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# **Effect of non-invasive ventilation after extubation in critically ill patients with obesity in France: a multicentre, unblinded, pragmatic randomised clinical trial**

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\*A full list of the EXTUB-OBESE investigators is provided in appendix

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#### **Research in context**

##### **Evidence before this study**

We searched PubMed for articles published in English or with abstracts in English language up to Sept 23, 2022, with the Medical Subject Heading terms (“non-invasive ventilation”, “high-flow nasal oxygen”, “extubation failure”, “prevention”) and either the supplementary concept (“obese”) or (“obesity”). The search identified 11 manuscripts; review of these identified three additional manuscripts. Of the total 14 publications, one manuscript reported a post-hoc analysis of a randomised controlled trial, that did not focus on the specific population of obesity, that analysed clinical data from non-invasive ventilation (NIV) and high-flow nasal oxygen (HFNO) to prevent extubation failure in patients with obesity.

##### **Added value of this study**

In this randomised clinical trial that included 981 patients, the use of NIV following extubation of critically ill adult patients with obesity resulted in significantly lower treatment failure within 3 days (primary outcome) than did the use of oxygen therapy alone. There was no significant difference on the reintubation rate in the intention-to-treat analysis. The use of NIV also resulted in lower reintubation rate within 3 days in the per-protocol and post-hoc crossover analyses. NIV, whether associated with standard oxygen or high-flow nasal oxygen, was superior to both standard oxygen alone or high-flow nasal oxygen alone.

##### **Implications of all the available evidence**

For routine management following extubation of critically ill patients with obesity, using NIV is safe and decreases treatment failure within 72 h. High-flow nasal oxygen should not replace NIV for preventing reintubation in the specific population of critically ill patients with obesity. Most of the difference in the primary outcome was due to patients in the oxygen therapy group switching to NIV, and more evidence is needed to conclude that an NIV strategy leads to improved patient-centred outcomes.

# Summary

## Background

Non-invasive ventilation (NIV) and oxygen therapy (high-flow nasal oxygen [HFNO] or standard oxygen) following extubation have never been compared in critically ill patients with obesity. We aimed to compare NIV (alternating with HFNO or standard oxygen) and oxygen therapy (HFNO or standard oxygen) following extubation of critically ill patients with obesity.

## Methods

In this multicentre, parallel group, pragmatic randomised controlled trial, conducted in 39 intensive care units in France, critically ill patients with obesity undergoing extubation were randomly assigned (1:1) to either the NIV group or the oxygen therapy group. Two randomisations were performed: first, randomisation to either NIV or oxygen therapy, and second, randomisation to either HFNO or standard oxygen (also 1:1), which was nested within the first randomisation. Blinding of the randomisation was not possible, but the statistician was masked to group assignment. The primary outcome was treatment failure within 3 days after extubation, a composite of reintubation for mechanical ventilation, switch to the other study treatment, or premature discontinuation of study treatment. The primary outcome was analysed by intention to treat. Effect of medical and surgical status was assessed. The reintubation within 3 days was analysed by intention to treat and after a post-hoc crossover analysis. This study is registered with ClinicalTrials.gov, number NCT04014920.

## Findings

From Oct 2, 2019, to July 17, 2021, of the 1650 screened patients, 981 were enrolled. Treatment failure occurred in 66 (13.5%) of 490 patients in the NIV group and in 130 (26.5%) of 491 patients in the oxygen-therapy group (relative risk 0.43; 95% CI 0.31–0.60,  $p < 0.0001$ ). Medical or surgical status did not modify the effect of NIV group on the treatment-failure rate. Reintubation within 3 days after extubation was similar in the non-invasive ventilation group and in the oxygen therapy group in the intention-to-treat analysis (48 (10%) of 490 patients and 59 (12%) of 491 patients,  $p = 0.26$ ) and lower in the NIV group than in the oxygen-therapy group in the post-hoc cross-over (51 (9%) of 560 patients and 56 (13%) of 421 patients,  $p = 0.037$ ) analysis. No severe adverse events were reported.

## Interpretation

Among critically ill adults with obesity undergoing extubation, the use of NIV was effective to reduce treatment-failure within 3 days. Our results are relevant to clinical practice, supporting the use of NIV after extubation of critically ill patients with obesity. However, most of the difference in the primary outcome was due to patients in the oxygen therapy group switching to NIV, and more evidence is needed to conclude that an NIV strategy leads to improved patient-centred outcomes.

## Introduction

The growing obesity epidemic worldwide has been well documented.<sup>1</sup> Patients with obesity can become critically ill and require invasive mechanical ventilation.<sup>2,3</sup> Following amelioration of the conditions that led to mechanical ventilation, the process of weaning ensues, culminating in extubation. The need for reintubation after extubation and discontinuation of mechanical ventilation is not uncommon and is associated with increased mortality.<sup>4,5</sup>

Non-invasive ventilation (NIV)<sup>6,7</sup> has been used to prevent acute respiratory failure in selected patients who are critically ill.<sup>8,9</sup> Physiological effects of NIV, providing positive pressure, are more important in patients with obesity,<sup>4</sup> suffering from reduced functional residual capacity and propensity to atelectasis. Observational studies with low level of proof have suggested the superiority of NIV over standard oxygen (providing no positive pressure) to reduce acute respiratory failure following extubation of patients with obesity.<sup>4,10</sup> High-flow nasal oxygen (HFNO), providing warm and humidified gas, with very low positive pressure, has been introduced and increasingly used over the past decade.<sup>11–13</sup> In a post-hoc analysis of a randomised multicentre controlled trial of postoperative thoracic patients,<sup>14</sup> NIV seemed to be not superior to HFNO among the 272 patients with obesity. The primary outcome was treatment failure within 3 days defined as reintubation, switch to the other study treatment, or premature treatment discontinuation. However, in another randomised controlled trial performed in patients with obesity following cardiac surgery,<sup>15</sup> no difference was reported between HFNO and standard oxygen to prevent acute respiratory failure. The literature available regarding respiratory support after extubation in patients with obesity reports conflicting results. However, none of these studies compared in the same randomised controlled trial all the devices available: NIV on one side (alternating with HFNO or standard oxygen, allocated after randomisation) and oxygen therapy alone on the other side (HFNO or standard oxygen, allocated after randomisation).<sup>16</sup>

To summarise, the best after-extubation strategy in critically ill patients with obesity is currently unknown. No conclusive evidence is available at present in literature, regarding the effectiveness of using NIV after extubation. We designed the study to compare two strategies: one with positive pressure (NIV group) versus one without or very low positive pressure (oxygen therapy group).

To determine whether NIV could reduce the rate of treatment failure in comparison with oxygen therapy within 3 days after extubation of critically ill patients with obesity, we conducted the non-invasive ventilation versus oxygen therapy after extubation in patients with obesity in intensive care units (EXTUB-OBESE) trial. We hypothesised that NIV could reduce the rate of treatment failure in comparison with continuous oxygen therapy alone in patients with obesity within 3 days after extubation in an intensive care unit (ICU).

## Methods

### Study design

We conducted a multicentre, parallel-group, unblinded, pragmatic, randomised trial comparing prophylactic NIV applied immediately after extubation alternating with HFNO or standard oxygen between NIV sessions (NIV group) with oxygen therapy alone (oxygen therapy group, HFNO or standard oxygen). The trial was approved for all centres by a central Ethics Committee (Comité de Protection des Personnes Ile de France V, France, 2019-A00956–51) according to French law. Written informed consent was required before the first inclusion in the trial. Gender data were collected as stated in the medical record of the patient. The protocol and statistical analysis plan have been published.<sup>17</sup>

## Participants

The trial was conducted in 39 French ICUs (appendix pp 12–13). Patients were eligible for participation in the trial if they were older than 18 years of age, admitted to the ICU and covered by public health insurance. Patients were included in the trial if they met criteria for extubation in ICU after a period of mechanical ventilation of more than 6 h and had obesity, defined by a body-mass index (BMI) of 30 kg/m<sup>2</sup> or higher on the day of extubation. Patients were excluded if they had hypercapnia before extubation (partial pressure of carbon dioxide, PaCO<sub>2</sub> ≥50 mm Hg before extubation, which is a mandatory indication for NIV after extubation, an arterial blood gas was not mandatory and its realisation was left at the clinician appreciation in case of suspected hypercapnia); isolated cardiogenic pulmonary oedema; a tracheotomy; home ventilation (defined as NIV, which delivers two positive levels of pressure, or as continuous positive airway pressure [CPAP], which delivers only one positive level of pressure for obstructive sleep apnoea syndrome or obesity hypoventilation syndrome); end-of-life decision with decision of “do not reintubate”; anatomical factors precluding the use of NIV or HFNO; and previous extubation during the same ICU stay with previous inclusion in the study. Complete lists of inclusion and exclusion criteria are provided in appendix (pp 4–5).

## Randomisation and masking

Two randomisations were performed. Patients first underwent central randomisation (1:1) to receive either NIV (NIV group) or oxygen therapy (oxygen therapy group) and a subsequent second central randomisation (1:1) that determined the method of oxygen administration in each group: HFNO or standard oxygen. Randomisation was done using a computer-generated and blinded assignment sequence, stratified by the length of mechanical ventilation at the centre (<48 h vs ≥48 h), the type of admission (surgical vs medical), and the centre, balanced with minimisation with a deterministic algorithm.<sup>18</sup> Blinding of the intervention was not possible, but treatment assignments were concealed from the statistician. The analyses were performed by the statisticians with the names of the treatment groups masked. The research team who assessed the outcomes were aware of study group assignments. It was not a factorial design, since the second randomisation assigned only the type of oxygen administration.

## Procedures

In the NIV group, the first NIV session was offered to the patient within 30 min after extubation. Recommended positive end-expiratory pressure value was set to 10 cm H<sub>2</sub>O. The value of pressure support was set to obtain a respiratory rate between 20 and 30 breaths per min and an expired tidal volume between 6 mL/kg and 8 mL/kg of predicted bodyweight. The recommended length of the intermittent NIV sessions was standardised as follows: sessions of 30–60 min spread through the day and night for a cumulated time of at least 4 h with no upper limit during the first 24 h. In both groups, HFNO was administered at a flow of 50 L/min during the first 24 h, with a fractional inspired oxygen concentration (FiO<sub>2</sub>) set to target oxygen saturation (SpO<sub>2</sub> ≥94%). After 24 h, the device was pursued if the patient still needed oxygen, until ICU discharge or the absence of need of oxygen. The follow-up was stopped at 3 months. Details regarding the interventions and switch from one group to another group (NIV to oxygen therapy and vice versa) are provided in the appendix (pp 5–7).

## Outcomes

The primary outcome was treatment failure rate within 3 days after extubation, a composite of reintubation for mechanical ventilation, switch to the other study treatment, or premature study-treatment discontinuation (at the request of the patient or for medical reasons such as gastric distension).<sup>19</sup> For a given patient, only one component of the composite outcome was considered in the following order: first reintubation, then in absence of reintubation switch to the other study treatment, then premature study-treatment discontinuation.

The prespecified secondary outcome was incidence of acute respiratory failure within 7 days after extubation (additional details regarding acute respiratory failure definition are provided in appendix). Other outcomes were evaluated as prespecified exploratory clinical outcomes: oxygenation evaluated by the ratio of pressure of arterial oxygen (PaO<sub>2</sub>) to FiO<sub>2</sub> (PaO<sub>2</sub>/FiO<sub>2</sub>) until day 7, organ failure until day 7 assessed with the sequential organ failure assessment (SOFA) score, reintubation rates within 7 days, 14 days, and 28 days after extubation, length of stay in ICU and in hospital, ICU mortality rate, and day-28 and day-90 mortality rates. No severe adverse events (death or cardiac arrest during the interventions) were reported.

## Statistical analysis

Details regarding the determination of the sample size have been reported previously.<sup>17</sup>

Assuming a composite outcome rate of 12% in the oxygen therapy group<sup>20</sup> and 6% in the NIV group,<sup>10</sup> we determined that the enrolment of 954 patients would provide a power of 80% at a two-sided  $\alpha$  level of 0.05 to detect an absolute between-group difference of 6 percentage points in the composite outcome. To take into account loss of follow-up and withdrawal of consents, we planned to include 1000 patients.

The first primary outcome analysis was an unadjusted, intention-to-treat comparison of the primary outcome rate among patients in the two trial groups with the use of the uncorrected  $\chi^2$  square test. The absolute difference, relative risk, and corresponding 95% CIs were calculated. Prespecified subgroups derived from randomisation (HFNO vs standard oxygen), stratification (medical vs surgical, length of ventilation <48 h vs  $\geq$ 48 h) and subgroup (SARS-CoV-2 infection) variables were displayed as a forest plot. A logistic regression was used for the primary outcome analysis with odds ratio of primary outcome calculation after adjustment on confounding variables despite the randomisation. An unadjusted Kaplan-Meier plot was performed for cumulative incidence of primary outcome (treatment failure within 3 days after extubation), followed by a Cox model, before and after adjustment. An unadjusted Kaplan-Meier plot was also performed for cumulative incidence of reintubation within 3 days.

A second prespecified primary outcome analysis was a per-protocol analysis, after excluding the patients with reintubation for surgical procedures without criteria of acute respiratory failure, with BMI less than 30 kg/m<sup>2</sup> or with home ventilator.

A third post-hoc analysis of the reintubation rate was conducted given the number of switch (crossover) procedures from the oxygen therapy group to NIV group (post-hoc crossover analysis). We reallocated in the NIV group the patients that received rescue NIV in the oxygen therapy group (whether followed by reintubation within 3 days after extubation or without subsequent intubation), and computed the reintubation rate in patients who actually received NIV, compared with patients who received oxygen therapy only.<sup>21</sup>

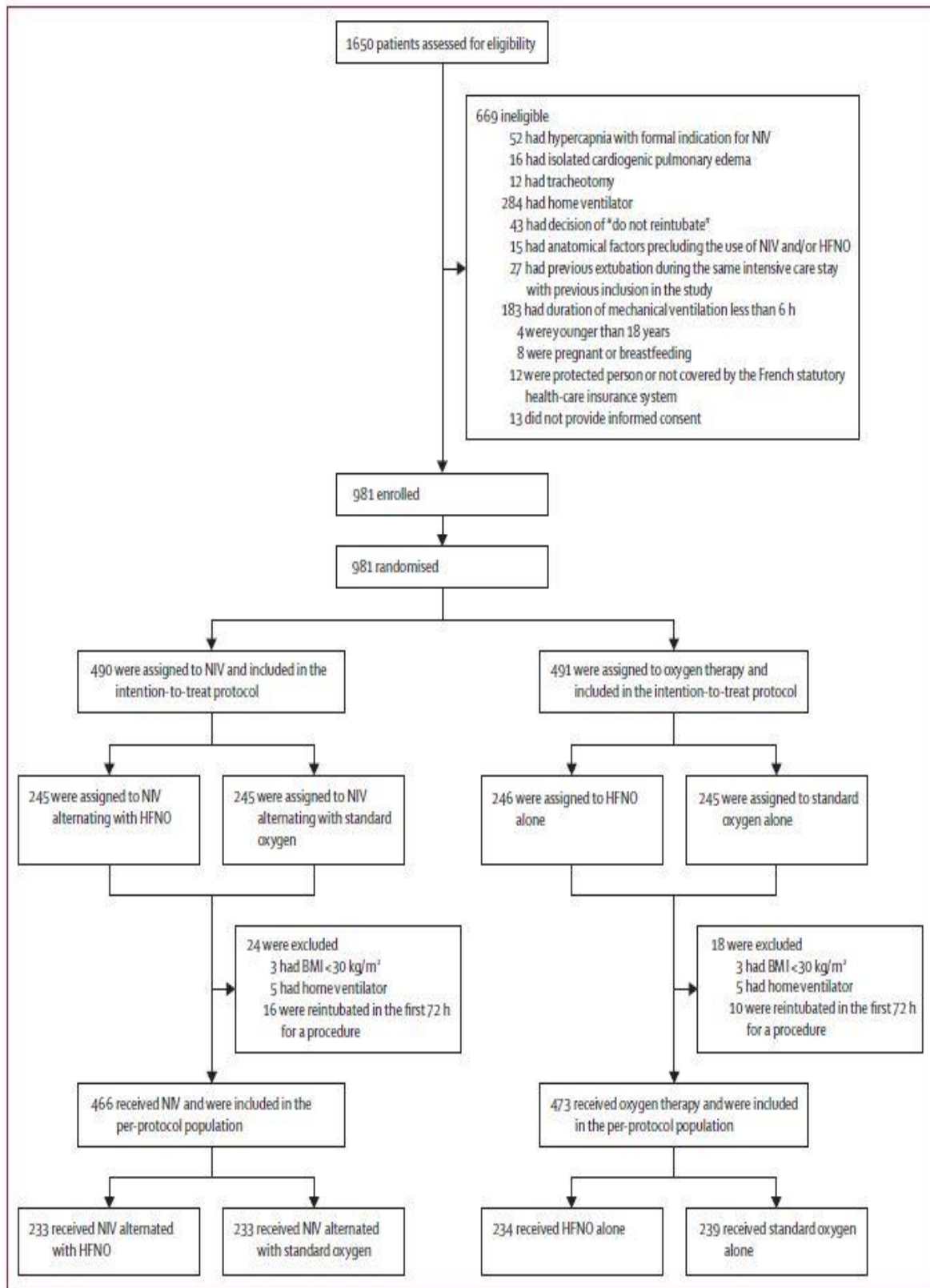
Relative risks and absolute differences in primary, secondary, and exploratory outcomes were reported with the use of point estimates and 95% CIs. To adjust for multiple testing for the exploratory outcomes, we reported the false discovery rate using the linear step-up method of Benjamini and Hochberg.<sup>22</sup> There was no imputation for missing data. A post-hoc analysis was done for the cumulative incidence of reintubation within 28 days, per

study group, using the log-rank test. A Cox model was performed without adjustment. A sensitivity analysis was performed for the primary, secondary, and exploratory outcomes after adjustment for the stratification variables. All analyses were done with the use of SAS Enterprise Guide (version 7.13) or statistical software R (version 4.0.3; R Foundation for Statistical Computing). There was no data monitoring committee. Additional details regarding the statistical analysis are provided in appendix. This study is registered with ClinicalTrials.gov, NCT04014920.

### **Role of the funding source**

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.





**Figure 1: Trial profile**

NIV=non-invasive ventilation. HFNO=high-flow nasal oxygen.

	NIV group (n=490)	Oxygen therapy group (n=491)
Age, years	61 (14)	61 (14)
Male sex	311 (63%)	286 (58%)
BMI at admission, kg/m <sup>2</sup>	35.1 (4.8)	35.2 (5.4)
BMI the day of extubation, kg/m <sup>2</sup>	35.4 (4.9)	35.5 (5.3)
SAPS II at admission*	43 (18)	43 (18)
SOFA score at admission†	7.0 (3.7)	7.0 (3.7)
Comorbidities		
Obesity type android	309/451 (69%)	302/463 (65%)
Alcohol abuse	92 (19%)	80 (16%)
Active smoking	116 (24%)	107 (22%)
Psychotropic treatment	57 (12%)	58 (12%)
Diabetes	153 (31%)	167 (34%)
Systemic hypertension	271 (55%)	267 (54%)
Coronary disease	68 (14%)	68 (14%)
Cardiac insufficiency	31 (6%)	21 (4%)
Chronic renal failure	36 (7%)	50 (10%)
Chronic liver failure	26 (5%)	26 (5%)
Cirrhosis	57 (12%)	59 (12%)
Chronic respiratory failure	14 (3%)	12 (2%)
Chronic Obstructive Pulmonary disease	37 (8%)	36 (7%)

### Main reason for ICU admission

Post operative	189 (39%)	196 (40%)
Cardiac arrest	17 (3%)	10 (2%)
Septic shock	69 (14%)	57 (12%)
Cardiogenic shock	5 (1%)	8 (2%)
Haemorrhagic shock	20 (4%)	29 (6%)
Anaphylactic shock	2 (<1%)	1 (<1%)
Trauma	21 (4%)	26 (5%)
Drug overdose	10 (2%)	6 (1%)
Ascitic decompensation	8 (2%)	6 (1%)
Acute renal failure	5 (1%)	5 (1%)
Acute respiratory failure	112 (23%)	119 (24%)
Others	32 (7%)	28 (6%)

### Main reason for intubation

Acute respiratory failure	150/487 (31%)	147 (30%)
Shock	23/487 (5%)	27 (5%)
Cardiac arrest	18/487 (4%)	10 (2%)
Coma	52/487 (11%)	51 (10%)
Before procedure‡	220/487 (45%)	238 (48%)
Others	24/487 (5%)	18 (4%)
COVID-19 disease	60/485 (12%)	60 (12%)

### Length of invasive mechanical ventilation before extubation, h

Overall patients	53 (13–183)	56 (14–179)
Medical patients§	144 (69–282)	164 (69–269)
Surgical patients¶	17 (10–76)	21 (10–72)

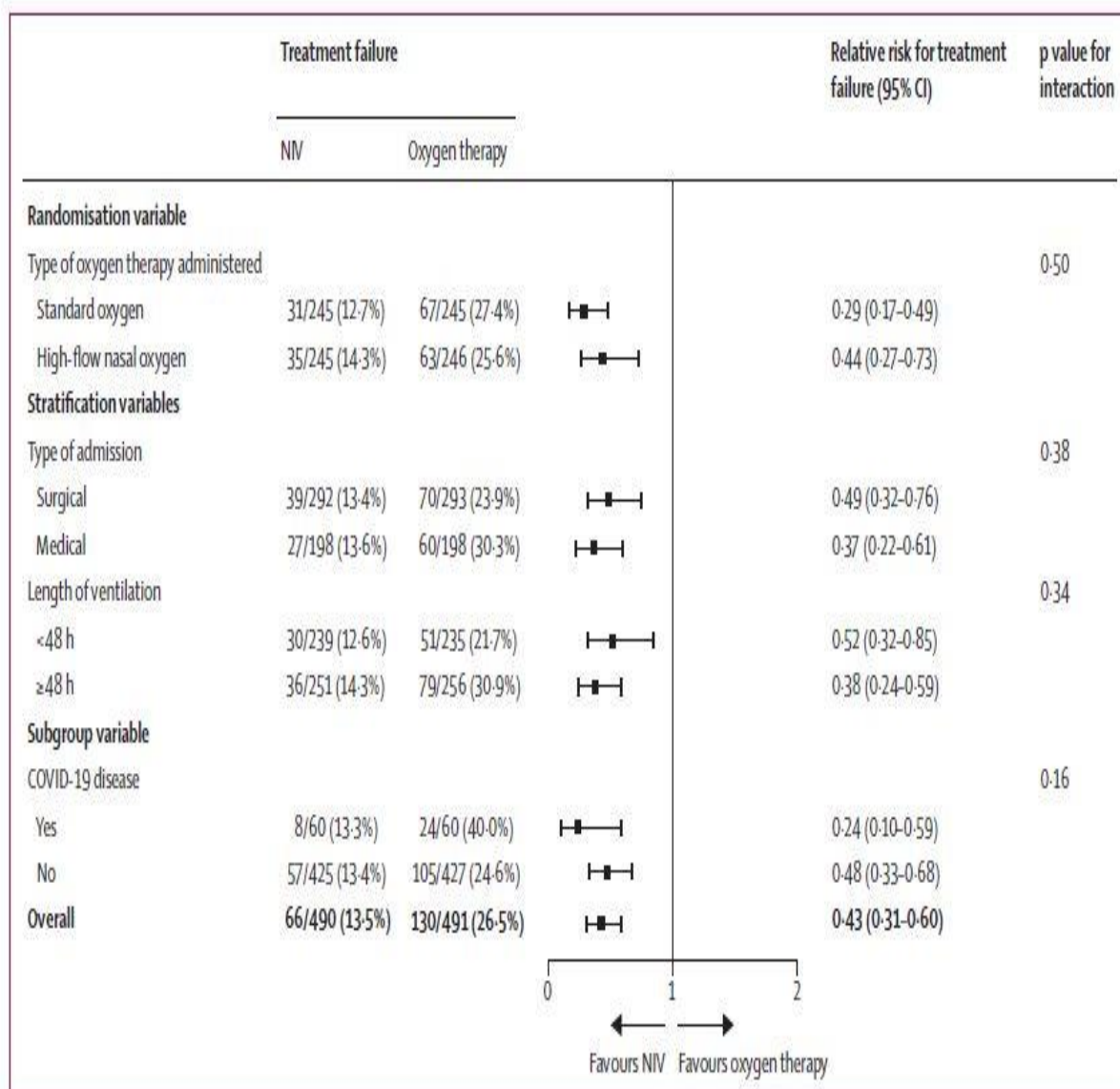
Data are n/N (%), and mean (SD), or median (IQR). BMI=body-mass index. ICU=Intensive Care Unit. NIV=non-invasive ventilation. SAPS=Simplified Acute Physiologic Score. SOFA=Sequential Organ Failure Assessment. \*At admission to the ICU, data on SAPS II were missing for 20 (4%) patients in the NIV group and 13 (3%) in the oxygen group; the SAPS II is calculated from 17 variables and has a total range from 0 to 163, with higher scores indicating greater severity of disease. †At admission to the ICU, data on SOFA score were missing for 45 (9%) patients in the NIV group and 35 (7%) in the oxygen group. ‡Before procedure denoted that patients were intubated for a procedure, surgical or endoscopic. §Data for medical patients are reported for the 396 medical patients, 198 in the NIV group and 198 in the oxygen group. ¶Data for surgical patients are reported for the 585 surgical patients, 292 in the NIV group and 293 in the oxygen group.

**Table 1: Baseline characteristics of the participants**

	NIV group (n=490)	Oxygen therapy group (n=491)	Absolute difference (95% CI)	Relative risk (95% CI)	p value
Primary outcome: treatment failure	66 (13%)	130 (26%)	-13.0 (-17.9 to -8.1)	0.43 (0.31 to 0.60)	<0.0001
Reintubation within 3 days after extubation	48 (10%)	59 (12%)	-2.2 (-6.1 to 1.7)	0.80 (0.53 to 1.19)	0.26
Switch to the other study treatment*	0	67 (14%)	-13.7 (-16.7 to -10.6)	0.0064 (0.0004 to 0.10)	<0.0001
Premature discontinuation of study treatment†	18 (4%)	4 (1%)	2.9 (1.0 to 4.7)	4.2 (1.5 to 12.0)	0.002
Main secondary outcome: acute respiratory failure within 7 days after extubation	54/489 (11%)	70/490 (14%)	-3.2 (-7.4 to 0.92)	0.75 (0.51 to 1.09)	0.13
Exploratory‡					
Reintubation within 7 days after extubation	68/489 (14%)	77/490 (16%)	-1.8 (-6.3 to 2.6)	0.87 (0.61 to 1.23)	0.94
Reintubation within 14 days after extubation	81/489 (17%)	95/490 (19%)	-2.8 (-7.6 to 2.0)	0.83 (0.60 to 1.15)	0.94
Reintubation within 28 days after extubation§	87/489 (18%)	105/490 (21%)	-3.6 (-8.6 to 1.3)	0.79 (0.58 to 1.09)	0.94
ICU length of stay¶ (days)	6.7 (6.7)	6.9 (7.2)	-0.19 (-1.1 to 0.68)	..	0.94
Hospital length of stay¶ (days)	24.1 (22.7)	23.6 (21.4)	0.48 (-2.3 to 3.3)	..	0.94
ICU mortality	29/486 (6%)	31/490 (6%)	-0.36 (-3.4 to 2.7)	0.94 (0.56 to 1.58)	0.94
28-day mortality	26/486 (5%)	30/490 (6%)	-0.77 (-3.7 to 2.1)	0.87 (0.51 to 1.49)	0.94
90-day mortality	50/486 (10%)	52/490 (11%)	-0.32 (-4.2 to 3.5)	0.97 (0.64 to 1.45)	0.94

Data are n/N (%) and mean (SD). HR=hazard ratio. ICU=intensive care unit. NIV=non-invasive ventilation. \*Switch to the other study treatment was considered in case of use of the other treatment as rescue therapy without subsequent intubation. In case of reintubation, the patient experiencing rescue therapy was considered in the reintubation within 3 days after extubation group. †Premature study-treatment discontinuation was defined as discontinuation of NIV or oxygen therapy at the request of the patient before completion of one session of NIV of at least 30 minutes in the NIV group or before 12 hours of oxygen therapy in the oxygen therapy group or for medical reasons such as gastric distention. ‡The p value for the exploratory clinical outcomes was corrected by the false discovery rate method. §A post-hoc analysis was done for the cumulative incidence of reintubation within 28 days, per study group, using the log rank test. A Cox model was performed without adjustment (HR 0.81, 95% CI 0.61-1.01, p=0.15; figure S2 in appendix). ¶Data on ICU and hospital length of stay were missing for one (<1%) patient in the NIV group and one (<1%) patient in the oxygen therapy group.

**Table 2: Outcomes**



**Figure 2: Subgroup analyses of the primary outcome**

None of the prespecified characteristics, including length of mechanical ventilation, type of admission, or SARS-CoV-2 infection appeared to modify the effect of NIV group on the treatment failure rate. NIV=non-invasive ventilation.

## Results

From Oct 2, 2019, to July 17, 2021, of the 1650 screened patients who met the inclusion criteria, 981 (59%) were enrolled (figure 1). A total of 490 patients were assigned to the NIV group and 491 were assigned to the oxygen therapy group. The characteristics of the patients at baseline were well balanced between the two treatment groups (see table 1 and appendix [pp 14–16] for additional characteristics at baseline, arterial blood gases, and spontaneous breathing trial characteristics). Characteristics of NIV and oxygen therapy are presented in the appendix (pp 17–18).

In the intention-to-treat analysis, 66 (13%) of 490 patients in the NIV group had treatment failure within 3 days compared with 130 (26.5%) of 491 patients in the oxygen therapy group (absolute risk difference –13.0,

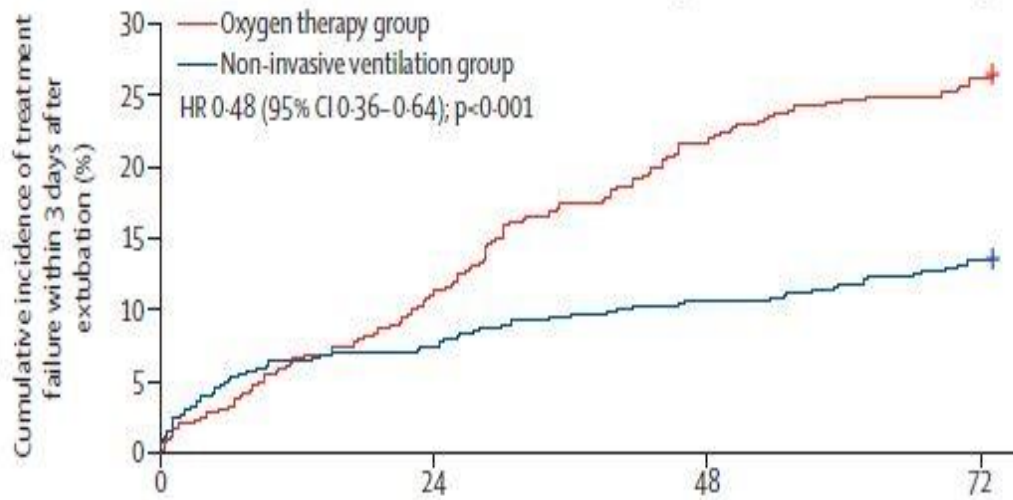
95% CI  $-17.9$  to  $-8.1$ ; relative risk  $0.43$ , 95% CI  $0.31$  to  $0.60$ ;  $p < 0.0001$ ; table 2). The method of oxygen delivery, while on oxygen therapy (HFNO vs standard oxygen) did not modify the effect of NIV group on the treatment failure rate (figure 2,  $p$  for interaction= $0.50$ ). Treatment failure rate for each method of oxygenation is presented in the appendix (p 19). None of the prespecified characteristics, including length of mechanical ventilation, type of admission, or SARS-CoV-2 infection appeared to modify the effect of NIV group on the rate of treatment failure (figure 2).

After adjustment for baseline covariates (SARS-CoV-2 infection and simplified acute physiology score II  $\geq 41$ ) and centre effect, the frequency of treatment failure was still lower in the NIV group than in the oxygen therapy group (adjusted odds ratio  $0.42$ , 95% CI  $0.30$ – $0.59$ ;  $p < 0.0001$ ; appendix, p 20). Similarly, cumulative incidence of treatment failure within 3 days after extubation was significantly lower in the NIV group, in comparison with the oxygen therapy group (hazard ratio [HR]= $0.48$ , 95% CI  $0.36$ – $0.64$ ,  $p < 0.0001$ ; figure 3A and appendix, p 21). The results of the per-protocol analysis were consistent with those of the primary intention-to-treat analysis (appendix pp 22, 25).

The reintubation rate within 3 days was  $48$  ( $10\%$ ) in the NIV group and  $59$  ( $12\%$ ) in the oxygen therapy group ( $p=0.26$ ) in the intention-to-treat analysis (table 2). Cumulative incidence of reintubation within 3 days after extubation did not differ between the NIV oxygen therapy group (HR= $0.80$ ; 95% CI  $0.55$  to  $1.18$ ;  $p=0.26$ , figure 3B).

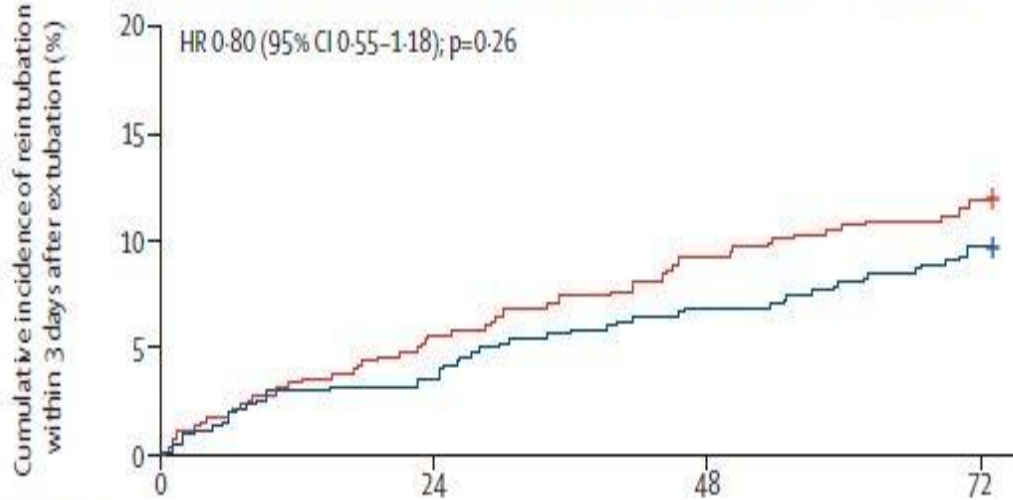
The reintubation rate within 3 days after extubation was lower in the NIV group than in the oxygen therapy group in the per-protocol analysis ( $31$  [ $7\%$ ] of  $466$  patients in the NIV group vs  $49$  [ $10\%$ ] of  $473$  patients in the oxygen therapy group,  $p=0.042$ , appendix p 22) and in the post-hoc crossover analysis ( $51$  [ $9\%$ ] of  $560$  patients in the NIV group vs  $56$  [ $13\%$ ] of  $421$  patients in the oxygen therapy group,  $p=0.037$ ). After per-protocol analysis, cumulative incidence of reintubation within 3 days after extubation was lower in the NIV group than in the oxygen therapy group (HR= $0.63$ ; 95% CI  $0.40$  to  $0.99$ ;  $p=0.04$ , figure 3C). Crossover to NIV group occurred  $29$  h (SD  $17$ ) after randomisation in  $70$  patients ( $14\%$ ) in the oxygen therapy group, with  $67$  of these patients receiving rescue therapy without subsequent intubation. After reallocating the patients receiving rescue therapy in the oxygen therapy group ( $70$  patients) to the NIV group in the post-hoc crossover analysis, cumulative incidence of reintubation within 3 days after extubation was lower in the NIV group than in the oxygen therapy group (HR= $0.67$ ; 95% CI  $0.46$  to  $0.97$ ;  $p=0.03$ , figure 3D).

**A Cumulative incidence of treatment failure within 3 days after intention-to-treat analysis**

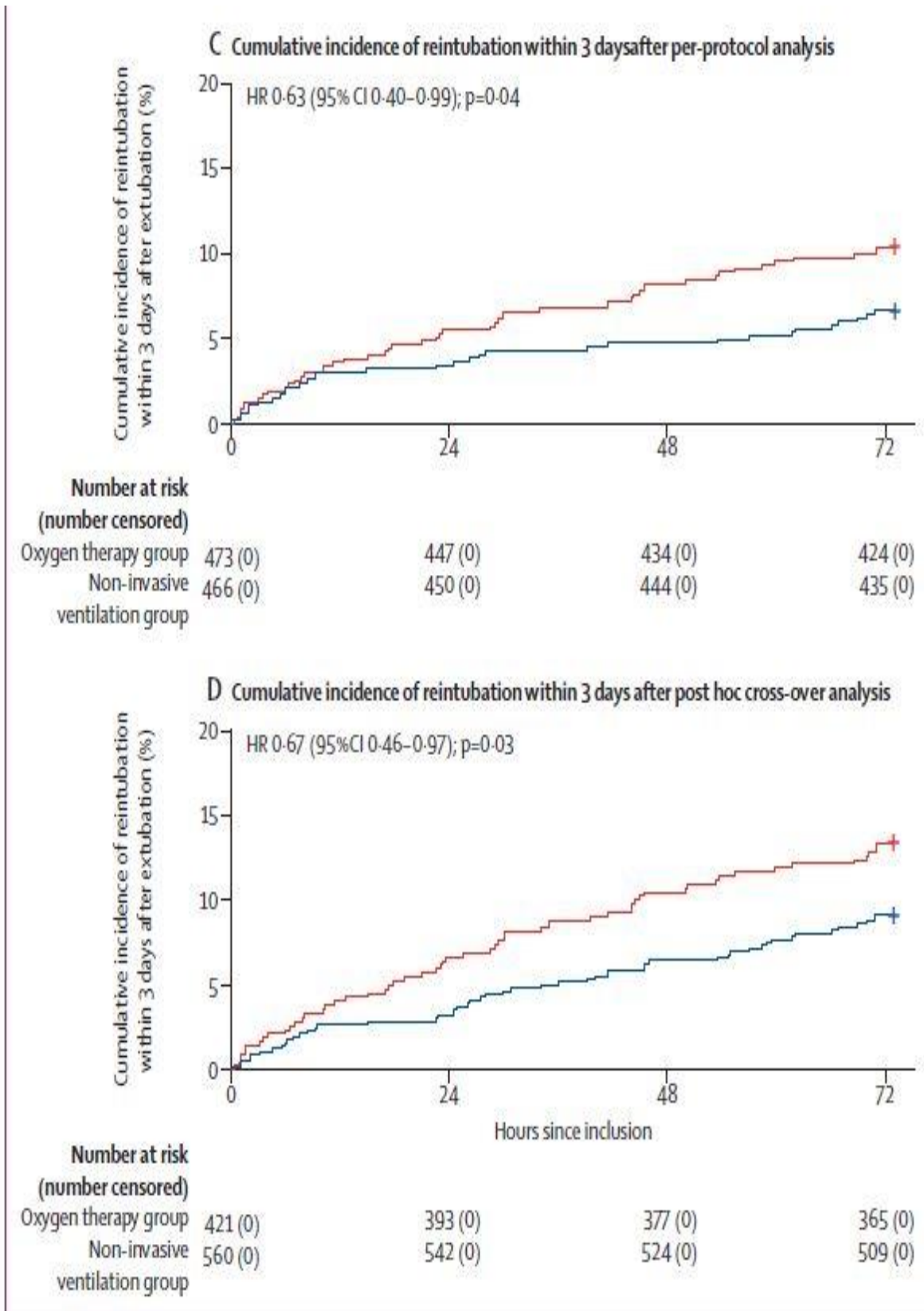


Number at risk (number censored)		0	24	48	72
Oxygen therapy group		491 (0)	437 (0)	385 (0)	362 (0)
Non-invasive ventilation group		490 (0)	454 (0)	438 (0)	424 (0)

**B Cumulative incidence of reintubation within 3 days after intention- to-treat analysis**



Number at risk (number censored)		0	24	48	72
Oxygen therapy group		491 (0)	463 (0)	445 (0)	432 (0)
Non-invasive ventilation group		490 (0)	472 (0)	456 (0)	442 (0)



**Figure 3: Kaplan-Meier plots**

(A) Cumulative incidence of treatment failure within 3 days after extubation in the intention-to-treat analysis). (B) Cumulative incidence of reintubation within 3 days after extubation in the intention-to-treat analysis. (C) Cumulative incidence of reintubation within 3 days after per-protocol analysis; per-protocol analysis excluded the patients with reintubation for surgical procedures without criteria of acute respiratory failure, with BMI less



than 30 kg/m<sup>2</sup> or with home ventilator. (D) Cumulative incidence of reintubation within 3 days after post-hoc crossover analysis. Crossover to NIV group occurred 29 h (SD 17) after randomisation in 70 (14%) patients in the oxygen therapy group, with 67 of these patients with rescue therapy without subsequent intubation. After reallocating the patients switched from oxygen therapy to NIV (70 patients) in the NIV group, cumulative incidence of reintubation within 3 days after extubation after posthoc crossover analysis was lower in the NIV group, in comparison with the oxygen therapy group. HR=hazard ratio. NIV=non-invasive ventilation.

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54 (11%) patients in the NIV group had acute respiratory failure within 7 days after extubation, as compared with 70 (14%) patients in the oxygen therapy group (absolute risk difference -3.2; 95% CI -7.4 to 0.9; relative risk 0.75, 95% CI 0.51 to 1.09; p=0.13; table 2 and appendix p 19 for each method of oxygenation in appendix). The delay between extubation and the occurrence of acute respiratory failure in those who had respiratory failure, did not differ between groups (1.88 days [SD 1.71] in the NIV group and 1.84 days [1.62] in the oxygen therapy group; p=0.93). The causes of acute respiratory failure did not differ between groups (appendix p 23).

The NIV group and the oxygen therapy group did not significantly differ regarding the incidence of reintubation rates within 7 days, 14 days, or 28 days after extubation (appendix p 26), length of ICU or hospital stay, or day-28 and day-90 mortality rates (table 2). The PaO<sub>2</sub> to FiO<sub>2</sub> ratio and SOFA scores did not differ between groups from day 0 to day 7 (appendix pp 27–28). No death or cardiac arrest was recorded. The exploratory outcomes rates for each method of oxygenation are presented in the appendix (p 19).

The results of the per-protocol analysis were consistent with those of the primary intention-to-treat analysis (appendix p 22), as the results of the analyses adjusted for the stratification variables (appendix p 24).

## Discussion

In this multicentre, randomised trial, performed in critically ill adults with obesity undergoing endotracheal extubation, the use of NIV resulted in a significantly lower primary outcome (defined as treatment failure) than did the use of oxygen therapy, whether HFNO or standard oxygen. The results suggest that for every eight critically ill patients with obesity undergoing endotracheal extubation, using NIV would prevent treatment failure in one patient. Moreover, the effects were consistent across subgroups, defined according to the presence of SARS-CoV-2 infection, type of admission, and length of mechanical ventilation.

To our knowledge, this is the first study performed in critically ill patients with obesity that assessed the older and the most recent methods of oxygen administration and ventilatory support following extubation. Surgical and medical patients (including patients with and without SARS-CoV-2 infection) were both assessed, irrespective of the duration of invasive mechanical ventilation.

Two methods are now largely used for oxygen therapy in clinical practice: HFNO and standard oxygen administration. In this pragmatic study, we first compared NIV with oxygen therapy through the first randomisation, and thereafter assessed the interaction between the method of oxygen therapy (second randomisation, HFNO *vs* standard oxygen) and treatment failure rate.

Contemporary strategies to improve clinical trial design for critical care research include the choice of an appropriate study outcome reflecting the real life and, therefore, the real efficiency of a treatment in clinical practice.<sup>23</sup> For these reasons, we chose a pragmatic composite primary outcome that was previously used in the

multicentre randomised trial of Stephan and colleagues.<sup>19</sup> As NIV might be associated with premature discontinuation of study treatment (at the request of the patient or for medical reasons such as gastric distension), it was mandatory to take premature study treatment discontinuation into account.<sup>19</sup> Similarly, a change in study treatment was allowed as a rescue therapy before reintubation of a patient,<sup>19</sup> as it is the case in real life.<sup>24</sup> For this reason, no switch was observed from NIV to oxygen therapy (table 2), as it is not done in routine practice to avoid intubation. Accordingly, treatment failure at the bedside (the primary outcome) was defined as a composite of reintubation, change of study treatment, or premature discontinuation of study treatment, as previously reported.<sup>19</sup> Most of the difference in the primary outcome was due to patients in the oxygen therapy group switching to NIV, and more evidence is needed to conclude that an NIV strategy leads to improved patient-centred outcomes. Reintubation rate did not differ between groups in the intention-to-treat analysis, which highlights the potential bias associated with the inclusion of treatment switching or discontinuation in the definition of the primary outcome. However, this outcome was previously used in a large multicentre trial performed in the field of preventive and curative NIV.<sup>19</sup> Moreover, the per-protocol analysis and a post-hoc crossover analysis, in which patients who switched from oxygen therapy to NIV for rescue therapy were reallocated to the NIV group, the NIV group had a significantly lower rate of reintubation within 3 days.

Our results are consistent with the results in the published literature. Observational studies have suggested superiority of NIV over standard oxygen following extubation of critically ill patients with obesity.<sup>2,4,10</sup> In the post-hoc analysis of the multicentre trial of Thille and colleagues<sup>25</sup> comparing NIV (alternating with HFNO) with HFNO alone after extubation in patients with obesity,<sup>26</sup> the rates of reintubation within 7 days after extubation were significantly lower in the NIV alternating with HFNO group than in the HFNO alone group. In that trial, NIV alternating with standard oxygen or standard oxygen alone were not assessed.<sup>27</sup>

All these results are supported by physiological data about NIV use in patients with obesity. Patients with obesity have a decreased pulmonary and thoracic compliance and a reduction of functional residual capacity compared with patients without obesity.<sup>4</sup> They are therefore prone to atelectasis, a risk factor for reintubation.<sup>10</sup> Obstructive apnoea syndrome is more frequent in patients with obesity, and it is often underdiagnosed.<sup>12</sup> For all these reasons, NIV, which consists of delivery of pressure support ventilation plus positive end-expiratory pulmonary pressure, is likely to prevent or reverse atelectasis formation in patients with obesity, increase lung ventilation, and therefore decrease the incidence of treatment failure after extubation.<sup>4</sup> In the current study, it is worth noting that NIV was provided in a preventive, rather than curative, way. As this strategy was applied to avoid occurrence of acute respiratory failure, and not to treat acute respiratory failure, the sessions were shorter and more spaced, to be better tolerated by the patient.<sup>28</sup> Ventilatory support was still provided, as shown by several physiological studies.<sup>4,28</sup> However, we cannot exclude that longer durations of NIV might have further improved outcomes.

Our trial has several strengths and limitations. To our knowledge, this is the first randomised controlled trial with a large sample size evaluating the effect of NIV after extubation in patients with obesity. The trial design included randomisation to balance baseline confounders and was conducted at multiple centres to increase generalisability. However, almost 50% of the patients were enrolled in six of the 39 participating centres. Together with the unblinded design of the study,<sup>29</sup> and the lack of systematic spontaneous breathing trial performed, this issue could potentially have affected the outcome. The inclusion criteria were wide, including both surgical and medical patients, with short and long duration of ventilation, and patients with and without SARS-CoV-2 infection. The subgroup analyses of the primary outcome showed no modification of treatment effect by these patient characteristics. Rates of missing data were low. However, the study was not designed nor powered to conclude on the prespecified strata and the results should be considered exploratory. Moreover, mixing surgical and medical patients can be confounding providing that the pathophysiology and the aetiology of the respiratory failure can be very different. A second limitation is that the most frequent reason for intubation was a procedure, which is biased toward surgical patients who are likely to turnaround more quickly

than medical ICU patients with their many comorbidities. However, no modification of treatment effect was observed according to the medical or surgical status of patients. Another limitation is that most patients were intubated for acute respiratory failure or for a procedure, which are very broad categories. Specific types of acute respiratory failure or specific procedures were not recorded.

In summary, in this multicentre, randomised trial involving critically ill adults with obesity undergoing extubation, the use of NIV following extubation was associated with reduced treatment failure within 3 days when compared with the use of oxygen therapy alone (HFNO or standard oxygen). Our findings have important implications, for informing clinicians and policy makers with respect to the most appropriate after-extubation strategy in critically ill patients with obesity. Furthermore, centres should consider developing systematic NIV use and assess long-term outcomes after applying this extubation strategy in patients with obesity.

## **Contributors**

ADJ, AB, FS, TG, J-MC, KA, AS, JS, RB, MFe, PS, SL, AR, P-MF, LM, EP, NT, SR, BJ, P-SA, PG, BS, HR, CD, JC, MFa, VL, BC, GC, FB, and SJ included patients. ADJ, AB, FS, TG, J-MC, KA, AS, JS, RB, MFe, PS, SL, AR, P-MF, LM, EP, NT, SR, BJ, P-SA, PG, BS, HR, CD, JC, MF, VL, BC, GC, FB, HH, EF, EA, NM, and SJ wrote the manuscript. HH and NM were the study statisticians. ADJ and SJ obtained the funding. SJ (member of the academic team), ADJ (member of the academic team), HH, and NM had directly accessed and verified the underlying data in all research articles. The corresponding author (SJ), ADJ, HH, and NM had full access to all the study data. The corresponding author (SJ) had final responsibility for the decision to submit for publication. All authors were involved in the data analysis and interpretation. All authors read and approved the manuscript.

## **Declaration of interests**

SJ reports receiving consulting fees from Drager, Medtronic, Mindray, Fresenius, Baxter, and Fisher & Paykel. ADJ reports receiving remuneration for presentations from Medtronic, Drager and Fisher & Paykel. VL reported being a member of a research group that has received grants from Alexion, Baxter, MSD, Gilead, Sanofi, Celgène. All other authors declare no competing interests.

## **Data sharing**

Research data and other material (eg, study protocol and statistical analysis plan) will be made available to the scientific community, immediately on publication, with as few restrictions as possible. All requests should be submitted to the corresponding author who will review with the other investigators for consideration. A data use agreement will be required before the release of participant data and institutional review board approval as appropriate.

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## References

- 1 Abu Dayyeh BK, Bazerbachi F, Vargas EJ, et al. Endoscopic sleeve gastropasty for treatment of class 1 and 2 obesity (MERIT): a prospective, multicentre, randomised trial. *Lancet* 2022; **400**: 441–51.
- 2 Schetz M, De Jong A, Deane AM, et al. Obesity in the critically ill: a narrative review. *Intensive Care Med* 2019; **45**: 757–69.
- 3 Jaber S, Citerio G, Slutsky AS. Acute respiratory failure and mechanical ventilation in the context of the COVID-19 pandemic: why a special issue in ICM? *Intensive Care Med* 2020; **46**: 2131–2.
- 4 De Jong A, Wrigge H, Hedenstierna G, et al. How to ventilate obese patients in the ICU. *Intensive Care Med* 2020; **46**: 2423–35.
- 5 Maggiore SM, Battilana M, Serano L, Petrini F. Ventilatory support after extubation in critically ill patients. *Lancet Respir Med* 2018; **6**: 948–62.
- 6 Weerakkody S, Arina P, Glenister J, et al. Non-invasive respiratory support in the management of acute COVID-19 pneumonia: considerations for clinical practice and priorities for research. *Lancet Respir Med* 2022; **10**: 199–213.
- 7 Gorman E, Connolly B, Couper K, Perkins GD, McAuley DF. Non-invasive respiratory support strategies in COVID-19. *Lancet Respir Med* 2021; **9**: 553–56.
- 8 Jaber S, Chanques G, Jung B. Postoperative noninvasive ventilation. *Anesthesiology* 2010; **112**: 453–61.
- 9 Demoule A, Chevret S, Carlucci A, et al. Changing use of noninvasive ventilation in critically ill patients: trends over 15 years in francophone countries. *Intensive Care Med* 2016; **42**: 82–92.
- 10 El-Solh AA, Aquilina A, Pineda L, Dhanvantri V, Grant B, Bouquin P. Noninvasive ventilation for prevention of post-extubation respiratory failure in obese patients. *Eur Respir J* 2006; **28**: 588–95.
- 11 Chanques G, Riboulet F, Molinari N, et al. Comparison of three high flow oxygen therapy delivery devices: a clinical physiological cross-over study. *Minerva Anestesiol* 2013; **79**: 1344–55.
- 12 Rochweg B, Einav S, Chaudhuri D, et al. The role for high flow nasal cannula as a respiratory support strategy in adults: a clinical practice guideline. *Intensive Care Med* 2020; **46**: 2226–37.
- 13 Coudroy R, Frat JP, Ehrmann S, et al. High-flow nasal oxygen alone or alternating with non-invasive ventilation in critically ill immunocompromised patients with acute respiratory failure: a randomised controlled trial. *Lancet Respir Med* 2022; **10**: 641–49.
- 14 Stephan F, Berard L, Rezaiguia-Delclaux S, Amaru P. High-flow nasal cannula therapy versus intermittent noninvasive ventilation in obese subjects after cardiothoracic surgery. *Respir Care* 2017; **62**: 1193–202.
- 15 Corley A, Bull T, Spooner AJ, Barnett AG, Fraser JF. Direct extubation onto high-flow nasal cannulae post-cardiac surgery versus standard treatment in patients with a BMI  $\geq 30$ : a randomised controlled trial. *Intensive Care Med* 2015; **41**: 887–94.
- 16 Jung B, Vaschetto R, Jaber S. Ten tips to optimize weaning and extubation success in the critically ill. *Intensive Care Med* 2020; **46**: 2461–63.

- 17 De Jong A, Huguet H, Molinari N, Jaber S. Non-invasive ventilation versus oxygen therapy after extubation in patients with obesity in intensive care units: the multicentre randomised EXTUB-OBESE study protocol. *BMJ Open* 2022; **12**: e052712.
- 18 Scott NW, McPherson GC, Ramsay CR, Campbell MK. The method of minimization for allocation to clinical trials. a review. *Controlled Clin Trials* 2002; **23**: 662–74.
- 19 Stephan F, Barrucand B, Petit P, et al. High-flow nasal oxygen vs noninvasive positive airway pressure in hypoxemic patients after cardiothoracic surgery: a randomized clinical trial. *JAMA* 2015; **313**: 2331–39.
- 20 Jaber S, Quintard H, Cinotti R, et al. Risk factors and outcomes for airway failure versus non-airway failure in the intensive care unit: a multicenter observational study of 1514 extubation procedures. *Crit Care* 2018; **22**: 236.
- 21 Combes A, Hajage D, Capellier G, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *N Engl J Med* 2018; **378**: 1965–75.
- 22 Arabi YM, Asiri AY, Assiri AM, et al. Interferon Beta-1b and lopinavir-ritonavir for Middle East Respiratory Syndrome. *N Engl J Med* 2020; **383**: 1645–56.
- 23 Harhay MO, Casey JD, Clement M, et al. Contemporary strategies to improve clinical trial design for critical care research: insights from the First Critical Care Clinical Trialists Workshop. *Intensive Care Med* 2020; **46**: 930–42.
- 24 Casey JD, Beskow LM, Brown J, et al. Use of pragmatic and explanatory trial designs in acute care research: lessons from COVID-19. *Lancet Respir Med* 2022; **10**: 700–14.
- 25 Thille AW, Coudroy R, Nay MA, et al. Beneficial effects of noninvasive ventilation after extubation in obese or overweight patients: a post hoc analysis of a randomized clinical trial. *Am J Respir Crit Care Med* 2022; **205**: 440–49.
- 26 Thille AW, Muller G, Gacouin A, et al. Effect of postextubation high-flow nasal oxygen with noninvasive ventilation vs high-flow nasal oxygen alone on reintubation among patients at high risk of extubation failure: a randomized clinical trial. *JAMA* 2019; **322**: 1465–75.
- 27 Grieco DL, Jaber S. Preemptive noninvasive ventilation to facilitate weaning from mechanical ventilation in obese patients at high risk of reintubation. *Am J Respir Crit Care Med* 2022; **205**: 382–83.
- 28 Jaber S, Antonelli M. Preventive or curative postoperative noninvasive ventilation after thoracic surgery: still a grey zone? *Intensive Care Med* 2014; **40**: 280–83.
- 29 Wick KD, Aggarwal NR, Curley MAQ, et al. Opportunities for improved clinical trial designs in acute respiratory distress syndrome. *Lancet Respir Med* 2022; **10**: 916–24.

