GUY'S & ST THOMAS' CHARITY

KING'S College LONDON

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Guy's and St Thomas' NHS

NHS Foundation Trust

London Respiratory Muscle Group

Clinical Trials of Home Non-Invasive Ventilation in COPD:

Who, How and When?

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THORAX

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Which COPD patients should we consider for home non-invasive ventilation based on the current evidence?

Unstable Post AECOPD Patients

VS

Chronic Stable COPD Patients

Unstable Post AECOPD Patients

VS

Chronic Stable COPD Patients

Nocturnal non-invasive ventilation in COPD patients with prolonged hypercapnia after ventilatory support for acute respiratory failure: a randomised, controlled, parallel-group study

F M Struik,[1,2] R T M Sprooten,[3] H A M Kerstjens,[1,2] G Bladder,[1] M Zijnen,[4] J Asin,[5] N A M Cobben,[3] J M Vonk,[2,6] P J Wijkstra[1,2]

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RESCUE TRIAL

Primary Outcome: Admission Free Survival

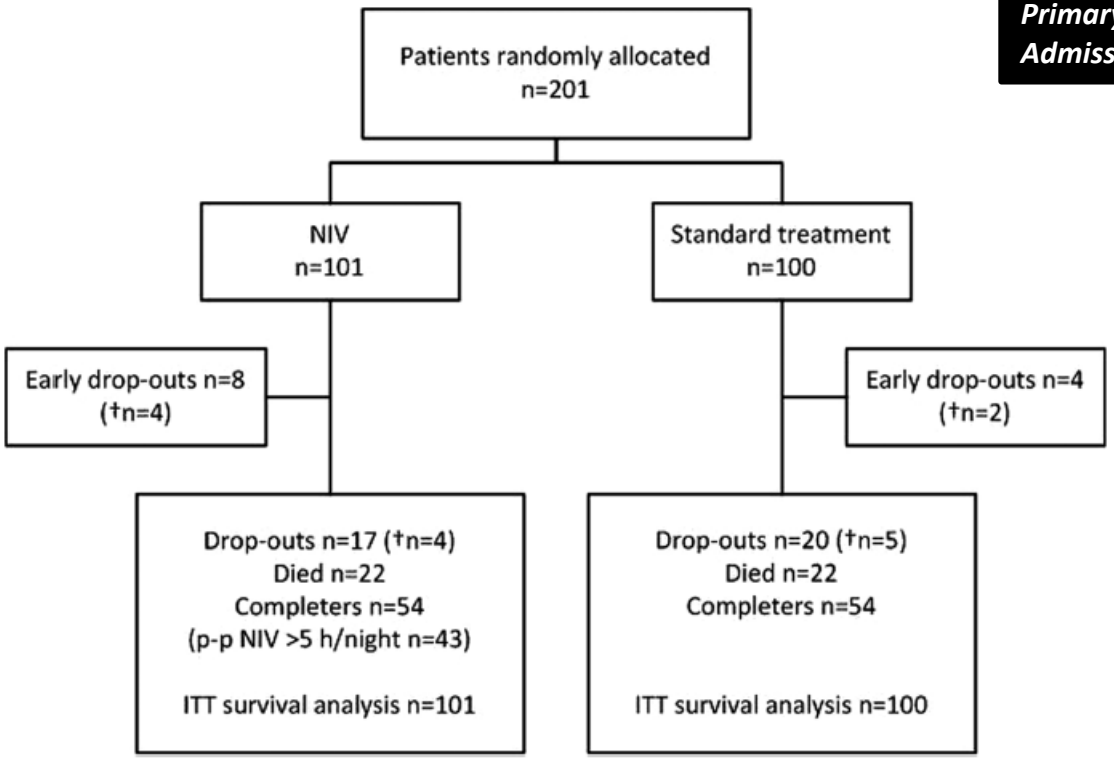

Table 1 Baseline characteristics

	ITT NIV n=101	ITT controls n=100
Age (years)	63.92 (8.6)	63.5 (7.9)
Gender, n (% female)	60 (59%)	58 (58%)
Pack years*	38 (0–140)	44 (0–125)
BMI (kg/m^2)	24.6 (5.4)	24.8 (6.3)
LTOT, n (%)	76 (75%)	78 (78%)
Invasive, n (%)†	13 (13%)	12 (12%)
Duration ventilation*‡ (days)	5.0 (1–19)	5.0 (1–24)
Admissions* ($year^{-1}$)	2.0 (1–9)	2.0 (1–10)
Total admission days/patient* ($year^{-1}$)	28.5 (8–108)	22.0 (6–115)§
Rehabilitation, n (%)	50 (50%)	51 (51%)
FEV_1 (L)	0.67 (0.23)	0.65 (0.23)
FEV_1 (% pred)	25.6 (7.8)	25.7 (8.6)
FVC (% pred)	64.3 (19.8)	63.6 (17.0)
FEV_1 to FVC (%)	32.5 (9.0)	33.0 (9.5)
$PaCO_2$¶ (kPa)	7.9 (1.2)	7.7 (1.3)
PaO_2¶ (kPa)	7.9 (2.1)	7.5 (1.7)

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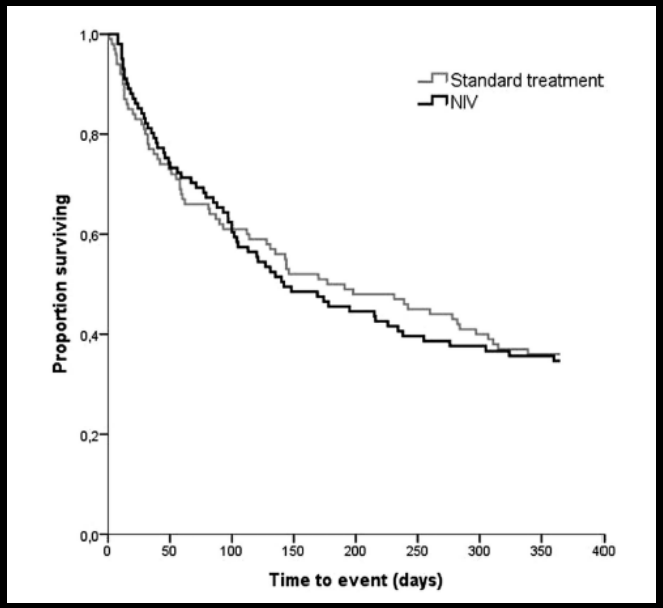

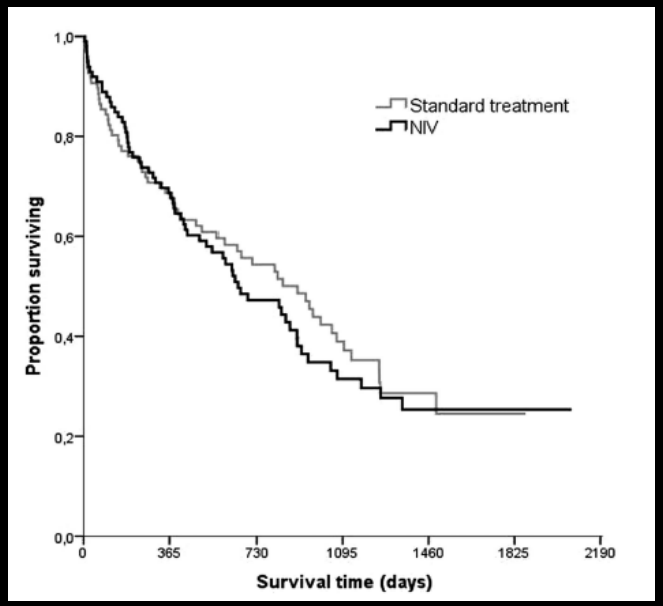

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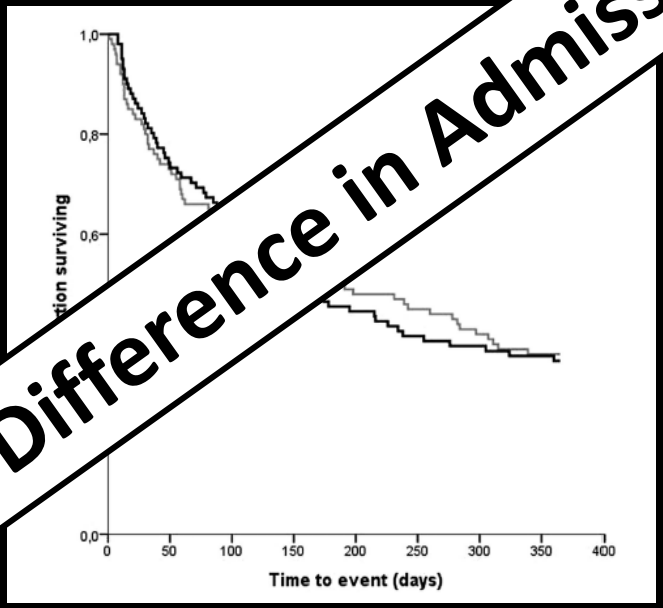

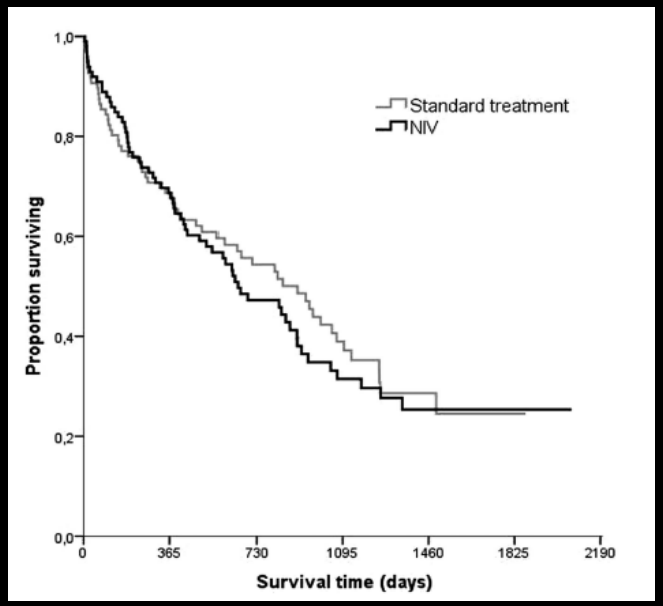

No Difference in Admission Free Survival at 12 months

Why was there a lack of effect with NIV?

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Trials of home mechanical ventilation in COPD: what have we learnt?

P B Murphy, N Hart

- **Failure to deliver the treatment intervention**
  - IPAP 19.2 ± 3.4 cmH_2O EPAP 4.8 ± 3.4 cmH_2O BUR 15 ± 3 bpm
  - Nocturnal $TcCO_2$ of 0.8kPa lower at one year in the HMV group
  - No difference in $PaCO_2$ at 12 months as improvement in standard treatment group
- **Inappropriate primary outcome**
  - 1 year admission free survival (65% HMV vs. 64% Standard Treatment)
  - Most appropriate clinical and cost effective outcome
- **Inappropriate target population**
  - RESCUE targeted high risk group
  - Borderline hypercapnic respiratory failure ($PaCO_2$ <6kPa) enrolled
- **Failure of the intervention itself**
  - Only acceptable conclusion when all three above are met

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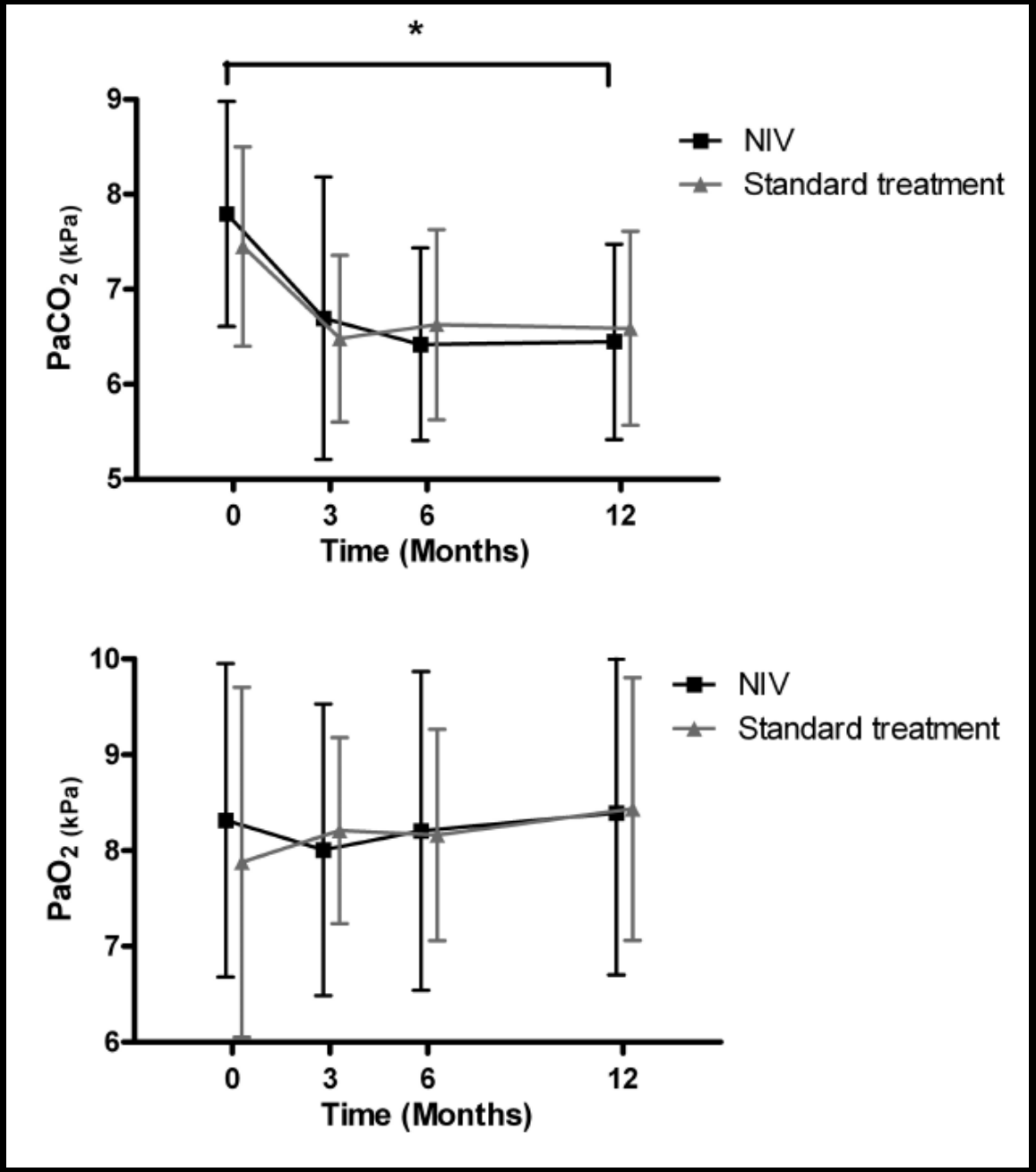
*
9
8
7
6
5
PaCO2 (kPa)
0
3
6
12
Time (Months)
NIV
Standard treatment
10
9
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Unstable Post AECOPD Patients

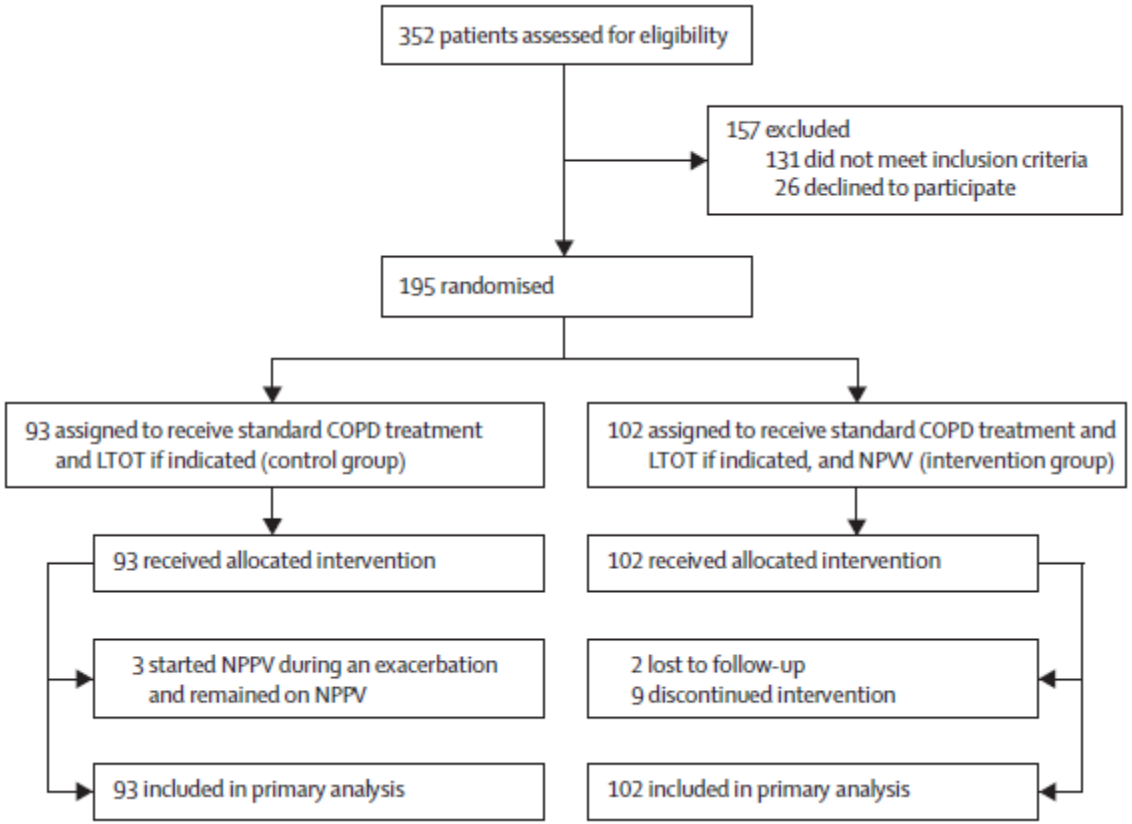
VS

Chronic Stable COPD Patients

Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial

Thomas Köhnlein, Wolfram Windisch, Dieter Köhler, Anna Drabik, Jens Geiseler, Sylvia Hartl, Ortrud Karg, Gerhard Laier-Groeneveld, Stefano Nava, Bernd Schönhofer, Bernd Schucher, Karl Wegscheider, Carl P Criée, Tobias Welte

Lancet Respiratory On Line First 2014



A cohort of COPD patients with advanced disease and established chronic respiratory failure and relatively well preserved exercise capacity

	Control group (n=93)	Non-invasive positive pressure ventilation group (n=102)
Age, years	64·4 (8·0)	62·2 (8·6)
Male, n (%)	56 (60%)	65 (64%)
Body-mass index, kg/m^2	24·5 (5·8)	24·8 (5·8)
FVC, % predicted	53·3% (13·8)	50·4% (13·3)
FEV_1, % predicted	27·5% (8·9)	26% (11·0)
FEV_1/FVC, %	41·2% (11·4)	40·4% (11·5)
Residual volume/total lung capacity, %	72·7% (8·9)	73·0% (8·5)
pH	7·39 (0·05)	7·39 (0·04)
$PaCO_2$, kPa	7·7 (0·7)	7·8 (0·8)
PaO_2, kPa*	8·7 (1·9)	8·6 (2·1)
SaO_2, %*	90·8% (5·9)	90·3% (6·2)
HCO_3^-, mmol/L	33·9 (4·1)	34·3 (4·0)
Base excess, mmol/L	8·0 (3·9)	7·8 (3·8)
6-min walk distance, m	249·6 (145·3)	226·7 (121·2)
Long-term oxygen treatment, n (%)	60 (65%)	67 (66%)

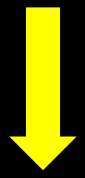
Low emergency admission rate

	3 months	6 months	9 months	12 months
Overall	0·8 (3·5)	2·1 (5·7)	0·9 (4·0)	2·6 (8·6)
Non-invasive positive pressure ventilation group	0·2 (1·1)	1·4 (4·7)	1·3 (4·9)	2·2 (10·2)
Control group	1·5 (4·9)	3·0 (6·9)	0·4 (1·9)	3·1 (5·4)

Values are mean (SD).

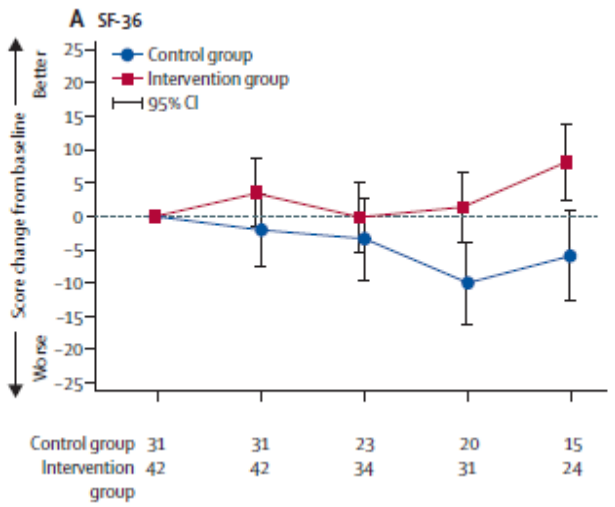
Greater reduction in daytime $PaCO_2$ in HMV group

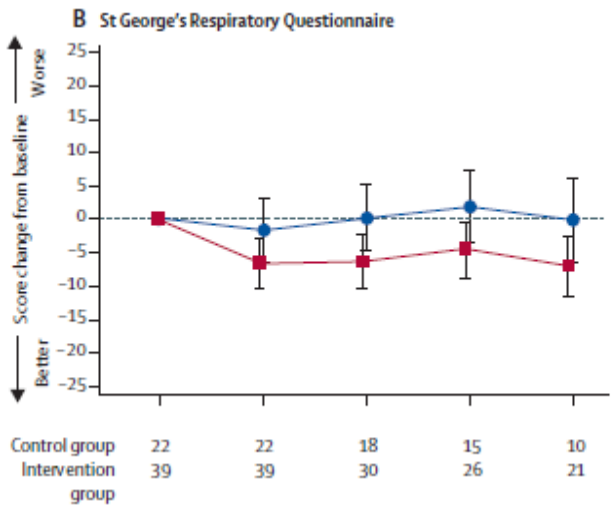
	Baseline	14 days	3 months	6 months	9 months	12 months
All patients	7·9 (0·8)	7·0 (1·1)	7·0 (1·1)	6·7 (1·0)	6·8 (0·9)	6·9 (1·1)
Control group	7·9 (0·7)	7·5 (1·1)	7·4 (0·9)	7·1 (1·0)	7·3 (0·8)	7·4 (1·2)
Non-invasive positive pressure ventilation group	8·0 (0·8)	6·6 (0·9)	6·6 (1·1)	6·4 (0·9)	6·4 (0·9)	6·5 (0·9)

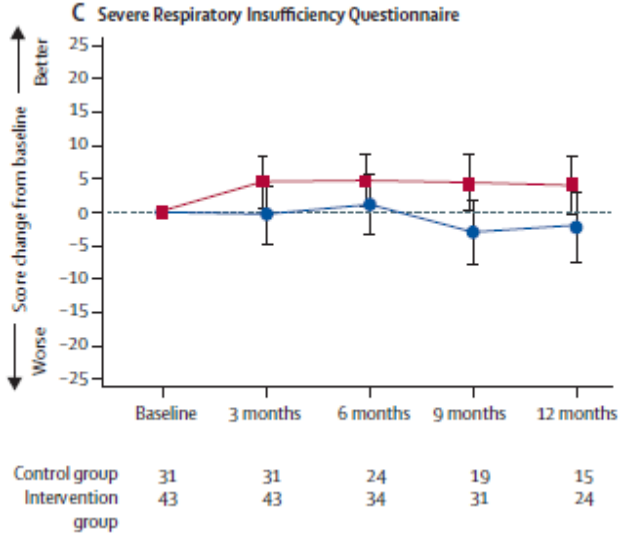


Target 20% reduction at 7 days in HMV Group

Subgroup Health Related Quality of Life Analysis







No difference in SF-36 except in the general health perception subscale

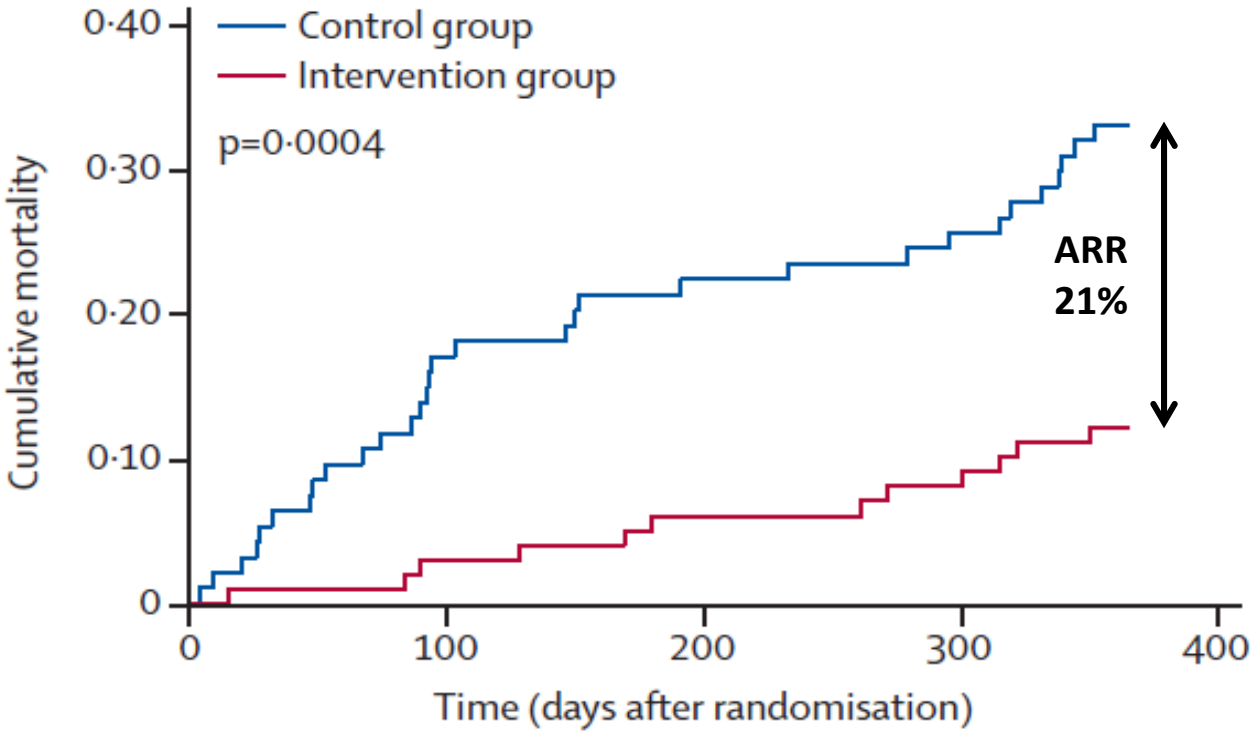
Difference in the SGRQ summary score

Difference in the SRI summary scale score

GENERIC HRQL

SPECIFIC HRQL

Lower all-cause mortality in the HMV vs. Standard Treatment Group



Number at risk

Control group	93	77	72	69
Intervention group	102	95	92	90

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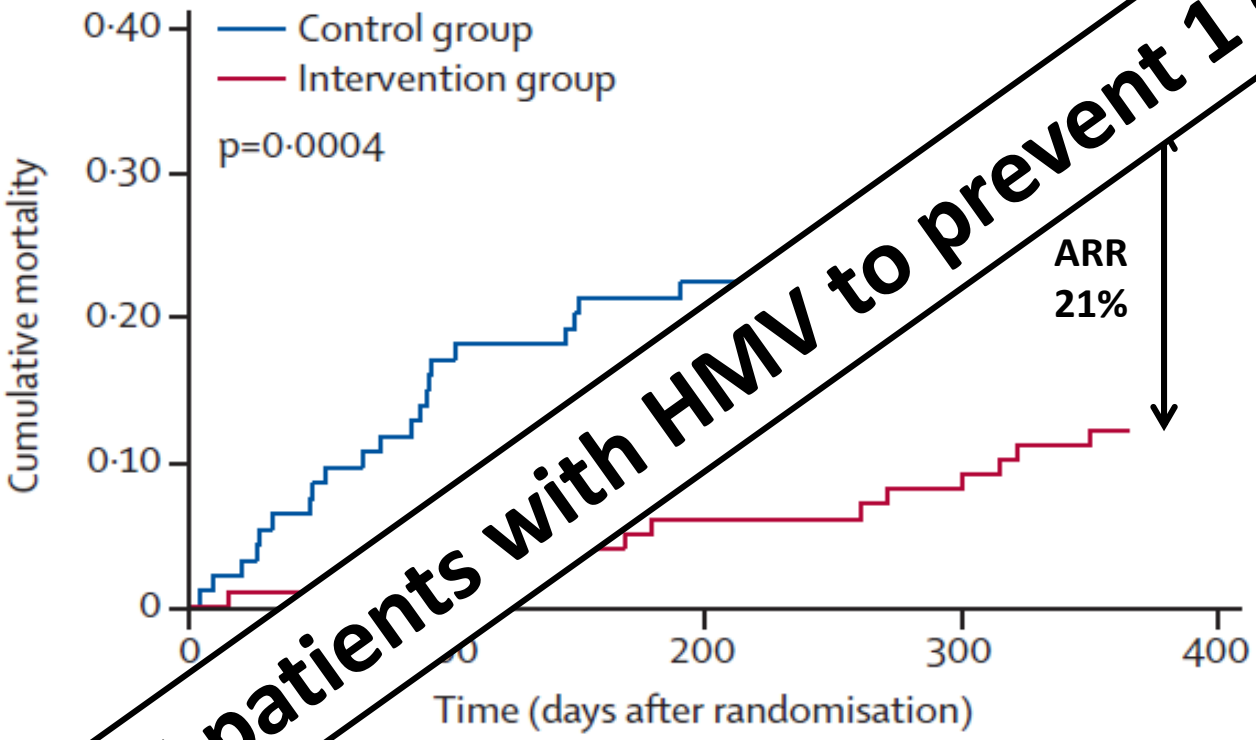

Need to Treat 5 patients with HMV to prevent 1 death

Why was there an effect with home non-invasive ventilation in this trial?

- **Delivery of the treatment intervention**
  - IPAP 21.6 ± 4.7 cmH_2O EPAP 4.8 ± 1.6 cmH_2O BUR 16.1 ± 3.6 (range 2-24) bpm
  - Targeted 20% reduction in $PaCO_2$ or less than 6.5kPa
  - 5.6 (1.1) days for elective inpatient set up of NIV vs. 2.5 (0.2) days for standard treatment group
  - Mean adherence of 5.9 (3.1) hours per night
- **Appropriate primary outcome**
  - 1 year all cause mortality
  - Although a useful clinical and cost effective outcome, cost effectiveness is offset by the extended inpatient set up and inpatient follow up
  - Trial terminated early as 'mortality effect was larger than anticipated'
- **Appropriate target population**
  - Targeted a group with severe hypercapnic respiratory failure ($PaCO_2$ > 7kPa)
  - Screening data lacking and therefore true clinical applicability unknown
- **Intervention Clinically Effective**
  - 1 year all cause mortality (12% HMV vs. 33% Standard Treatment)
  - HRQL difference is a selected subgroup

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SUMMARY

Patient Selection – Who?

Mode of NIV – How?

Timing of initiation – When?

Best Outcome – Which?

Patient Selection – Who?

Mode of NIV – How?

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Best Outcome – Which?

Patient Selection – Current Evidence

- Severe stable COPD (FEV_1 < 1L)
- Symptoms of nocturnal hypoventilation with high symptom load
- Baseline P_aCO_2 > 7kPa (50mmHg)
- Preserved exercise capacity (6MWT >200m)
- Low annual emergency admission rate prior to enrolment

Patient Selection – Ongoing Trial

- Severe COPD (FEV_1 < 1L)
- Post AECOPD requiring acute NIV
- P_aCO_2 > 7kPa (50mmHg) at 2-4 weeks post termination of acute NIV
- High annual emergency admission rate prior to enrolment
- Low health related quality of life

Guy's and St Thomas' NHS
NHS Foundation Trust

UKCRN
UK Clinical Research Network

MRC Clinical Trials Unit

HoT-HMV Trial

Independent Data Monitoring Committee

Open Report

Baseline characteristics	Total (N=76)
*Age (years)	66.6 (9.3)
*BMI (kg/m^2)	23.1 (5.4)
*Prior use of LTOT (n (%))	36 (70.6%)
*≥3 COPD related admissions in last year (n (%))	28 (54.9%)
Gender (female) (n (%))	30 (53.6%)
Smoking pack year history (n (%))	49.3 (21.5)
AHI (/hr) (median (25th percentile to 75th percentile))	1.7 (0.8 to 4.6)
Neck circumference (cm)	37.6 (4.8)
Waist circumference (cm)	90.6 (15.3)
FEV_1 (l)	0.6 (0.2)
FEV_1 (%)	24.7 (8.9)
FVC (l)	1.7 (0.7)
FVC (%)	57.1 (19.0)
FEV_1/FVC	0.4 (0.1)
PaO_2 on room air	6.4 (1.1)
$PaCO_2$ on room air	7.9 (1.0)
SGRQ Summary (QoL)	71.2 (12.6)
SRI Summary (QoL)	45.9 (14.2)

Home oxygen therapy vs. Home mechanical ventilation post acute exacerbation of COPD requiring NIV

Primary outcome
Admission free survival

Inclusion Criteria
PaCO2 > 7kPa
2-4 weeks post cessation of acute NIV

Patient Selection – Who?

Mode of NIV – How?

Timing of initiation – When?

Best Outcome – Which?

Mode of NIV – Current Evidence

- Pressure support ventilation
- High pressure (IPAP > 22cmH_2O)
- Back up rate > 16bpm
- Targeted reduction in P_aCO_2 > 20% from baseline or P_aCO_2 < 6.5kPa
- Adherence > 6 hours per night

Patient Selection – Who?

Mode of NIV – How?

Timing of initiation – When?

Best Outcome – Which?

Timing of Initiation – Current Evidence

- **Stable state**
- **P_aCO_2 > 7kPa (50mmHg)**

Timing of Initiation – Ongoing Trial

- Post AECOPD requiring acute NIV
- P_aCO_2 > 7kPa (50mmHg) at 2-4 weeks post termination of acute NIV
- High annual emergency admission rate prior to enrolment

Patient Selection – Who?

Mode of NIV – How?

Timing of initiation – When?

Best Outcome – Which?

Best Outcome Measures

CLINICAL EFFECTIVENESS

- **Daytime $PaCO_2$**
- **Health related quality of life**
- **Physical activity**

COST EFFECTIVENESS

- **Admission-free survival**

CONCLUSION

- **Nocturnal home non-invasive ventilation has been shown to improve outcome in the stable COPD patients with chronic respiratory failure and low hospital admission frequency and preserved exercise tolerance**
- **Nocturnal non-invasive ventilation has not been shown to be a useful treatment following an acute exacerbation of COPD**
- **The outcome of the HoT-HMV trial will be published in September 2016**

ERS INTERNATIONAL CONGRESS 2016
LONDON united kingdom, 3–7 september

HoT-HMV Trial: Home Mechanical Ventilation vs. Home Oxygen Therapy in COPD (NCT00990132)

Morning Symposium Monday 5th September 'Latest Developments in NIV'
Evening Symposium Tuesday 6th September 'HMV in COPD – Where are we now?'
Lunchtime Wednesday 7th September Press Release

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CanHELP Charity

Guy's & St Thomas' Charitable Foundation

European Intensive Care Society

European Respiratory Society

National Institute of Health Research

Medical Research Council

NHS Innovations London

Peel Medical Charity

Philips-Respironics (unrestricted grants)

Philips (unrestricted grant)

Resmed Charitable Foundation

Resmed (unrestricted grant)

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