Effect of protocolized weaning with early extubation to non-invasive ventilation vs invasive weaning on time to liberation from mechanical ventilation among patients with respiratory failure: **The Breathe randomized trial.**

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Key points

Question: In adults who are difficult to wean from invasive mechanical ventilation, does early extubation using a protocolized non-invasive weaning regime reduce the time to liberation from ventilation compared to protocolized invasive weaning?

Findings: In this randomized clinical trial that included 364 adults, the median time to liberation from ventilation for those randomized to non-invasive weaning versus invasive weaning was 4.3 days versus 4.5 days, a difference that was not statistically significant.

Meaning: Protocolized weaning with early extubation to non-invasive ventilation compared with invasive weaning did not significantly shorten time to liberation from all forms of mechanical ventilation.

Abstract

Importance: In adults who are difficult to wean from invasive mechanical ventilation, non-invasive ventilation may facilitate early liberation but there is uncertainty about its effectiveness in a mixed intensive care patient population.

Objective: To investigate, in patients who are difficult to wean, the effects of protocolized weaning with early extubation to non-invasive ventilation on time to liberation from ventilation compared to protocolized invasive weaning.

Design, Setting and Participants: A randomized, allocation concealed, open-label, multi-centre clinical trial. Patients were enrolled between March 2013 and October 2016 from 41 intensive care units in the UK National Health Service. Follow up continued until April 2017. Adults who received invasive mechanical ventilation for more than 48 hours and failed a spontaneous breathing trial were enrolled in the trial.

Intervention: Patients were randomized to receive either protocolised early extubation to non-invasive weaning (n=182) or protocolised invasive weaning (n=182).

Main outcomes: Primary outcome was time from randomization to successful liberation from all forms of mechanical ventilation amongst survivors, measured in days, with the minimally clinically important difference defined as 1 day. Secondary outcomes were duration of invasive and total ventilation (days), re-intubation or tracheostomy rates and survival.

Results: Among 364 randomized patients (mean age 63.1 years, [SD 14.8], 50.5% male), 319 were evaluable for the primary effectiveness outcome (41 died before liberation, 2 withdrew and 2 were discharged with on-going ventilation). The median time to liberation was 4.3 days (non-invasive) versus 4.5 days (invasive) (adjusted hazard ratio 1.1, 95% confidence interval (CI) 0.89 to 1.40). Competing risk analysis accounting for deaths had a similar result (adjusted hazard ratio 1.1, 95% CI 0.86 to 1.34). The non-invasive group received less invasive ventilation (median: 1 day vs 4 days, incidence rate ratio (IRR) 0.6 (95% CI: 0.47 to 0.87)) and less total ventilator days (median: 3 days vs 4 days, IRR 0.8 (95% CI: 0.62 to 1.0)). There was no significant difference in re-intubation, tracheostomy rates or survival. Adverse events occurred in 45 (24.7%) patients in the non-invasive group compared with 47 (25.8%) in the invasive group.

Conclusion and Relevance: Among patients requiring mechanical ventilation, protocolized weaning with early extubation to non-invasive ventilation compared with invasive weaning did not significantly shorten time to liberation from all forms of mechanical ventilation.

Trial Registration: ISRCTN 15635197.

Invasive mechanical ventilation is a lifesaving intervention. However prolonged ventilation is associated with increased morbidity and mortality.[1,2] Optimal processes for weaning from ventilation have been studied for many years and led to evidence based clinical practice guidelines to facilitate early liberation from invasive mechanical ventilation.[3] These guidelines recommend using spontaneous breathing trials, minimising sedation, using weaning protocols and early mobilization to promote liberation from ventilation.

Whilst most invasively ventilated patients have an uncomplicated (simple) weaning pathway around one third require more than one spontaneous breathing trial and are considered difficult to wean.[1,4,5] Patients who are difficult to wean face the physical discomfort of on-going tracheal intubation, are often unable to speak,[6] are at increased risk of ventilator associated pneumonia.[7,8] Mobilisation is often delayed due to concurrent sedation and concerns about accidental intubation.[9,10] This group of patients consume a disproportionate amount of intensive care unit (ICU) resources.[11]

Non-invasive mechanical ventilation, which is being used increasingly as an alternative to invasive ventilation,[12,13] may have a role to play in supporting early liberation from invasive mechanical ventilation in patients who are difficult to wean. Although the use of non-invasive ventilation as an adjunct to weaning has been tested in previous studies, the patient populations and interventions tested are not generalizable to contemporary clinical ventilation practice.[14]

In this multicentre randomized clinical trial conducted in the United Kingdom, it was hypothesized that weaning protocols which directed clinicians to extubate patients who were

difficult to wean to non-invasive ventilation compared to conventional weaning protocols for invasive mechanical ventilation, would reduce the time to liberation from ventilation.

Methods

Trial design

We conducted this randomized, allocation concealed controlled, open-label, multi-centre trial in 41 general adult intensive care units (ICUs) in the United Kingdom. The trial protocol was designed by the trial investigators (online supplement).[15] The trial was co-sponsored by Heart of England NHS Foundation Trust and University of Warwick and was approved by South Central C Research Ethics Committee (Reference 12/SC/0515). It was endorsed by the UK Intensive Care Foundation. Written consent was obtained from patients, their next of kin or a doctor who was independent from the trial prior to randomization in accordance with national laws. The study included an internal pilot, spanning the first six months of the trial at which point progress was reviewed by the funder. The same trial protocol was used for the internal pilot as the main study. Patients enrolled in the internal pilot were included as part of the main trial

Patients

Adult patients who had received invasive mechanical ventilation through an endotracheal tube continuously for more than 48 hours and were ready to commence weaning were considered for enrolment. Exclusion criteria were pregnancy, presence of a tracheostomy, contra-indications to non-invasive ventilation, profound neurological deficit, home ventilation prior to admission, treatment limitations, need for further surgery/sedation, or no non-invasive ventilator available. Readiness to wean was assessed by the treating clinician

before randomization according to pre-specified criteria.[16] Patients judged ready to start weaning underwent a spontaneous breathing trial (details in the electronic supplementary material). Patients who failed the spontaneous breathing trial and thus were defined as difficult to wean, were eligible for randomization. After obtaining consent, eligible patients were randomized using web-based secure electronic randomization designed by the study statistician. The minimization method was used to randomise patients in 1:1 (non-invasive or invasive) allocation. The stratifying factors used in the minimisation algorithm were centre, presence/absence of COPD, and post-operative/non-operative reason for ICU admission, and these ensured equal balance between treatment groups. COPD was defined by a pre-admission diagnosis of COPD requiring pharmacological treatment or evidence of FEV1: FVC ratio < 0.7 and FEV1 < 80% predicted or the presence of respiratory symptoms. Patients admitted to ICU after surgery were defined as the post-operative group. . Following the spontaneous breathing trial, patients were re-established on pressure support ventilation using the previous settings. If necessary, the level of pressure support was further titrated to achieve patient comfort and respiratory rate <30 breaths min^{-1}.

Non-invasive ventilation weaning protocol

When the treating clinician judged the patient was ready, the patient was extubated. The patient was then immediately provided with non-invasive ventilation via face mask. The non-invasive ventilator was configured to deliver an equivalent level of inspiratory positive airway pressure to the level of pressure support that was being provided by the invasive ventilator and expiratory positive airway pressure equivalent to the level of positive end expiratory pressure (PEEP). The level of inspiratory positive airway pressure was then titrated to achieve patient comfort and respiratory rate <30 breaths min^{-1} . Every two hours, the patient was assessed for signs of distress/fatigue. In the absence of distress/fatigue, the

treating clinician either removed the non-invasive ventilation mask to allow a self-ventilation trial or reduced the level of positive airway pressure by 2cm H_2O. The non-invasive weaning protocol was discontinued when the patient tolerated 12 hours of unsupported spontaneous ventilation.

Invasive ventilation weaning protocol

Every 2 hours, the clinician assessed the patient for signs of distress/fatigue. In the absence of distress/fatigue, pressure support was reduced by 2cm H_2O. This cycle was repeated every 2 hours as tolerated. If at any point the patient developed signs of distress/fatigue, then reversible causes were sought and corrective treatments initiated as appropriate. If this failed to resolve the situation, the level of pressure support was increased by 2cm H_2O. Spontaneous breathing trials were repeated daily to assess extubation readiness. This cycle continued until the patient was either extubated (due to passing the spontaneous breathing trial) or a tracheostomy was performed.

In both groups, the fraction of inspired oxygen was titrated to maintain arterial oxygen saturations >90%. Both active weaning protocols were implemented between 8am-10pm. Unless the patient developed signs of fatigue/distress, ventilator settings remained unchanged overnight.

The protocol encouraged use of a ventilator bundle (head up position; oral decontamination; sedation hold; peptic ulcer prophylaxis), and recommended deferral of tracheostomy until after 7 days of ventilation. Guidance was provided for the criteria for re-intubation but the decision to re-intubate was made by the patients' physician. The decision to initiate antibiotic therapy and other treatments was at the discretion of the patient's physician.

Outcome measures:

The primary outcome was time from randomization to successful liberation from ventilation defined as the time point at which the patient was alive and free of ventilator (invasive or non-invasive) support for >48 hours. Secondary outcomes were duration of invasive ventilation and total ventilator days (invasive and non-invasive); proportion of patients receiving antibiotics for presumed respiratory infection; total days receiving antibiotics; the rate of re-intubation; mortality at 30, 90 and 180 days; time to meeting ICU discharge criteria; the rate at which patients fulfilled pre-defined criteria indicating the need for re-intubation irrespective to whether they were re-intubated. The pre-defined criteria were cardiac or respiratory arrest, respiratory pauses with loss of consciousness or gasping for air, severe psychomotor agitation inadequately controlled by sedation, persistent inability to remove respiratory secretions, heart rate ≤ 50 or ≥ 140 breaths $min^{-1}$with loss of alertness, haemodynamic instability unresponsive to fluids and vasoactive drugs, requirement for surgery or other interventional procedure which requires deep sedation or anaesthesia; the proportion of patients receiving a tracheostomy and mortality at 30, 90 and 180 days after randomization. Post-hoc key process variables (weaning pathway, sedation use, length of intensive care stay) are also reported. Outcomes were extracted from the intensive care, hospital clinical records and from questionnaires returned by patients. By the nature of the intervention and clinical record designs (which typically record mode of ventilation alongside respiratory variables) it was not possible to blind those assessing core ventilation outcomes to the treatment allocation. Adverse events defined as the development of skin / mucosal damage, vomiting, gastric distension, non-respiratory infection and cardiac dysrhythmias. Health-related quality of life was assessed by EQ-5D-5L and SF-12 at baseline (estimated

retrospectively), 90 and 180 days after randomization. All outcomes are reported post randomization.

Statistical analysis

The original sample size was 920 patients but after a formal review requested by the funder, the sample size was revised to reflect a shorter than anticipated period of weaning. A median duration of weaning of 2.9 days and a difference of 1 day provided an associated hazard ratio (HR) of 1.53 and a minimum sample size of 280 with 90% power at a 5% significance level. One day was defined by the investigators and patient and public representatives as the minimally important difference. The sample size was inflated by 23%, to account for the rate of loss to follow-up seen up to the interim review of the data. It also accounted for the shape parameter, p which was estimated by the data as 0.918 and which allowed for non-constant hazards (as modelled by the Weibull distribution), resulting in a final sample size of 364 (182 patients in each group). Revision of the sample size meant that the primary outcome would be analysed using a Cox proportional hazards (PH) model as opposed to the competing risks regression model which was pre-specified in the protocol.

The primary analysis method was intention to treat. Analysis of the primary outcome, time from randomization to liberation from ventilation, and other time to event outcomes, used a Cox proportional hazards (PH) regression model to estimate the HR and 95% confidence interval (CI). In addition we used a competing risks regression model to account for the competing risk of death. Prior to the competing risk regression analysis, the cumulative incidence of liberation and death was plotted as a basic descriptive to understand the overall pattern over time. Mixed-effects logistic regression models were used to estimate the difference in mortality at 30, 90 and 180 days between the two groups where we reported the

odds ratio (OR) and 95% CI. Mixed-effects linear regression models were used to estimate the mean treatment difference and 95% CI for continuous outcomes including the HRQL measures (change from baseline). Mixed-effects negative binomial models were used to estimate the incidence rate ratio (IRR) and 95% CI for over-dispersed count data e.g. number of days on invasive ventilation with zero inflation where several participants had no days on invasive ventilation. The study was not powered to detect treatment differences in the secondary outcomes, hence these secondary analyses are considered exploratory.

We performed a *per protocol* analysis and two pre-defined subgroup analyses (presence or absence of COPD; post-operative / non-operative). It was not possible to perform the third planned sub-group analysis (physician versus nurse led weaning) as all sites used a multi-professional approach involving both physicians and nurses. Multiple imputation by chained equations was used to impute missing primary outcome data and the imputed dataset analysed as a sensitivity analysis.

All of the analyses used mixed-effects models adjusted for age, gender, centre, post-spontaneous breathing trial $PaCO_2$, presence/absence of COPD and non-operative/post-operative, where centre was included as a random effect in the models. Modelling assumptions were assessed for all models fitted. The proportional hazards assumption was assessed for the Cox PH regression model and the competing risks model using plots of the log(-log) survival function and the Schoenfeld residuals and by assessing the influence of time-varying covariates. Linear, logistic and negative binomial regression models were checked to ensure that the assumptions of linearity and constant variance were satisfied, using residual plots. In addition to this, all the covariates included in the model were assumed to be

independent of the outcome. All statistical tests were 2-sided using a 5% significance threshold. Statistical analyses were performed using STATA, version 15.1.

Results

Patients

Figure 1 presents the flow of patients through the trial. Recruitment took place between March 2013 and October 2016 during which 364 patients were recruited from across 41 hospitals. 182 patients were allocated to each group. Most patients received the allocated intervention (non-invasive 96.7% (175/182), invasive group 96.1% (175/182)).

Participant follow-up ended in April 2017. Overall baseline and physiological characteristics of patients were well matched (Table 1). Most patients had pneumonia (35.7%) or post-surgery respiratory failure (21.4%) as the main reason for mechanical ventilation.

Outcomes

The primary outcome, time from randomization to liberation from ventilation was median 4.3 days (95% CI 2.63 to 5.58) in the non-invasive group compared to 4.5 days (95% CI 3.46 to 7.25) in the invasive group (see Figure 2, adjusted hazard ratio 1.1, 95% CI 0.89 to 1.40). The competing risks regression analysis gave a similar result (see Figure 3, adjusted hazard ratio 1.1, 95% CI 0.86 to 1.34).

The non-invasive group required less invasive ventilation (median: 1 day vs 4 days, incidence rate ratio (IRR) 0.6, 95% CI 0.47 to 0.87) and required less total ventilator days (median: 3 days vs 4 days, IRR 0.8, 95% CI 0.62 to 1.0). Fewer non-invasive patients received antibiotics for respiratory infection, 60.4 % versus 70.3% (unadjusted absolute difference 9.9%, 95% CI 0.17%to 19.61%). Total days receiving antibiotics (respiratory and non-respiratory) were not significantly different (mean difference 1.3 days, 95% CI -1.31 to 3.88) with a mean of 9.1 days (SD 12.0) in the non-invasive group and 10.4 days (SD 13.2) in the invasive group.

A higher proportion of patients were extubated in the non-invasive group (181/182) compared to the invasive group 143/182. 67/181 (37.0%) of those extubated in the non-invasive group were re-intubated compared to 41/143 (28.7%) in the invasive group (OR 1.54, 95% CI 0.89 to 2.41). For the end-point of reaching the criteria for re-intubation, there were 63/181(34.8%) compared with 42/143 (29.4%) patients in the invasive group (OR 1.3, 95% CI 0.78 to 2.12).

The rate of tracheostomy was 23.6% in the non-invasive group and 30.2 % in the invasive group (OR 0.7, 95% CI 0.44 to 1.15). Survival rates were not significantly different at 30 days (86.8% (non-invasive) versus 86.3% (invasive), OR 1.1 (95% CI 0.58 to 1.96) through to 180 days (78% non-invasive, 73.1% invasive, OR 1.4 (95% CI 0.85 to 2.27)).(see electronic supplementary material – E2). There were no significant differences in the proportions of patients who experienced adverse events and serious adverse events. The distributions of adverse and serious adverse events were similar (Table 2).

Post-hoc key process measures showed that patients in the non-invasive group were extubated earlier than the invasive group (median 0.5 days (IQR 0.5 to 1) versus 3 (IQR 2 to 10), adjusted hazard ratio 2.5, 95% CI 2.01 to 3.15), P<0.001). Amongst those requiring re-intubation, the non-invasive group were re-intubated at a median of 2 days (IQR 0.9 – 3.0) after randomization compared with 3.2 days (IQR 2.3-4.7), P<0.001 in the invasive ventilation arm. The non-invasive group received sedation for fewer days (mean (SD) 4.1 days (5.0) versus 5.5 days (5.1) (IRR 0.7, 95% CI 0.61 to 0.91) and spent less time in critical care (10.8 (8.8) versus 12.2 (8.4), P=0.02). The median time from randomization to tracheostomy was a 5.8 days (IQR 3.71 to 8.46) in the invasive arm and 5.6 days (IQR 3.43 to 8.46) in the non-invasive arm. There was no significant difference between the two groups (non-parametric p-value=0.65).

Health-related quality of life (electronic supplementary material - Table E3) although impaired there was no significant difference between the two weaning groups at 3 and 6 months.

The per protocol analysis gave a similar result to the primary analysis (HR 1.1, 95% CI 0.90 to 1.44). The explored subgroups showed no significant difference in treatment effect (electronic supplementary material (E4). The sensitivity analysis using multiple imputation for the 45 participants with missing (censored) primary outcome found no difference between the two groups (HR 1.1, 95% 0.90 to 1.36). A further sensitivity analysis found no significant difference in outcome between the three highest recruiting centres (who recruited 161(44%)

of the patients) and the other participating centres. There were no major departures from the modelling assumptions for all of the regression models fitted.

Discussion

In this multi-centre randomized trial, early extubation to non-invasive ventilation compared to protocolized invasive weaning with sequential pressure support reduction prior to extubation, did not reduce the time to liberation from all form of ventilation. Consistent with the protocol design, patients in the non-invasive ventilation group were extubated earlier and spent less time receiving invasive ventilation. Mortality rates, the requirement for re-intubation or tracheostomy and adverse event rates were not significantly different.

The spontaneous breathing trial is used to identify patients who are ready for extubation.[17] The 59-86% of invasive ventilation patients who fail a spontaneous breathing trials are classified as difficult to wean.[1,4,18-20] These patients consume a disproportionate amount of ICU resource to achieve successful liberation.[11] Non-invasive ventilation has been suggested to be a useful tool to facilitate weaning but most previous studies recruited predominantly patients with chronic obstructive pulmonary disease (COPD).[21-25] In that patient group (COPD), non-invasive weaning reduced mortality, the duration of invasive ventilation, re-intubation and ICU length of stay.[14] The patients enrolled in the present study better reflects contemporary ICU practice, as fewer patients with COPD are now invasively ventilated.[26,27]

The rate of re-intubation was expected to be higher than those with simple weaning needs, where re-intubation rates of 10-20% are reported.[28] The 30% overall rate of re-intubation is consistent with findings in previous studies which recruited patients who are difficult to wean.[22,23,25] As more patients were extubated in the non-invasive arm, more were at risk of re-intubation. One of the major concerns about re-intubation is the association with increased mortality seen in some observational studies.[29,30] The survival rates in the present study were not significantly different in non-invasive and invasive weaning groups although these findings should be interpreted with caution as the study was not powered to show a difference in this outcome and was not designed to assess equivalence.

The design of this study afforded several advantages to previous studies. First, a protocolized weaning regimen in both groups allowed clear separation of the intervention from the effect of protocolizasion.[31] Best practice guidelines (ventilation bundle, daily spontaneous breathing trials, tracheostomy insertion) reduced heterogeneity between treatment groups. Second, antibiotic use was selected as a surrogate for ventilator associated pneumonia to limit the risk of detection bias arising from different approaches to obtaining respiratory samples for culture; this outcome is arguably more relevant than ventilator associated pneumonia diagnosis as it better reflects antibiotic stewardship and exposure.

Limitations

The study has several limitations. First, the nature of the intervention prevented blinding of clinicians, patients, or outcome assessors. This may have led to performance and/or detection bias. Second, the non-invasive weaning protocol mandated sequential reductions in respiratory support (either a decrease in inspiratory pressure support or a break from non-

invasive ventilation) as tolerated over a minimum of a 12 hour period. It is possible that this may have extended the period of ventilatory support for some patients. Third, in the invasive ventilation group, the protocol required once daily spontaneous breathing trials. It is possible that more frequent spontaneous breathing trials may have led to earlier recognition of readiness for extubation in some patients. Fourth, the patients enrolled were a heterogenous group of patients with differing relative contributions of respiratory, cardiac, neuromuscular, metabolic, pharmacological and neuro-psychological impairment. Whether a more physiologically based assessment process could identify a group more likely to benefit from non-invasive ventilation remains to be determined in future studies. Fifth, 44% of the patients were recruited from three centres, which could limit generalizability. It is possible that performance and outcomes may have improved as centres became more experienced in the use of the non-invasive weaning intervention.

Conclusion

Among patients requiring mechanical ventilation, protocolized weaning with early extubation to non-invasive ventilation compared with invasive weaning did not significantly shorten time to liberation from all forms of mechanical ventilation. ISRCTN 15635197.

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Access to Data and Data Analysis

Dr Ranjit Lall and Dr Dipesh Mistry had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Figure legends

Figure 1: Recruitment, randomization and patient flow through the study

Figure 2: Kaplan-Meier curve of the time to liberation from ventilation by treatment group

Hash marks are displayed on the curves at each censoring time. Median time to liberation from ventilation was 4.5 days (95% CI 3.46, 7.25) in the invasive arm and was 4.3 days (95% CI 2.63, 5.58) in the non-invasive arm. Log-rank test p-value=0.35.

Figure 3: Cumulative incidence of liberation summarised by treatment arm

551 **Table 1: Baseline characteristics**

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Characteristic	**Invasive weaning (n=182)**	**Non-invasive weaning (n=182)**
Age (years), mean(sd)	61.8 (15.8)	64.3 (13.6)
Gender (male), n(%)	94 (51.6%)	90 (49.5%)
Evidence of delirium† (CAM-ICU positive), n(%)	17 (9.3%)	23 (12.6%)
Body mass index, mean(sd)	27.7 (6.6)	28.2 (6.9)
Duration of ventilation prior to randomization (days), median(IQR)	4.7 (3.0, 7.4)	5.3 (3.3, 8.1)
Antibiotics for respiratory infection, n(%)	100 (55%)	98 (54%)
APACHE II score*, mean (sd)	18.8 (6.2)	18.9 (6.6)
Admission diagnosis, n(%)		
Pneumonia / Respiratory infection	73 (40.1%)	57 (31.3%)
Post-surgery respiratory failure	39 (21.4%)	39 (21.4%)
Cardiac	18 (9.9%)	27 (14.8%)
Non respiratory infection	21 (11.5%)	16 (8.8%)
Neuromuscular	8 (4.4%)	7 (3.9%)
COPD / Asthma Exacerbation	7 (3.9%)	7 (3.9%)
Traumatic injuries	5 (2.8%)	3 (1.6%)
GI Bleed	3 (1.7%)	7 (3.9%)
Pancreatitis	1 (0.5%)	4 (2.2%)
Stroke	1 (0.5%)	0
Other††	6 (3.2%)	15 (8.2%)
Ventilation parameters prior to spontaneous breathing trial		
Exhaled Minute Volume (L min^{-1}), median(IQR)	10.5 (8.2, 13.1)	10.2 (8.4, 12.6)
Total Respiratory Rate (Breaths min^{-1}),	21 (17, 27)	21 (16, 27)

median(IQR)		
PEEP (cmH_2O), median(IQR)	5 (5, 8)	5 (5, 8)
Pressure support cm H_2O), median(IQR)	11 (8, 15)	11 (9, 15)
PF Ratio** (mmHg), median(IQR)	242.2 (200.6, 315)	227.5 (196.9, 280.7)
Spontaneous tidal volume (ml kg^{-1}), median(IQR)	8.2 (6.5, 9.8)	7.9 (6.4, 9.5)
Arterial blood gas reading prior to spontaneous breathing trial		
$PaCO_2$*** (mmHg), mean(sd)[N]	42.8 (10.2)[181]	42.6 (8.9)[180]
pH, mean(sd)[N]	7.4 (0.06)[182]	7.4 (0.06)[181]
Hemoglobin (g dL^{-1}), mean(sd)[N]	9.7 (1.7)[182]	9.6 (1.6)[181]

† CAM-ICU is the confusion assessment method for screening for evidence of delirium in intensive care (http://www.icudelirium.org) * APACHE II score ranges from 0-71 where higher scores correspond to more severe disease and higher risk of death. An APACHE II score of 10-19 is associated with a 25% risks of in-hospital mortality. †† Other included pulmonary haemorrhage (n=1), bowel obstruction (n=2), acute renal failure (n=2), metabolic disturbance (n=2), liver failure (n=4), overdose (n=2), respiratory failure of unknown cause (n=5), vasculitis (n=1), burns (n=2). ** The P:F ratio is the partial pressure of oxygen in arterial blood (mm Hg) divided by the FiO_2. *** $PaCO_2$ is the arterial pressure of carbon dioxide in arterial blood.

Table 2: Adverse events

	Invasive weaning n (%)	**Non-invasive weaning** n (%)	**Unadjusted absolute difference (%) (95% CI)**
Antibiotics for presumed respiratory infection	128/182(70.3)	110/182(60.4)	9.9 (0.2, 19.6)
Re-intubation	41/143 (28.7)	67/181 (37.0)	8.3 (-1.9, 18.6)
Tracheostomy	55/182 (30.2)	43/182(23.6)	6.6 (-2.5, 15.7)
Death before ICU discharge	25/182 (13.7)	22/182 (12.1)	1.6 (-5.2, 8.5)
Adverse events	n=182	n=182	
Dysrhythmias	22 (12.1)	14 (7.7)	4.4 (-1.7, 10.5)
Nasal/skin/mouth sores/irritation	14 (7.7)	19 (10.4)	2.7 (-3.2, 8.6)
Non-respiratory infection	12 (6.6)	11 (6.0)	0.5 (-4.5, 5.6)
Vomiting	8 (4.4)	14 (7.7)	3.3 (-1.6, 8.2)
Gastric distension	6 (3.3)	7 (3.9)	0.5 (-3.3, 4.4)
Barotrauma (e.g. pneumothorax)	3 (1.7)	3 (1.7)	0 (-2.6, 2.6)

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Non-author contributions to design and conduct of the trial and to data collection

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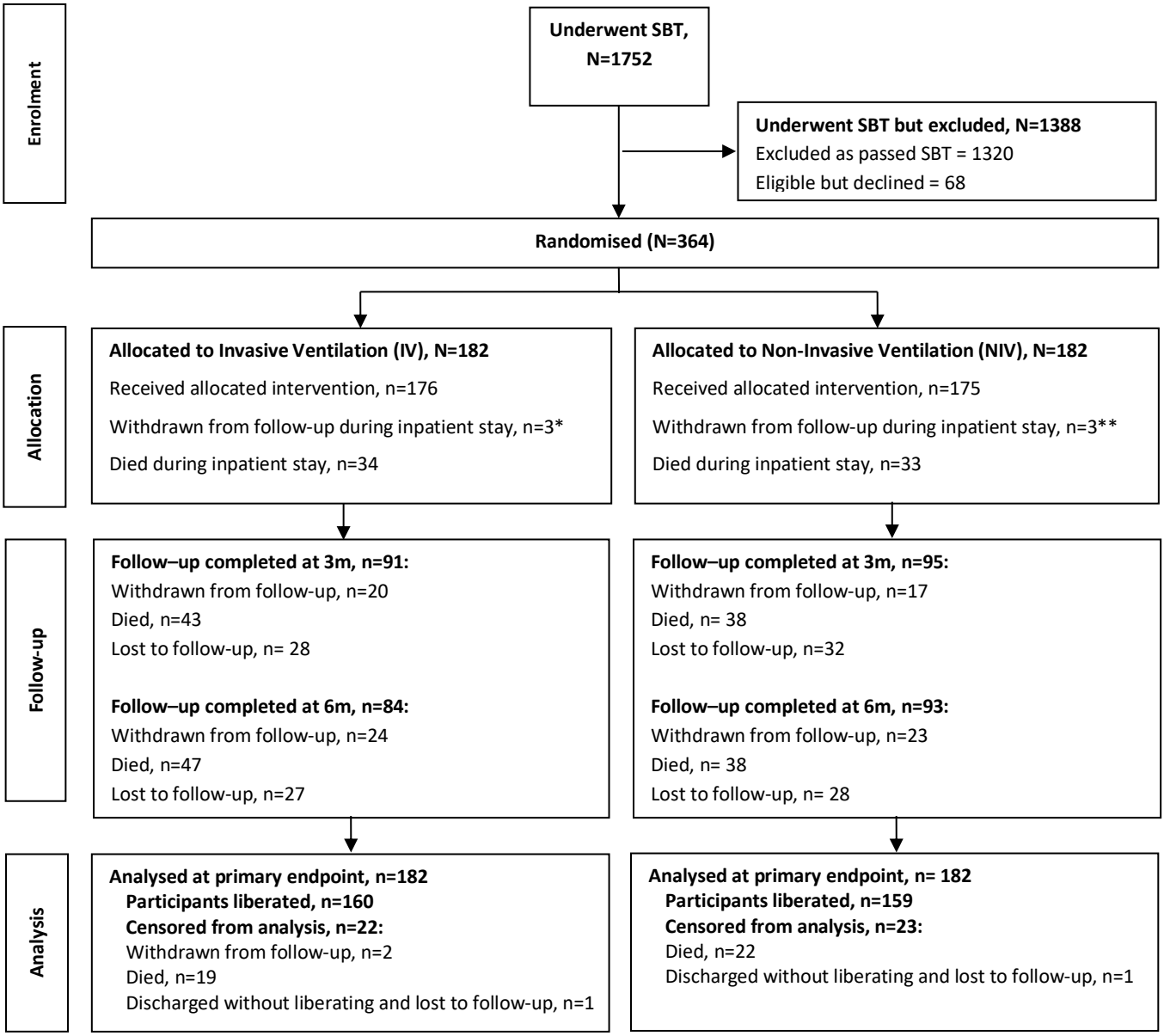
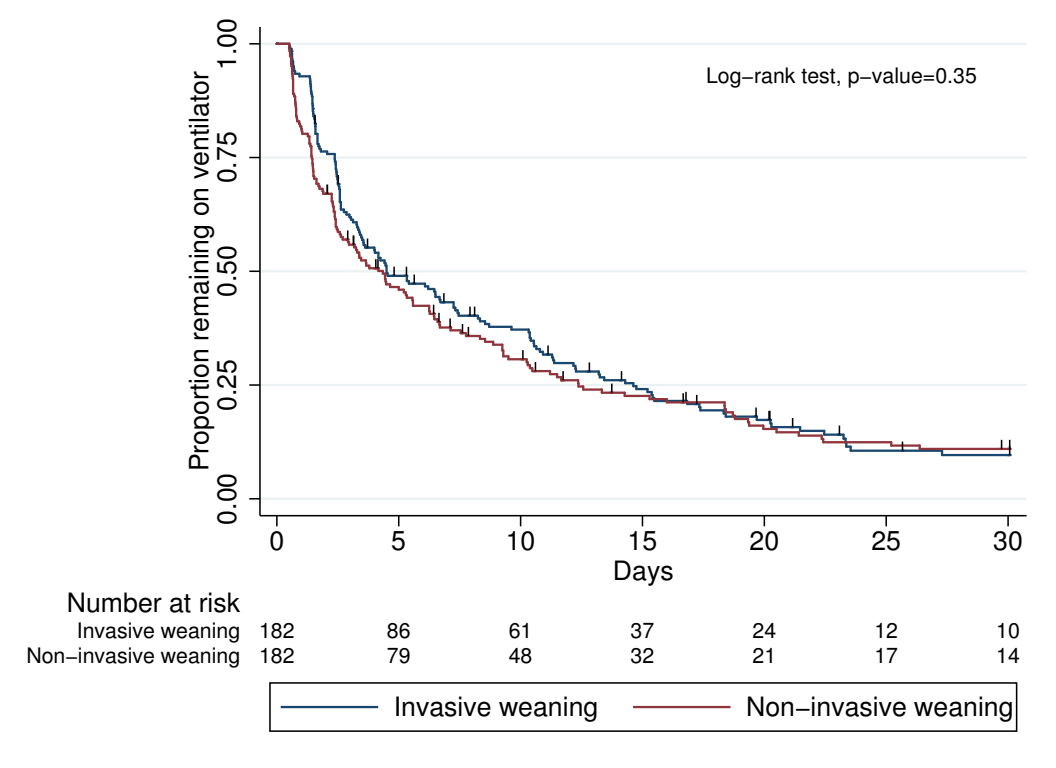
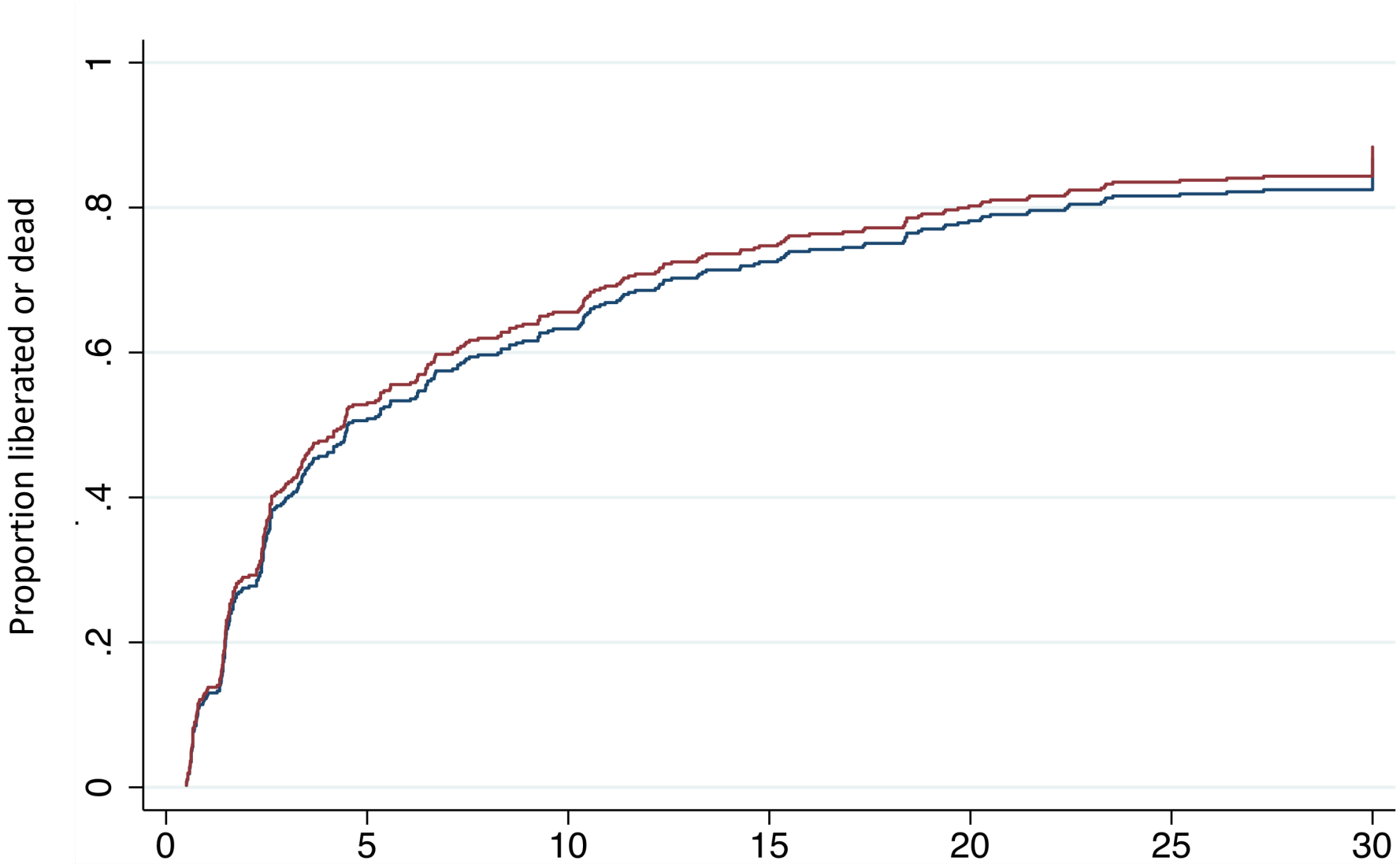


* One participant refused participation when approached for retrospective consent. The other two were withdrawn as their personal consultee/next of kin were not happy with them being in the study

** One participant didn't provide a reason for withdrawal. The other two didn't want to continue in the study as they felt it will require too much or they weren't the right person for the study.


Log−rank test, p−value=0.35
Proportion remaining on ventilator
0.00
0.25
0.50
0.75
1.00
0
5
10
15
20
25
30
Days
Number at risk
Invasive weaning 182 86 61 37 24 12 10
Non−invasive weaning 182 79 48 32 21 17 14
Invasive weaning
Non−invasive weaning



Number at risk

Invasive weaning	182	86	61	37	24	12	10
Non-invasive weaning	182	79	48	32	21	17	14