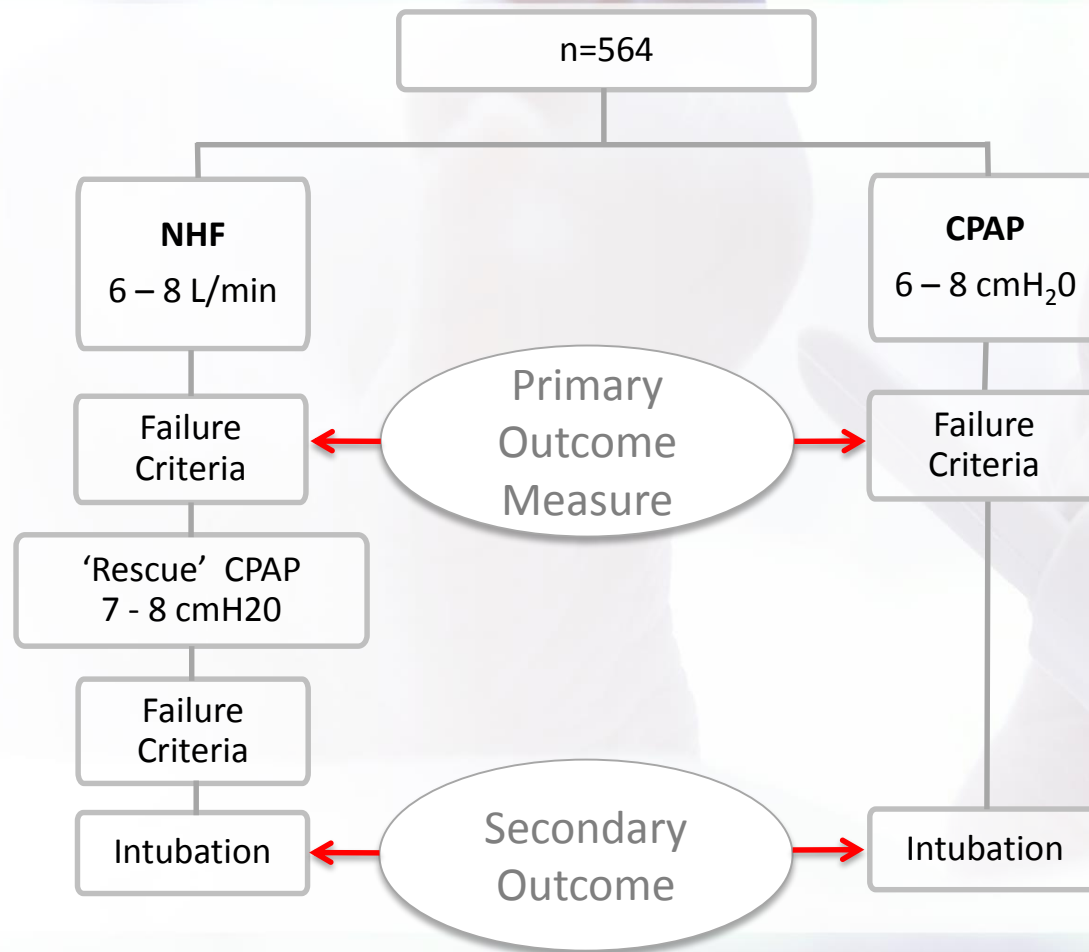


Therapy Outcome Assessed

Within **72 hours** of randomisation, infants meeting one or more of the following criteria while on maximal support are classified as 'therapy failure':

- **Increased Oxygen Requirement** (FiO_2 of 0.4 or higher)
- **Respiratory Acidosis** (pH of 7.2 or less with PCO_2 60mm Hg [8.0kPa])
- **Apneas** (two or more episodes requiring positive pressure ventilation within a 24 hour period, or six or more episodes requiring intervention within a 6 hour period)
- **Urgent Intubation** (determined by the treating clinician)

Aim and methods



Primary Outcome

- Assigned treatment failure within 72 hours
- Non-inferiority was determined by calculating the absolute risk difference in the **primary outcome**
- The chosen margin of non-inferiority was **10% points** (with the upper limit of the 95%CI* less than 10% and the lower limit of the 95% CI below zero)

To be considered non-inferior, NHF needed to be within 10% of CPAP in terms of initial therapy outcome

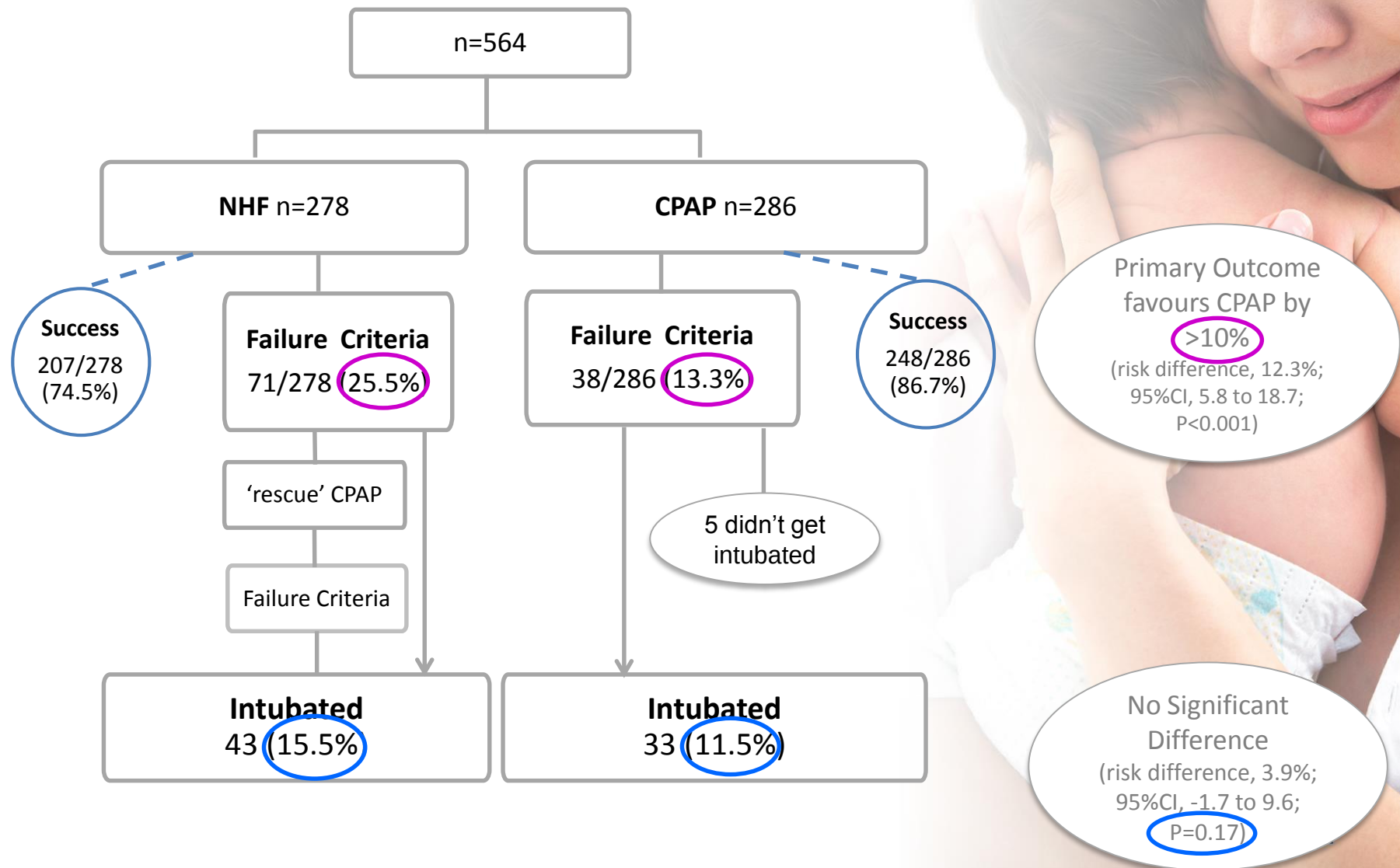
*95 percent confidence interval

Secondary Outcomes

Reported with
the Primary
Outcome

- **Intubation within 72 hours**
- Subgroup analysis by gestational age
- Reasons for treatment failure
- Other secondary outcomes e.g.:
 - Days of respiratory support
 - Supplemental oxygen
 - Surfactant treatment
- Adverse events e.g.:
 - Pneumothorax / air leak syndrome
 - Nasal trauma

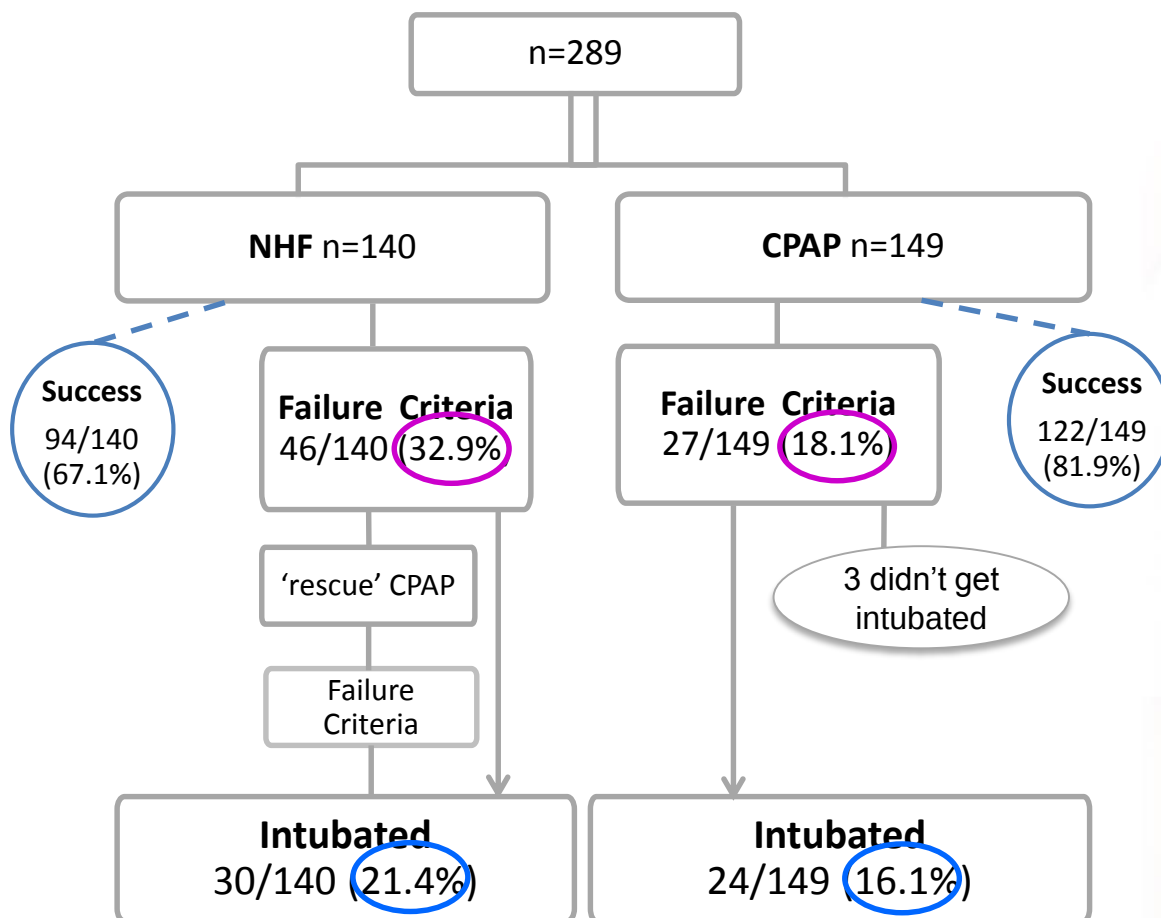
Results



Results

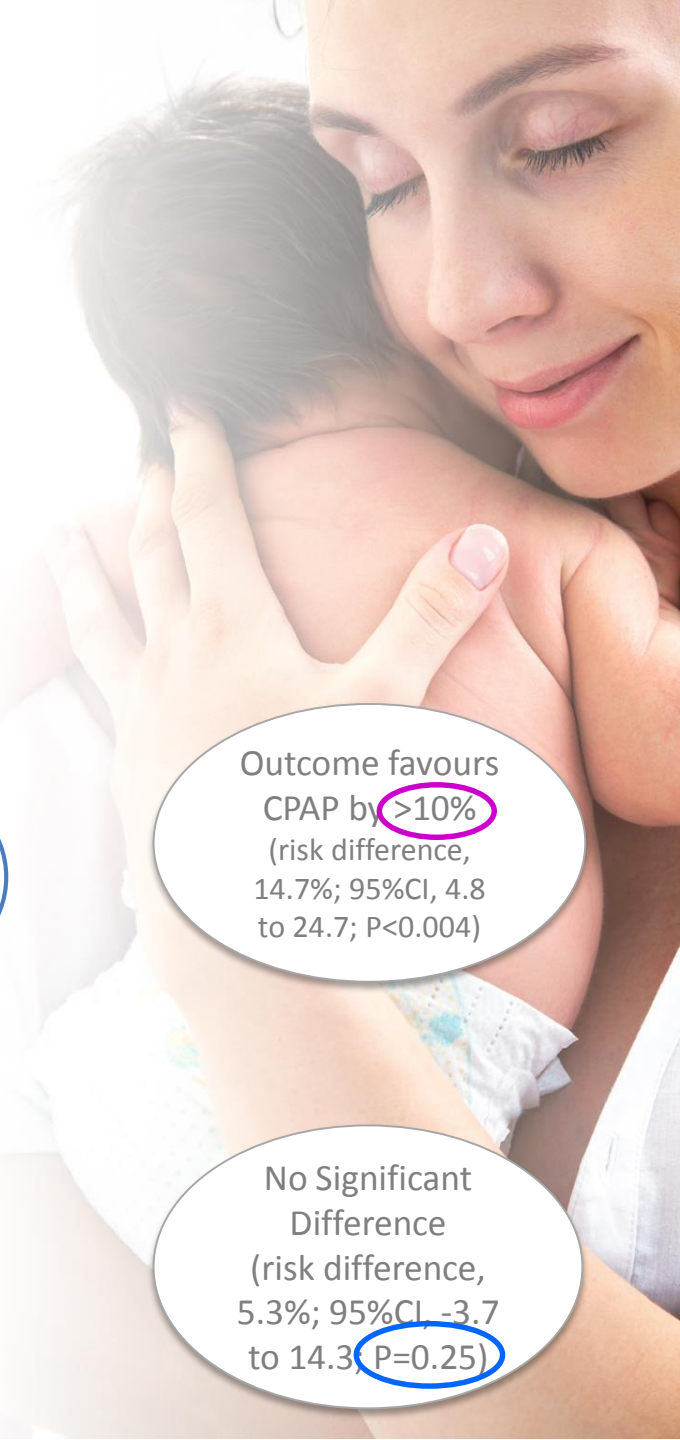
○ Subgroup Analysis by Gestational Age

- Infants < 32 weeks GA



Outcome favours CPAP by **>10%** (risk difference, 14.7%; 95%CI, 4.8 to 24.7; P<0.004)

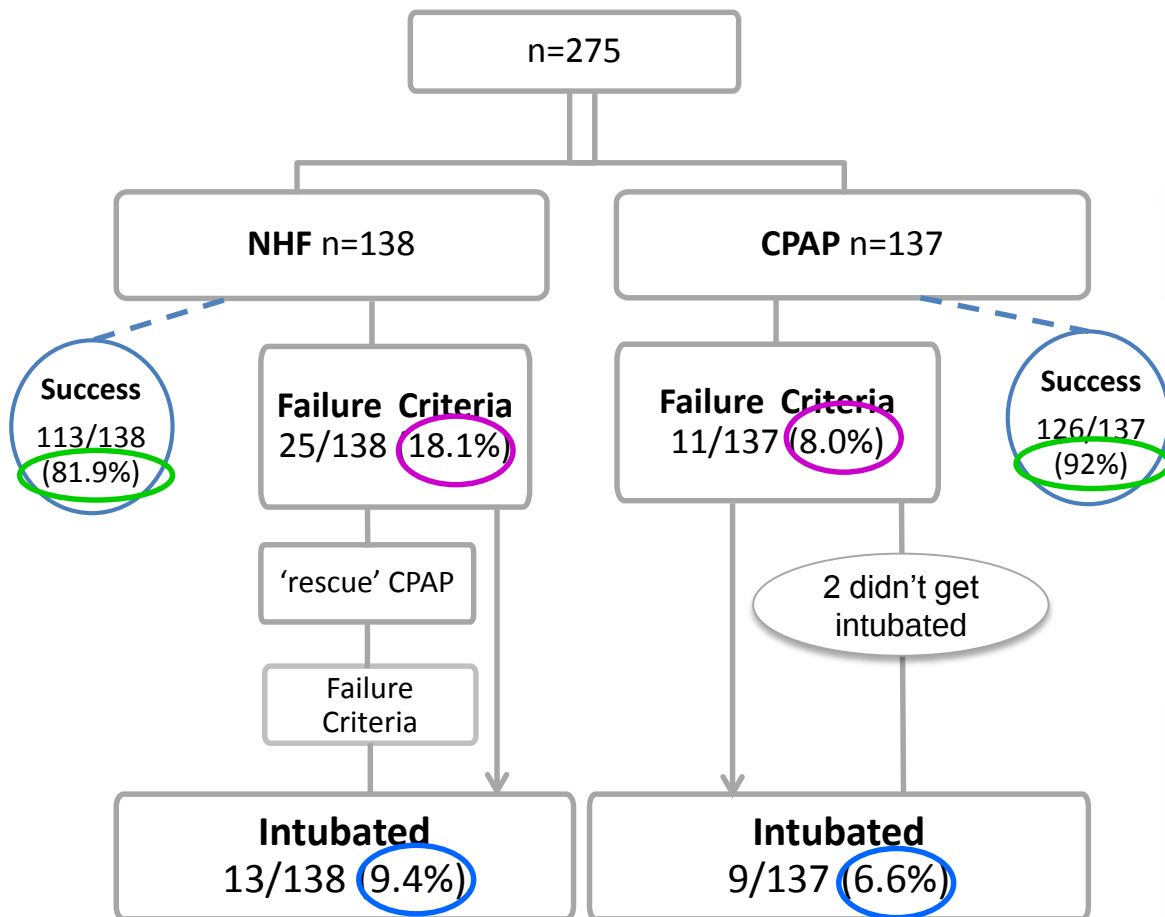
No Significant Difference (risk difference, 5.3%; 95%CI, -3.7 to 14.3, **P=0.25**)



Results

○ Subgroup Analysis by Gestational Age

- Infants ≥ 32 weeks GA



Initial therapy
success
high

Outcome favours
CPAP by >10%
(risk difference,
10.1%; 95%CI, 2.2 to
18.0, $P<0.01$)

No Significant
Difference
(risk difference,
2.9%; 95%CI,
-3.5 to 9.3)
 $P=0.38$

Results

- Reasons for treatment failure

- Apnea (NS)*
- Fraction of inspired oxygen ≥ 0.4 (NS)
- Respiratory acidosis (NS)
- **Urgent need for intubation**
(Risk difference -12.8% (95%CI, -26.2 to 0.7, $p = 0.03$)
- Clinician's decision (NS)

Outcome
favours
NHF

*Non Significant

Results

○ Other Secondary Outcomes

- Median time to treatment failure (NS)
- Surfactant treatment (NS)
- **Median no. days respiratory support during admission (P=0.005)**
- Supplemental oxygen therapy
 - **Any received during admission (P=0.02)**
 - Median age at cessation (NS)
- Discharge home with oxygen therapy (NS)
- Median age at start of full-suck feeding (NS)
- Discharge home with gastric tube feeding (NS)
- Weight at discharge (NS)
- Median no. days in tertiary care center (NS)
- Median no. days in any hospital (NS)

NHF group had
~1 extra day on
respiratory
support

NHF group more
likely to receive
brief supplemental
oxygen

Results

○ Adverse Events

- Death before discharge (NS)
- Oxygen supplementation, respiratory support or both at 36wks GA (corrected) (NS)
- Pneumothorax or other air leak syndrome
 - **During assigned treatment (P= 0.02)**
 - Any time during admission (NS)
- Postnatal glucocorticoid treatment for lung disease (NS)
- **Nasal trauma (<0.001)**
- Patent ductus arteriosus treated with medication or surgical ligation (NS)
- Confirmed sepsis (NS)
- Necrotising enterocolitis, Bell's stage ii or iii (NS)
- Isolated intestinal perforation (NS)
- Laser surgery for retinopathy of prematurity (NS)
- Intraventricular hemorrhage, grade 3 or 4 (NS)
- Cystic periventricular leukomalacia (NS)

Outcome
favours
NHF

Outcome
favours
NHF

Roberts et al. 2016 Key points

- Primary outcome favours CPAP
- Using **NHF first** (with CPAP as back up) resulted in a similar intubation rate compared to using CPAP first
- > 80% of infants ≥ 32 weeks GA were managed on NHF alone
- Using **NHF first** (with CPAP as back up) resulted in
 - less nasal trauma
 - fewer air leaks whilst on treatment
 - fewer emergency intubations
- Using **CPAP first** resulted in
 - 1 less day of respiratory support
 - fewer infants needing brief supplemental oxygen

Lavizzari et al. 2016

Heated, Humidified High-Flow Nasal Cannula vs
Continuous Positive Airway Pressure for Respiratory
Distress Syndrome of Prematurity.
A Randomized Clinical Noninferiority Trial

Lavizzari A, Colnaghi M, Ciuffini F. et al. Heated, humidified high-flow nasal cannula vs continuous positive airway pressure for respiratory distress syndrome of prematurity. A randomized clinical noninferiority trial. JAMA Pediatrics. Published online August 8, 2016.

Aim and methods

STUDY DESIGN

Single center, randomised noninferiority trial

AIM

To determine the efficacy of nasal high flow (NHF) as primary respiratory support

WHO?

316 preterm infants with mild to moderate respiratory distress (RDS) (Gestational age; 29 weeks 0 days to 36 weeks 6 days)

WHAT?

Randomised to receive NHF or nasal CPAP

HOW?

Assessed need for mechanical ventilation within 72hours

Who? What? Where?

ITALY



Ospedale Maggiore Policlinico,
Milano

SAMPLE SIZE



316 infants

INFANTS RANDOMLY ASSIGNED TO NHF OR CPAP

NHF:

- Precision Flow (Vapotherm)
 - Flow 4 – 6 L/min

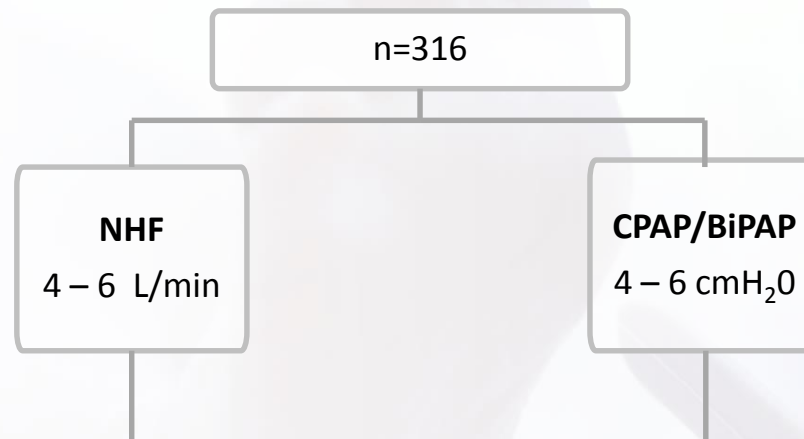


CPAP:

- SiPAP (Viasys Healthcare)
 - Pressure 4 – 6 cmH₂O
 - Increased to BiPAP settings for apneas or increased work of breathing

Fisher & Paykel
HEALTHCARE

Aim and methods

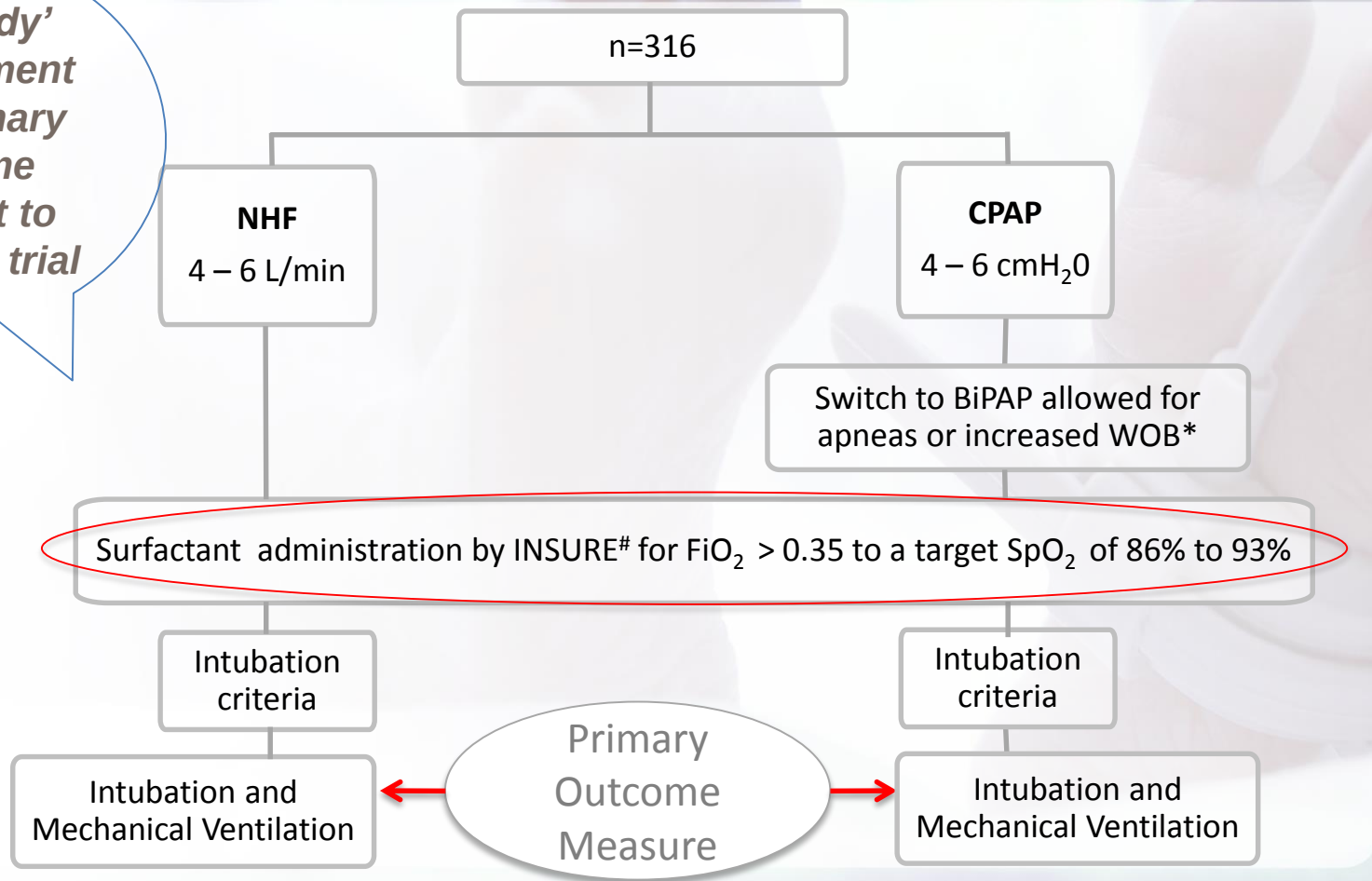


Criteria for **intubation and mechanical ventilation** assessed within 72 hours:

- **Oxygen Requirement** (persistent FiO_2 of > 0.4 to to a target spO_2 86% to 93% **after surfactant administration**)
- **Respiratory Acidosis** (persistent PCO_2 greater than 70 mmHg [8.66kPa] with a pH of less than 7.2 despite noninvasive respiratory support)
- **Severe Apnea** (> 4 apnea episodes per hour or > 2 apnea episodes per hour requiring positive pressure ventilation)

Aim and methods

*'On study'
management
and primary
outcome
different to
HIPSTER trial*



* Work of Breathing

Intubation, Surfactant, Extubation

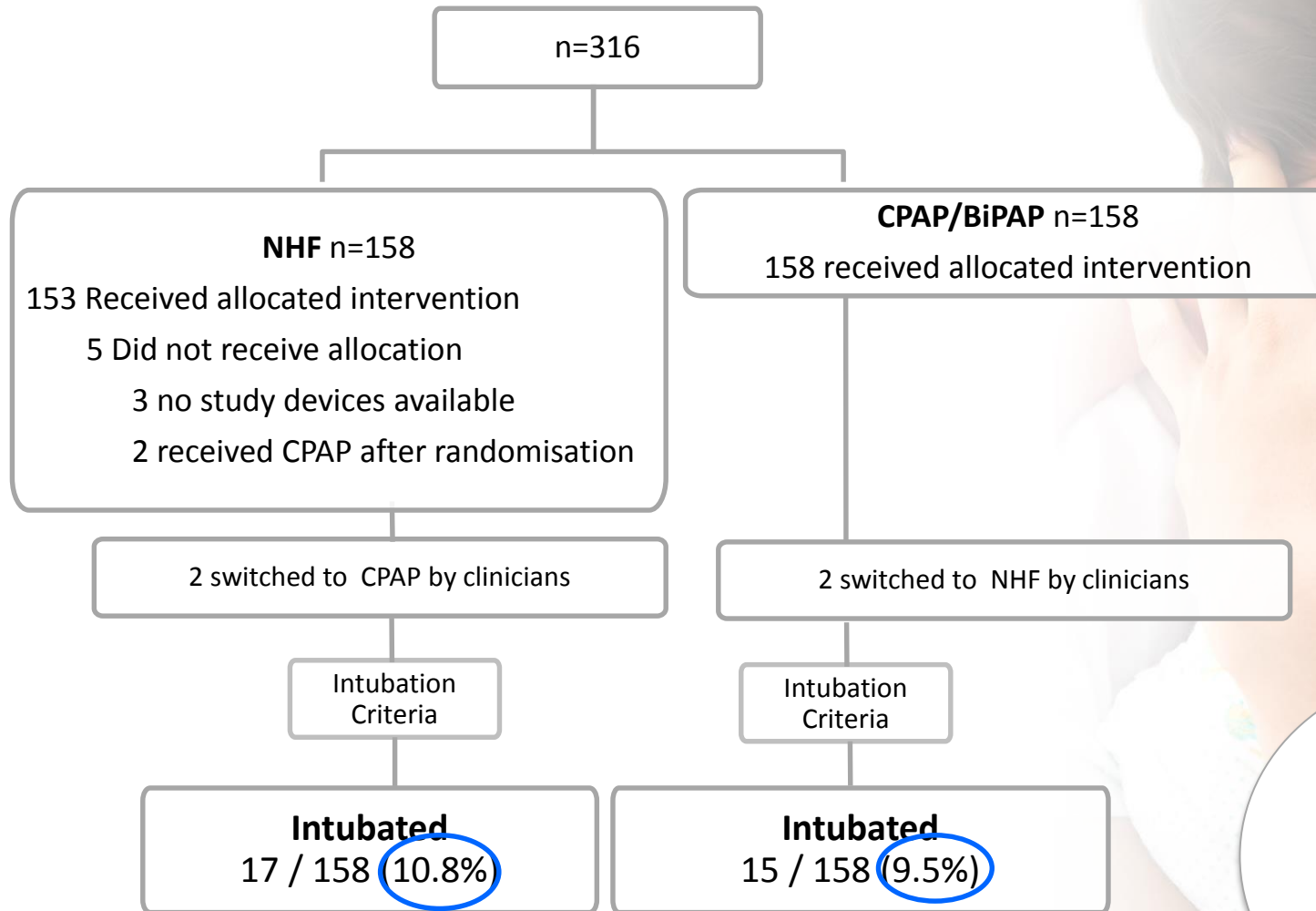
Primary Outcome

- **Intubation and mechanical ventilation** within 72 hours
- Non-inferiority was determined by calculating the absolute risk difference in the **primary outcome**
- The chosen margin of non-inferiority was **10% points** (with the upper limit of the 95%CI* less than 10% and the lower limit of the 95% CI below zero)

The primary outcome for the HIPSTER trial was failure of initial therapy

*95 percent confidence interval

Results



Primary Outcome
within the 10%
margin of
noninferiority

(risk difference, 1.3%;
95%CI, -6.0 to 8.6;
P=0.71)

Results

- NHF non inferior to CPAP/BiPAP in terms of the primary outcome
- No significant differences in secondary outcomes:
 - Subgroup analysis by gestational age (NS)
 - Duration of mechanical ventilation (NS)
 - Days of respiratory support (NS)
 - Days of oxygen supplementation (NS)
 - Caffeine treatment (NS)
 - **Surfactant treatment (44.3% vs 46.2%) (NS)**
- The median age at the start of mechanical ventilation for infants in the NHF group was significantly older than the CPAP group, as 3 infants were intubated for clinical signs of volvulus
- No significant differences in adverse events e.g.:
 - Pneumothorax / air leak syndrome (NS)

The overall rate of surfactant administration in the HIPSTER trial was lower; 14.4% vs 10.5%

Lavizzari et al. 2016 Key Point

- Lavizzari et al. showed that NHF has similar safety and efficacy to CPAP/BiPAP when used in the primary treatment of mild to moderate RDS in infants between 29⁺⁰ and 36⁺⁶ weeks GA

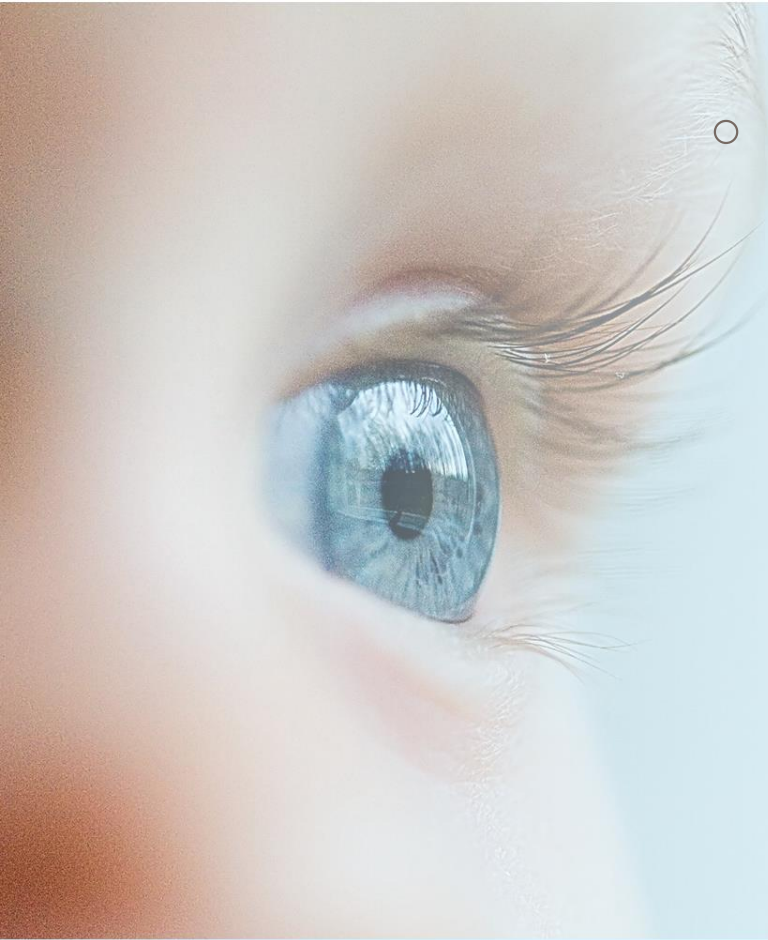
NHF or CPAP for Primary Support?

- For infants under 28 weeks GA?
- For infants under 28/29 to 32 weeks GA?
- For infants between > 32 weeks GA?

Good evidence to support the use of NHF for primary respiratory support in the more mature infants

But don't throw out your CPAP!

Future Directions

- 
- A close-up photograph of a newborn's eye, showing a light blue iris and dark eyelashes. The eye is looking slightly to the left. The background is a soft, out-of-focus light blue.
- More research required to establish:
 - Best combination strategies to avoid intubation and mechanical ventilation (NHF, CPAP, BiPAP, Surfactant)
 - Best weaning protocols to avoid prolonged NHF therapy
 - Best flow 'dose' in neonatal populations
 - Resource / economic implications (especially in the developing world context)