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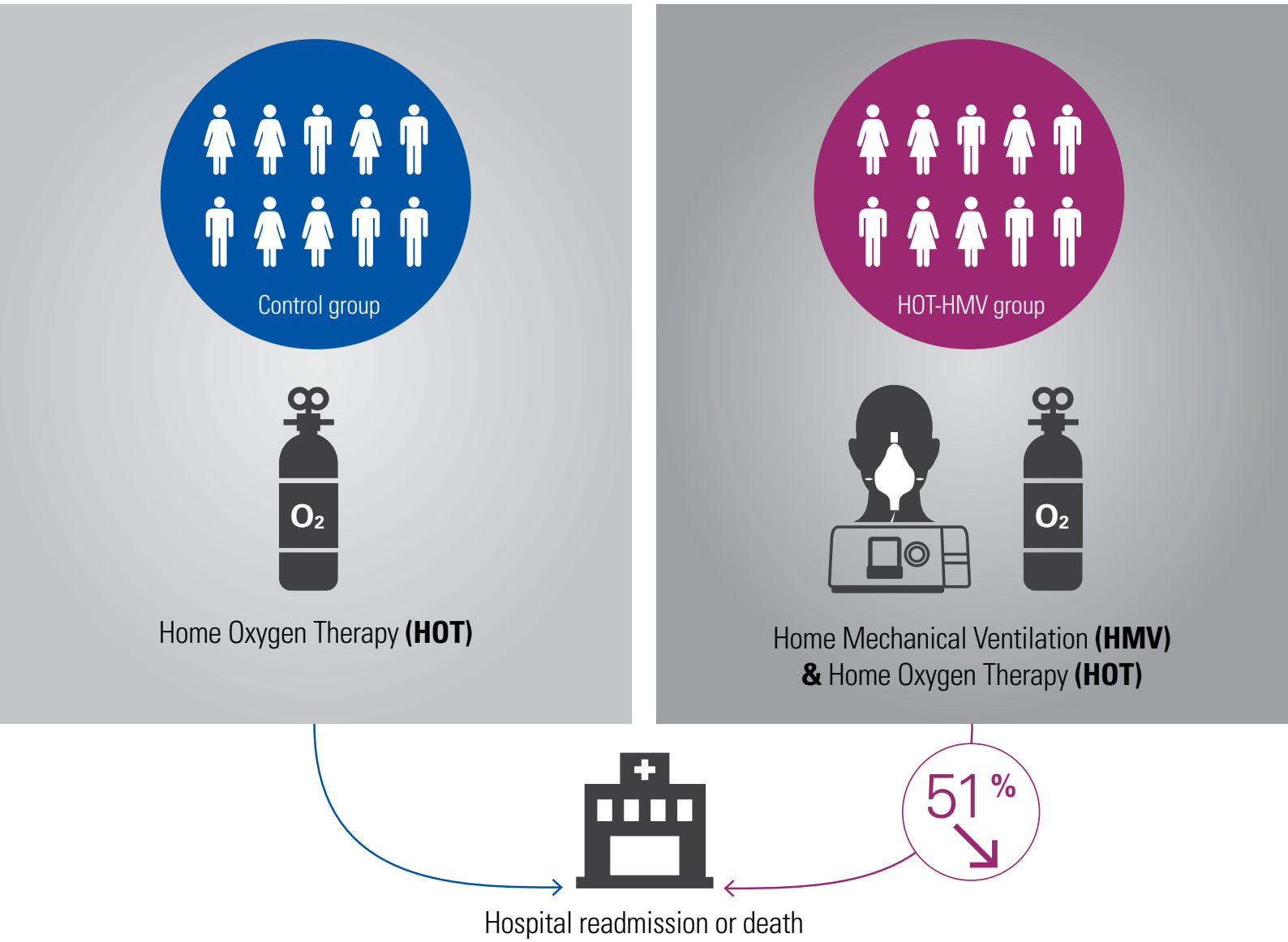
HOT HMV Changing the outcome in COPD



The HOT-HMV study:

51% reduction in risk of hospital readmission or death in hypercapnic COPD patients treated with home non-invasive ventilation and oxygen therapy

Moving the management of COPD forward, together

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Study snapshot

HOT-HMV[1] is the first multi-centre, open-label, parallel-group, randomised controlled trial to show that home mechanical ventilation (HMV) combined with home oxygen therapy (HOT) significantly reduces the risk of hospital readmission or death in severe COPD patients after an acute COPD exacerbation requiring NIV.

Study design

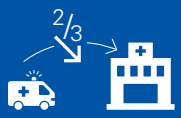
The study recruited severe COPD patients who remained hypercapnic after an acute exacerbation of COPD (AECOPD). This patient population had a history of frequent hospitalisations.

116 patients were randomised to two arms: the HOT arm treated with oxygen therapy and the HOT-HMV arm treated with both HOT and HMV. The primary outcome was admission-free survival, a combined endpoint of time to either hospital readmission or death by 12 months.

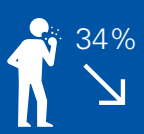
Study results

Results showed a 51% reduction in the risk of hospital readmission or death in the HOT-HMV arm compared to the HOT arm. Median admission-free survival time was 4.3 months in the HOT-HMV arm compared to 1.4 months for those in the control group - a 3-fold difference. These results were driven by a reduction in the risk of hospital readmissions. The effect on mortality was not statistically significant.

The absolute risk reduction at 12 months was **17%**, translating to a **need to treat 6 patients to avoid one hospital readmission or death in 12 months.**



Results showed a **74%** reduction in the risk of hospital readmission in the first 28 days after randomisation with **two-thirds fewer events** observed in this period.



In addition to the positive effect on time to first readmission or death*, further analysis showed that **the exacerbation rate was reduced by 34%** in the HOT-HMV arm

High pressure ventilation effectively reduced CO_2 levels and therapy was well tolerated as shown by results on QOL and compliance.

*Median time to first event

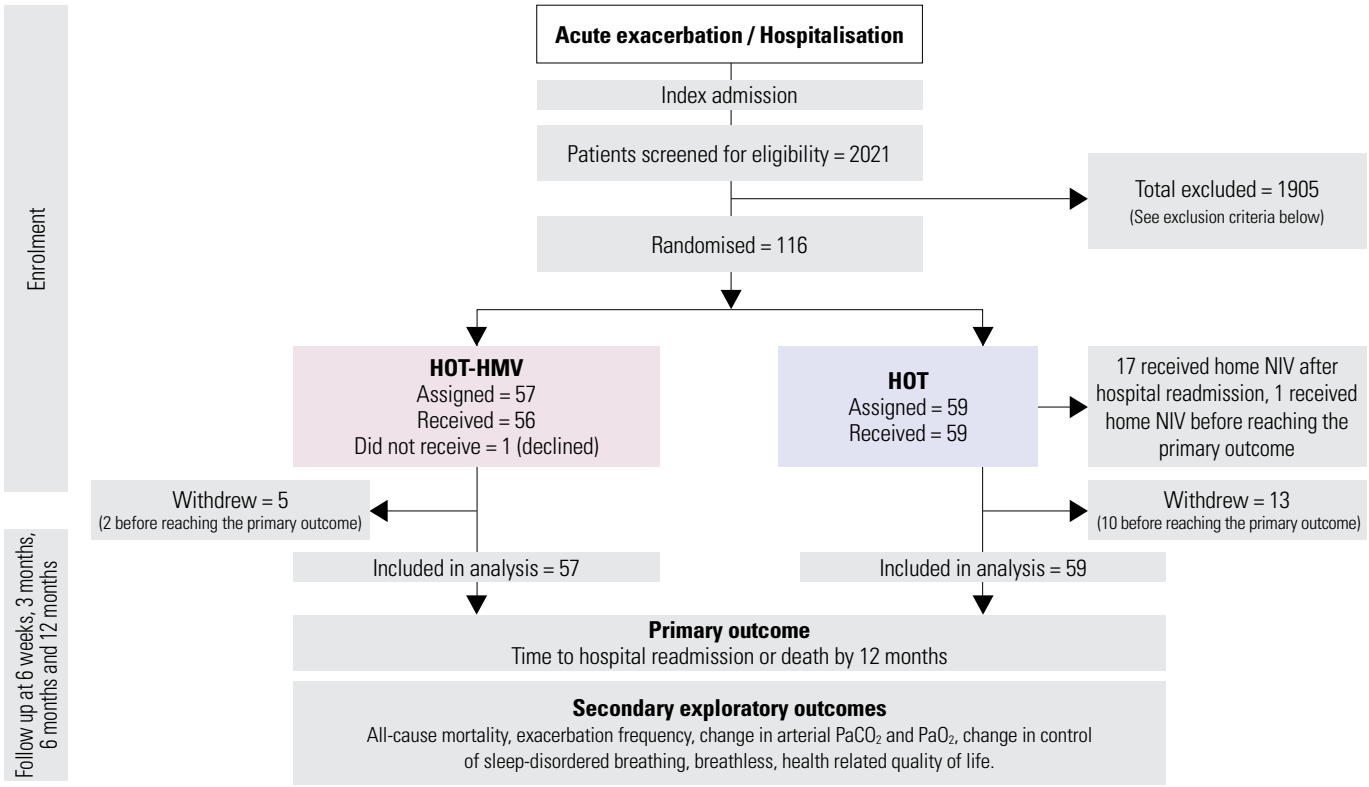
"HOT-HMV adds weight to the existing evidence[2,3] that home non-invasive ventilation (NIV) has clinical benefits for COPD patients in stable chronic hypercapnic respiratory failure and after hospitalisation due to acute exacerbation.

In particular, the results show that treatment can reduce hospital readmissions and exacerbation rates and improve patient outcomes. We hope that this evidence will encourage more healthcare professionals to consider home NIV as a promising way of managing patients affected by COPD;"

notes Dr Carlos M. Nunez,
Chief Medical Officer, ResMed

The trial design

- **The study population** included severe hypoxic and hypercapnic COPD patients who had been hospitalised for acute decompensated hypercapnic exacerbation of COPD requiring NIV.
- **The recruitment process** was designed to ensure that the effect of the therapy was assessed in patients who did not have any significant cause of sleep-disordered breathing and/or respiratory failure other than COPD like obesity, obstructive sleep apnoea, neuromuscular or chest wall disease.



- **The primary outcome** was a combined endpoint of time to readmission to hospital for any cause or death within 12 months after randomisation. The patients met the primary outcome if they experienced either endpoint.
- **A computer-assisted stratified randomisation was performed to guarantee the balance of the 2 arms of the study with regard to the following factors:** age (<65years, ≥65 years); body mass index (BMI) (≤20, >20), current long-term oxygen therapy (yes, no); frequency of COPD-related readmissions during previous 12 months (<3, ≥3); recruitment centre.
- **Recruitment of chronic hypercapnic patients was ensured by assessing hypercapnia at randomisation,** 2-4 weeks after the resolution of the acute exacerbation.
- **64 patients completed the 12 months study period** (28 in the HOT group, 36 in the HOT-HMV group).
- Follow-up assessments included health status and readmissions, exacerbations, arterial blood gas (ABG), sleep measures, and QOL measures (SRI, SGRQ, EQ5-D).
- All primary and secondary analysis were analysed on the **intention-to-treat principle.**

Inclusion criteria

- FEV_1 <50% of predicted - FEV_1/FVC <60%.
- In patient admission with acute hypercapnic exacerbation of COPD.
- **Persistent hypercapnia (pH >7.30, $PaCO_2$ ≥53 mmHg) evaluated 2 to 4 weeks after the resolution of the hypercapnic acidosis.**
- Chronic hypoxia PaO_2 <55 mmHg or <60 mmHg with secondary polycythaemia, pulmonary hypertension, peripheral oedema or significant nocturnal hypoxia (SpO_2 <90% for >30% sleep time).
- Smoking history of greater than 20 pack-years.

Exclusion criteria**

- Declined n=296 (16%)
- Inability to consent n=237 (12%)
- Admission not due to an acute exacerbation of COPD n=157 (8%)
- Died prior to screening n=128 (7%)
- Unable to screen within trial protocol n= 46 (2%)
- Unable to wean from NIV (pH <7.30) n=252 (13%)
- Post decanulation or extubation on index admission n=51 (3%)
- Unable to tolerate NIV n=131 (7%)
- Decompensated with oxygen therapy n=8 (<1%)
- Obstructive sleep apnoea n=76 (4%)
- BMI >35kg/m^2 n=96 (5%)
- Arterial blood gases not meeting inclusion criteria n=419 (22%)
- Other reasons n=8 (<1%)

** Percentage relative to the total number of excluded patients

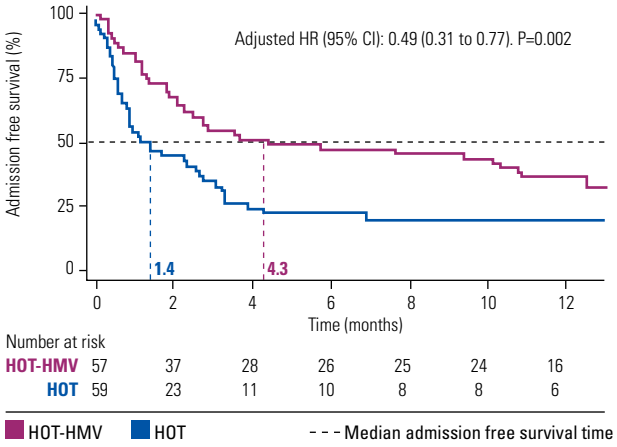
Key findings

51% reduction in risk of hospital readmission or death within 12 months

Patients receiving both HOT and HMV had a median admission-free survival of 4.3 months versus 1.4 months for those receiving HOT alone. This translates to an increase of over 90 days in the median time to first event for the HOT-HMV arm.

Time to readmission or death from randomisation to follow-up at 1 year

Intention to treat analysis



17% absolute risk reduction

The risk of hospital readmission or death measured at the end of the 12 months was 63.4% in the group receiving both HOT and HMV and 80.4% in the group receiving HOT alone, with an absolute risk reduction of 17% (95% CI, 0.1%-34.0%).

This translates to a need to treat 6 patients with HMV and HOT to avoid one hospital readmission or death in 12 months.

Given the significant cost of hospital admissions for severe COPD, this implies that HOT-HMV could help to reduce the economic burden of this disease.[4]

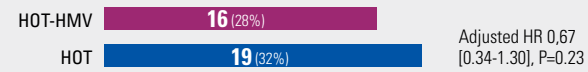
Positive results driven by hospital readmission

These results were driven by a reduction in hospital readmission. **The effect on mortality between the two groups was not statistically significant** both at 12 months and for the event triggering the primary outcome.

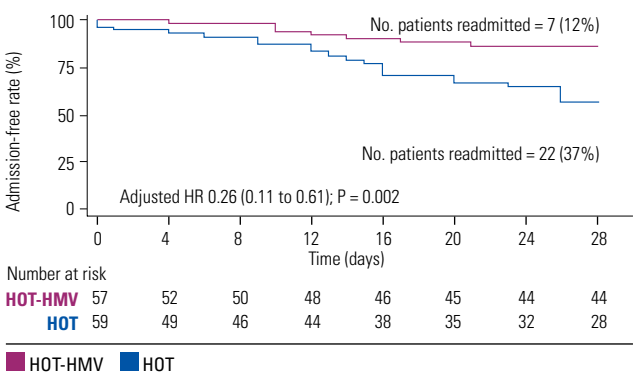
When interpreting these mortality results, it is useful to note that the study was not powered to detect a difference for this outcome.[4]

Number of death triggering the primary outcome

Cumulative number of deaths at 12 months



Time to hospital readmission by treatment arm

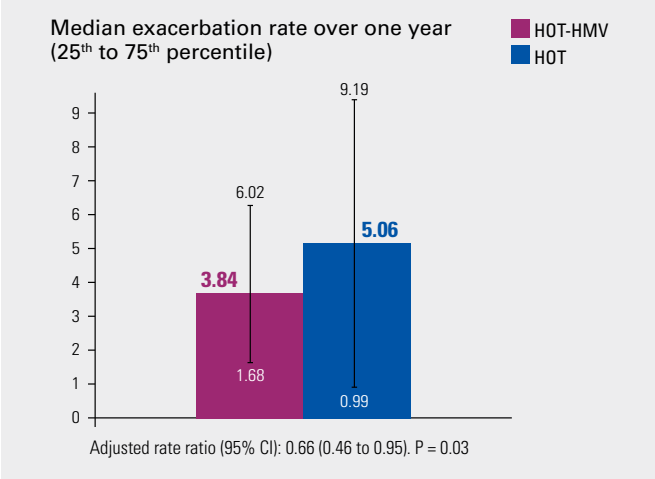


In addition a post-hoc analysis showed a significant reduction of 74% in the risk of readmission within the first 28 days after randomisation in the group receiving HMV and HOT. Two-thirds fewer readmissions were observed in this period in this patient group compared to the HOT group.

Exacerbation rate reduced by 34%

As well as prolonging the time to first hospitalisation, **HOT-HMV therapy reduced the exacerbation rate over one year.**

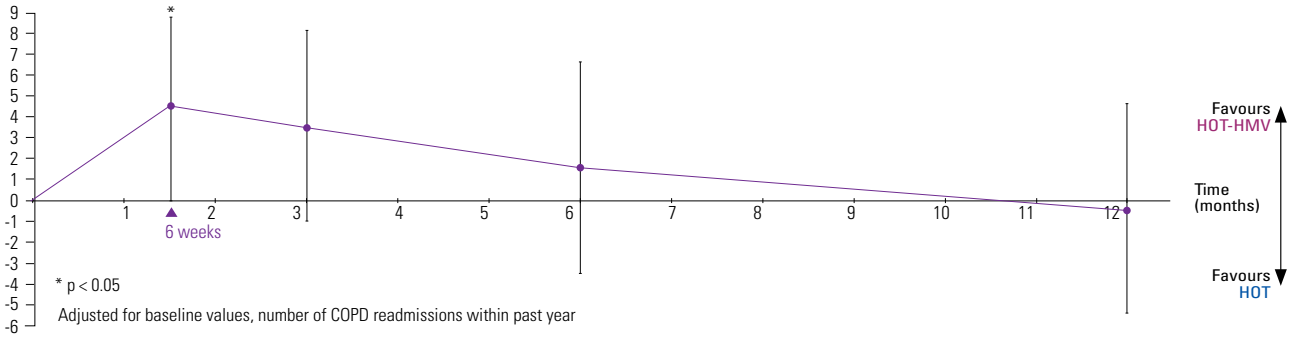
This suggests that patients receiving HOT-HMV may experience better outcomes.[4]



QOL maintained and therapy well tolerated

Patients in the HOT-HMV arm experienced significant health-related QOL benefits in the first 6 weeks according the results of the severe respiratory insufficiency (SRI) questionnaire and at 3 months according the results of the St George's respiratory questionnnaire. These benefits became less marked over time, with no statistically significant difference thereafter.
Patient compliance with the therapy in the HOT-HMV arm also indicates a positive response to home ventilation. Usage increased from a median of 4.7 hours per night at 6 weeks to 7.6 hours per night at 12-month follow up.

SRI questionnaire



SRI questionnaire

Visit	Mean (95% CI)		Between-Group difference fully adjusted model (95% CI); p-value
	HOT-HMV	HOT	
Baseline	45.8 (41.9 to 49.7)	46.9 (42.9 to 50.9)	
Week 6	**50.6 (46.0 to 55.1)**	**49.2 (44.1 to 54.3)**	**4.5 (0.0 to 8.9) p = 0.05**
3 months	52.1 (47.6 to 56.5)	49.9 (45.4 to 54.3)	3.5 (-1.0 to 8.1) p = 0.13
6 months	50.7 (46.4 to 54.9)	53.2 (47.0 to 59.5)	1.5 (-3.5 to 6.6) p = 0.56
12 months	49.8 (44.3 to 55.3)	53.9 (47.6 to 60.2)	-0.4 (-5.4 to 4.7) p = 0.89

St George's respiratory questionnaire

Visit	Mean (95% CI)		Between-Group difference fully adjusted model (95% CI); p-value
	HOT-HMV	HOT	
Baseline	71.9 (68.1 to 75.7)	69.0 (65.6 to 72.5)	
Week 6	68.3 (63.8 to 72.8)	65.7 (62.2 to 69.3)	0.7 (-3.2 to 4.5) p = 0.74
3 months	**62.9 (58.0 to 67.7)**	**66.0 (62.4 to 69.5)**	**-4.9 (-8.8 to -0.9) p = 0.02**
6 months	67.3 (62.8 to 71.9)	61.9 (56.0 to 67.7)	3.0 (-2.0 to 8.0) p = 0.24
12 months	69.0 (64.0 to 74.0)	64.5 (59.4 to 69.5)	2.3 (-2.6 to 7.1) p = 0.36

The therapy was well tolerated and QOL was maintained despite the use of high pressures. Hours of use increased over the course of the study, possibly because patients felt it was alleviating their symptoms.[4]
The modest effect on QOL is unsurprising: *the patient population had* ***severe disease*** *and high levels of* ***physical impairment*** *at baseline. After the first 3 months there was a* ***dilution of treatment effect as 18 patients from the HOT group were allowed to receive the ventilation therapy,*** *in line with study protocol.*[4]

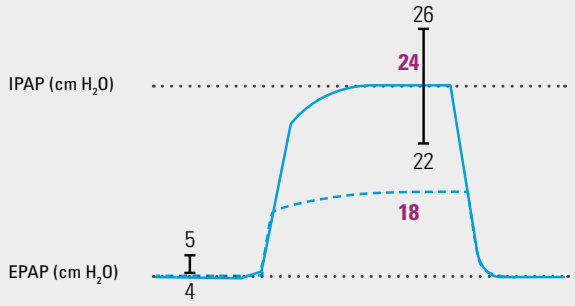
Therapy initiation and settings

Oxygen therapy (HOT)

- Both groups received HOT.
- Oxygen was started in both arms, at the lowest flow rate required to increase PaO_2 above 60mmHg without producing a decompensated respiratory failure.
- Both arms received a median of 1 litre/minute of oxygen.

Home NIV therapy

- The HOT-HMV arm received HMV in addition to HOT.
- A high-pressure strategy was used.
- In-patient NIV titration was performed during the night after a daytime acclimatisation, and with O_2 therapy set at daytime flow rate.
- Inspiratory pressure was initially set at 18 cmH_2O and was **titrated up to the highest level tolerated by the patient under SpO_2 and $tcCO_2$ monitoring**, reaching a median IPAP of 24 cmH_2O.
- **The back up rate was moderate (median 14 bpm)**, as high rates have not been found to be beneficial in previous trials.



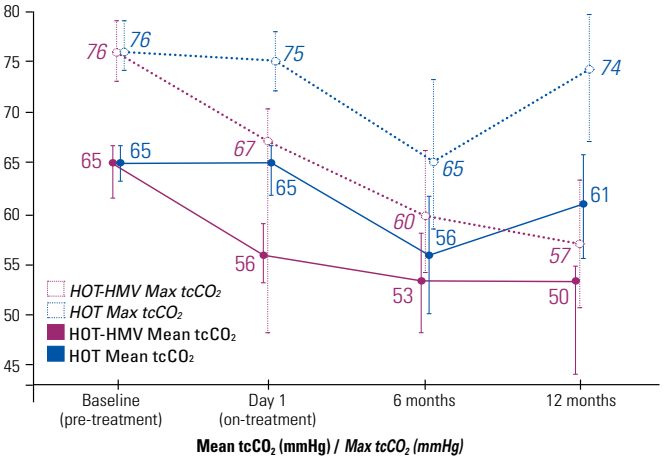
Median (25th and 75th percentile)	
IPAP	24 cm H_2O (22, 26)
EPAP	4 cm H_2O (4, 5)
Back up Rate	14 bpm (14, 16)

Home NIV effectively corrected hypoventilation and reduced CO_2 level

Mean / Max $tcCO_2$

- Significant improvements were observed in nocturnal mean $tcCO_2$ and maximum $tcCO_2$ in the HOT-HMV arm showing that ventilation therapy was effective in correcting the hypoventilation.

Control of nocturnal transcutaneous carbone dioxide at baseline and following initiation of treatment, at 6 and 12 months

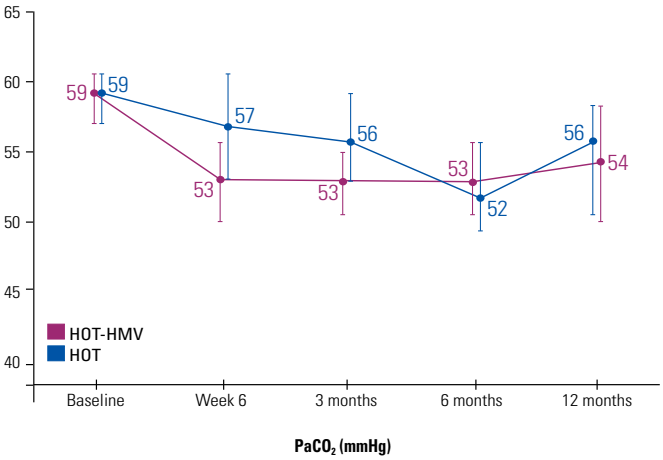


Visit	Mean between group difference from baseline adjusted effect* (95% CI); p-value	
	Mean $tcCO_2$	Max $tcCO_2$
Baseline		
Day 1	-9.1 (-11.6 to -6.6) p<0.001	*-9.2 (-12.5 to -5.6) p<0.001*
6 months	-4.7 (--11.6 to 2.3) p = 0.18	*-8.2 (-16.1 to 0.3) p=0.04*
12 months	-10.7 (-16.4 to -5.1) p<0.001	*-16.2 (-24 to -8.5) p<0.001*

Mean $PaCO_2$

- HMV therapy was effective in reducing daytime levels of CO_2, as measured by ABG. Patients receiving HOT-HMV obtained a statistically significant benefit at 6 weeks and 3 months.

Control of arterial carbone dioxide at baseline and following initiation of treatment, at 6 and 12 months



Visit	Mean between group difference fully adjusted model** (95% CI); p-value
Baseline	
Week 6	-5.0 (-9.0 to -1.3) p = 0.01
3 months	-4.0 (-7.1 to -0.8) p = 0.02
6 months	0.6 (-3.0 to 4.1) p = 0.75
12 months	-2.3 (-6.5 to 1.9) p = 0.28

The dilution in the therapy effect on $TcCO_2$ and $PaCO_2$ can be explained by the 18 patients from the HOT group who required and were permitted to receive ventilation therapy.[4]

*Adjusted for number of COPD admissions in previous year, prior use of long term oxygen therapy (LTOT), age and BMI
** Adjusted for baseline values, number of chronic obstructive pulmonary disease readmissions within past year

The HOT-HMV study: new prospects for treating severe COPD patients

What are the implications for clinical practice?

Wider adoption of home NIV for hypercapnic COPD patients
The HOT-HMV study should prompt changes in the clinical management of severe COPD patients with chronic respiratory failure following a life-threatening exacerbation.
This severely ill patient group currently has few treatment options. The results confirm the value of offering home NIV therapy to these patients, a practice already adopted by many expert ventilation centres.
They also support the argument that home NIV should be adopted more widely as part of the therapy strategy for severe hypercapnic COPD patients after hospitalisation for AECOPD.

Systematic screening
The positive results of the HOT-HMV trial suggest that patients with severe COPD should be systematically screened following a hospitalisation for AECOPD requiring acute NIV to assess their suitability for home NIV therapy.

GOLD guidelines[5]
The HOT-HMV findings confirm the value of the new recommendations provided by the GOLD guidelines. The guidelines now include home NIV as a therapy to consider for the treatment of hypercapnic COPD patients.

High-pressure strategy
HOT-HMV confirms the efficacy and feasibility of using high pressures to treat COPD patients. High pressures were effective in correcting hypoventilation and reducing hypercapnia while QOL assessments and usage statistics indicate that patients tolerated the therapy well.

What are the implications for health economics?

Home NIV has the potential to reduce the healthcare costs associated with the management of patients with severe COPD. HOT-HMV significantly increased time to hospital readmissions, which place a signifiant burden on healthcare systems. Reductions in the exacerbation rate also imply that HOT-HMV has the potential to reduce the costs and resources required to treat this group outside hospital.
Furthermore, HOT-HMV may have amplified effects on cost reduction in some systems which apply penalties for recurrent hospital readmissions due to AECOPD.[6]

"The trial results could potentially change clinical practice and improve the way we manage our sickest COPD patients."

Professor Nicholas Hart and Dr Patrick Murphy,
who led the HOT-HMV trial from St Thomas' Hospital in London

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Baseline characteristics

	HOT-HMV	HOT
Age (SD)	66.4 (10.2)	67.1 (9.0)
Gender (female) (n (%))	29 (51%)	32 (54%)
Median BMI (kg/m^2) (25^{th} to 75^{th} percentile)	**21.5 (18.8 to 24.5)**	**22.2 (17.9 to 26.9)**
Prior use of LTOT (n (%))	40 (70%)	40 (68%)
≥3 COPD related admissions in last year	**30 (53%)**	**31 (53%)**
Median smoking pack year history (25^{th} to 75^{th} percentile)	42.0 (30.5 to 60.0)	45.0 (31.0 to 55.0)
PULMONARY FUNCTION		
FEV_1, mean (SD), L	0.6 (0.2)	0.6 (0.2)
FEV_1 % predicted, mean (SD)	24.0 (8.6)	22.9 (8.6)
FVC, mean (SD), L	1.8 (0.8)	1.5 (0.6)
FVC % predicted, mean (SD)	57.4 (19.7)	49.3 (20.4)
FEV_1/FVC, mean (SD)	0.3 (0.1)	0.4 (0.1)
HYPOXAEMIA / HYPERCAPNIA		
PaO_2 while breathing room air, mean (SD), mmHg	**48 (9)**	**48 (8)**
$PaCO_2$ while breathing room air, mean (SD), mmHg	**59 (7)**	**59 (7)**
Arterial pH while breathing room air, mean (SD)	**7.40 (0.04)**	**7.40 (0.03)**
QUALITY OF LIFE		
Median SGRQ summary (25^{th} to 75^{th} percentile)	74.7 (63.7 to 81.7)	71.0 (62.6 to 78.6)
SRI summary	45.8 (15.0)	46.9 (15.6)
Median MRC dyspnoea score (25^{th} to 75^{th} percentile)	5.0 (4.0 to 5.0)	5.0 (4.0 to 5.0)

- Baseline characteristics were well matched between the intervention and control groups.
- Baseline characteristics of the enrolled patients show a population with severely compromised pulmonary function, high levels of $PaCO_2$, and a high rate of hospitalisations per year.
- Over 50% of patients had ≥3 COPD-related hospital admissions in the previous year.
- On room air, mean PaO_2 was 48 mmHg and $PaCO_2$ was 59 mmHg, indicating hypoxaemia with hypercapnia in both patient groups.
- HRQOL was significantly impaired, as measured by the St. George's Respiratory Questionnaire (SGRQ), SRI, and by the Medical Research Council (MRC) breathlessness scale, indicating degree of dyspnoea.

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