

When Should a Mechanically Ventilated Patient Undergo Tracheostomy?

Derek C. Angus, MD, MPH

EACH YEAR, APPROXIMATELY 800 000 US RESIDENTS UNDERGO mechanical ventilation for acute respiratory insufficiency, often for a period of days or weeks.¹ Although mechanical ventilation can be lifesaving, it is unnatural and invasive, can be extremely uncomfortable, and requires expensive intensive care support. Endotracheal intubation is the most efficient and convenient method by which to initiate mechanical ventilation. However, intubation is often not well tolerated by an awake patient; is prone to potentially disastrous dislodgement; and interferes with oral care, feeding, and communication.

Consequently, if mechanical ventilation is likely to be prolonged, physicians often consider converting the patient to ventilation via a tracheostomy, a surgical procedure to access the lower respiratory tract directly from the lower neck. With tracheostomy, the head and face are freed of encumbrances and oral care is considerably easier. The tracheostomy site matures quickly over a few days, at which point unintentional dislodgement is of less consequence. With a tracheostomy, it can also be possible for the patient to talk and to swallow food and liquids. Furthermore, the tube can be easily, safely, and repeatedly removed and replaced via the tracheostomy, which permits trials of unassisted breathing. Unassisted breathing trials are key components to effective and faster weaning from mechanical ventilation. However, tracheostomy is not without complications and requires a set of procedural skills and adequate care and maintenance.

Thus, the most appropriate way to mechanically ventilate a patient appears to be via endotracheal intubation initially, with conversion to tracheostomy when necessary. However, the challenge is knowing “when” a tracheostomy is necessary, a problem that requires a 2-part solution: prediction of which patients will require prolonged ventilation and a decision about when the tracheostomy should be performed. If prediction is imperfect, then a strategy of early tracheostomy will lead to some patients undergoing a tracheostomy unnecessarily, whereas a strategy of late tracheostomy will result in others facing unnecessarily pro-

longed exposure to an endotracheal tube and a potentially difficult or prolonged weaning from the ventilator.

For many years, the only evidence to guide this decision came from observational studies and small, single-center randomized trials. In general, this evidence supported the concept that early tracheostomy was beneficial. At the same time, external factors likely had an important influence on patterns of care. First, long-term acute care facilities, which have increased considerably in recent years, can assume the care of a patient who is mechanically ventilated but typically only after a tracheostomy. Second, due to development of a simple percutaneous technique, tracheostomy is now commonly performed at the bedside. Both of these factors drive more and earlier use of tracheostomy.

To date, no large, randomized trial of tracheostomy timing has been completed in the United States. In 2010, Terragni et al² reported the results of an **Italian** study, which was the first large multicenter randomized trial of early vs late tracheostomy. Conducted in 12 intensive care units, the trial enrolled 600 patients who had undergone 24 hours of ventilation. The 600 patients were followed up for another 48 hours and the 419 patients (70%) who were deemed eligible for a potential tracheostomy were randomized to early or late tracheostomy. **Early** was defined as **6 to 8** days after initiation of ventilation and **late** was defined as **13 to 15** days after initiation.

In the early group, 145 patients (69%) underwent tracheostomy, and 119 patients (57%) underwent tracheostomy in the late group. The primary end point of ventilator-associated **pneumonia** was **not different** between the 2 groups, although the effect on secondary end points was somewhat mixed. Importantly, **adverse events** associated with the **tracheostomy** were reported in **39%** of patients, although most were minor. In an accompanying editorial, Scales and Ferguson³ highlighted the difficulty clinicians had in predicting who needed a tracheostomy, given that **nearly half** of the **late** treatment group **never required a tracheostomy** and therefore **favor**ed the **late wait-and-see strategy**.

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See also p 2121.

In this issue of *JAMA*, Young et al⁴ report the results of a considerably larger trial examining early vs late tracheostomy. This trial was conducted at 72 centers in the United Kingdom and randomized 909 patients who had been mechanically ventilated for less than 5 days and were expected to require at least one more week of ventilation. In contrast to the Italian study, patients randomized to the early group were scheduled immediately for tracheostomy. According to the authors, the rationale for such an early intervention was that existing data from the United Kingdom showed more than one-fifth of all tracheostomies were performed within 5 days, and more than 10% within 2 days of ventilation. The late group, similar to the Italian study, was scheduled for a tracheostomy after 10 days of ventilation.

Ninety-two percent of patients in the early group received a tracheostomy, but only 45% of patients in the late group underwent tracheostomy. There were no differences in the primary end point of 30-day all cause mortality, nor in any other clinical outcome, including 2-year mortality. Approximately 7% of patients had significant bleeding complications from the tracheostomy. Even though this is the largest study to date, the study had in fact been designed to enroll 1208 patients, and the study protocol was revised to enroll more than 1600 patients, based on expected effects on mortality. The study was stopped early due in part, according to the authors, to “study fatigue,” but additional recruitment seems highly unlikely to have changed the result.

Thus, 2 large, multicenter European trials show very similar findings: a strategy to perform tracheostomy early (within the first week) offers no benefit over a wait-and-see strategy that delays tracheostomy until after 10 days of mechanical ventilation. However, the consistently poor ability of clinicians to predict in the first few days which patients would eventually require prolonged ventilation means the early strategy inadvertently leads to a large increase in the number of unnecessary tracheostomies.

In retrospect, it is not surprising that clinicians are unable to identify accurately which patients require prolonged ventilation. A cornerstone of ventilator weaning is the need to perform a daily spontaneous breathing trial.⁵ The reason the breathing trial must be conducted every day is that prior performance is poorly predictive of success. In other words, even proximate predictions are extremely difficult, let alone judging ventilator dependency days or weeks in advance. Therefore, until development of a robust tool to predict prolonged need of ventilation, tracheostomy generally should be delayed until at least 10 days after initiating mechanical ventilation.

This finding has potentially important implications for current reimbursement rules in the United States. For instance, Medicare and many commercial insurers currently provide high reimbursement to hospitals for patients who undergo tracheostomy. A patient who undergoes 96 hours of mechanical ventilation can be recoded to diagnosis related groups (DRGs) 003 or 004 if a tracheostomy is performed. These are 2 of the most highly reimbursed DRGs.⁶ Current practice in the United States is highly variable, and it is not the case that all patients routinely undergo tracheostomy at 96 hours. Nevertheless, if clinicians were to uniformly adopt a wait-and-see strategy, the number of tracheostomies would decline. Given the significant difference in DRG payments for patients who are mechanically ventilated with and without a tracheostomy, hospital reimbursement also would decline. How hospital profitability would be affected by such a significant change in practice is unclear. It is, however, important to consider the possibility that hospital financial incentives may be at odds with the evidence about the limited benefits of early tracheostomy.

In coming years, payment reforms that bundle hospital, physician, and postacute care for inpatient episodes may make this quandary less important. However, as long as hospitals are reimbursed using a DRG system, it would seem prudent to revise the reimbursement strategies for patients facing potentially prolonged mechanical ventilation to better align financial incentives with the best clinical evidence.

Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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Effect of Early vs Late Tracheostomy Placement on Survival in Patients Receiving Mechanical Ventilation

The TracMan Randomized Trial

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A TRACHEOSTOMY IS COMMONLY performed when clinicians predict a patient will need prolonged mechanical ventilation. The use of this procedure has increased, especially following the introduction of a practical bedside percutaneous tracheostomy technique in 1985,¹ such that up to one-third of patients requiring prolonged mechanical ventilation now receive a tracheostomy.^{2,3} The perceived advantages of a tracheostomy over prolonged translaryngeal endotracheal intubation include improved patient comfort and reduced sedative drug use, faster weaning from mechanical ventilation, a reduced incidence of nosocomial pneumonia, and shorter hospitalization.⁴ These beneficial effects might be maximized if tracheostomies were performed early in a patient's illness.

The United Kingdom has a very limited intensive care provision, with about one-seventh of the intensive care beds per 10 000 population provided in the United States and a third of those provided in France.⁵ As a result, patients treated in UK intensive care units (ICUs) tend to be more severely ill, with

For editorial comment see p 2163.

Importance Tracheostomy is a widely used intervention in adult critical care units. There is little evidence to guide clinicians regarding the optimal timing for this procedure.

Objective To test whether early vs late tracheostomy would be associated with lower mortality in adult patients requiring mechanical ventilation in critical care units.

Design and Setting An open multicentered randomized clinical trial conducted between 2004 and 2011 involving 70 adult general and 2 cardiothoracic critical care units in 13 university and 59 nonuniversity hospitals in the United Kingdom.

Participants Of 1032 eligible patients, 909 adult patients breathing with the aid of mechanical ventilation for less than 4 days and identified by the treating physician as likely to require at least 7 more days of mechanical ventilation.

Interventions Patients were randomized 1:1 to early tracheostomy (within 4 days) or late tracheostomy (after 10 days if still indicated).

Main Outcomes and Measures The primary outcome measure was 30-day mortality and the analysis was by intention to treat.

Results Of the 455 patients assigned to early tracheostomy, 91.9% (95% CI, 89.0%-94.1%) received a tracheostomy and of 454 assigned to late tracheostomy, 44.9% (95% CI, 40.4%-49.5%) received a tracheostomy. All-cause mortality 30 days after randomization was 30.8% (95% CI, 26.7%-35.2%) in the early and 31.5% (95% CI, 27.3%-35.9%) in the late group (absolute risk reduction for early vs late, 0.7%; 95% CI, -5.4% to 6.7%). Two-year mortality was 51.0% (95% CI, 46.4%-55.6%) in the early and 53.7% (95% CI, 49.1%-58.3%) in the late group ($P = .74$). Median critical care unit length of stay in survivors was 13.0 days in the early and 13.1 days in the late group ($P = .74$). Tracheostomy-related complications were reported for 6.3% (95% CI, 4.6%-8.5%) of patients (5.5% in the early group, 7.8% in the late group).

Conclusions and Relevance For patients breathing with the aid of mechanical ventilation treated in adult critical care units in the United Kingdom, tracheostomy within 4 days of critical care admission was not associated with an improvement in 30-day mortality or other important secondary outcomes. The ability of clinicians to predict which patients required extended ventilatory support was limited.

Trial Registration isrctn.org Identifier: ISRCTN28588190

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more than two-thirds mechanically ventilated on admission compared with less than one-fifth of other countries such as the United States.⁶ The low provision of, and hence increased pressure on, intensive care beds in the United

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Kingdom means that techniques that may reduce the duration of mechanical ventilation, ICU stay, or both generate considerable interest. This low-intensive care bed provision and increased severity of illness on admission to intensive care means that interventions such as tracheostomy are often considered early in a patient's ICU stay.

A clinical research priority-setting exercise among the 2200 members of the UK Intensive Care Society in 2004 gave the highest priority to studies investigating the timing of tracheostomy in patients mechanically ventilated. A subsequent systematic review of the literature and meta-analysis⁷ suggested that early tracheostomy placement reduced the duration of mechanical ventilation and hospital stay. In the largest of the reviewed studies,⁸ a considerable reduction in hospital mortality was also identified.

There are probably large numbers of tracheostomies being performed on patients mechanically ventilated each year. Based on a prestudy survey of 37 of the 252 ICUs in the United Kingdom, we estimated there were up to 15 000 tracheostomies annually. Audit data from Scottish ICUs⁹ and a systematic review of all the published case series of tracheostomy use revealed that the median time to insertion of a tracheostomy was 10 to 11 days after the start of admission to a critical care unit, but up to 13% of tracheostomies were placed within 2 days of admission. Another survey reflecting UK practice in 2005¹⁰ suggested that half of all tracheostomies were placed within a week of critical care admission, and a subsequent survey suggested 21% of tracheostomies were placed within 5 days of admission.¹¹

With the suggestion from the meta-analysis that early tracheostomy might reduce the duration of mechanical ventilation, data from a single-center study suggesting that early tracheostomy might confer a survival advantage, and evidence that early tracheostomy placement was already occurring, the TracMan (Tracheostomy Manage-

ment) study was commenced. The hypothesis tested was that tracheostomy as early as practicable (early) vs deferred placement until after 10 days and then only if required (late) would be associated with a lower mortality in adult patients requiring mechanical ventilation in critical care units.

METHODS

Patients

TracMan enrolled mechanically ventilated patients in adult critical care units, who were identified by the treating clinician in the first 4 days after admission as likely to require at least 7 more days of ventilatory support. We excluded patients requiring an immediate, life-saving tracheostomy; those in whom a tracheostomy was contraindicated for anatomical or other reasons; and those with respiratory failure due to chronic neurological disease because our study centers indicated these patients usually receive early tracheostomies.

Written, informed consent or signed agreement from the patients' legal representative/welfare guardian was obtained. The study was approved by a multicenter research ethics committee and each hospital's local research ethics committee.

Randomization and Blinding

Randomization was conducted using an automated 24-hour telephone service using an algorithm that minimized the imbalance between groups of the study by allocating each patient, with 80% probability, to the group which minimized the imbalance in the following covariates: center, age, sex, and 7 major diagnostic groups (intracranial pathology, altered consciousness due to drug or metabolic causes, acute peripheral nerve or muscle disorder, pulmonary pathology, burns, heart failure, and other).¹² Treatment assignment could not be blinded to the caring team nor to the analysis team because it was apparent from the data to which group a patient had been assigned. Patients were randomly assigned in a 1:1 ratio, either to early tracheostomy or to late tracheostomy (FIGURE 1).

Procedures

As a condition of participation, all senior physicians in participating units agreed to include all eligible patients and to abide by randomization to reduce both inclusion bias and cross-overs between the groups. All participating units maintained a screening log of eligible patients not enrolled.

By protocol the early tracheostomies were to be placed within 4 days of critical care unit admission and the late tracheostomies were to be placed on day 10 or later and then only if the treating clinician deemed the procedure still clinically indicated. Tracheostomies were performed according to each critical care unit's local practice (percutaneous or surgical tracheostomy). All other care was at the discretion of the treating clinicians.

Data

During the first 24 hours in the critical care unit, clinicians recorded data for the acute physiology, age, and chronic health evaluation II (APACHE II) severity scoring system.¹³ In both groups of the study, details of the tracheostomy procedure were collected including timing, location, type (percutaneous or open surgical), immediate complications, and the seniority of the individual performing the procedure. From randomization, daily information on respiratory support was recorded using the Critical Care Minimum Data Set definitions of organ failure used routinely in all UK critical care units. Antimicrobial and sedative drug use was recorded for the duration of care on the critical care unit. Patients' vital status was determined for 2 years following randomization from the UK Office for National Statistics (ONS) and the NHS Strategic Tracing Service (NHSSTC), both of which hold registers of all deaths in the United Kingdom.

The primary outcome measure was all-cause mortality 30 days from randomization. Secondary outcome measures were mortality at critical unit and hospital discharge and at 1 and 2 years, length of stay in the critical care unit

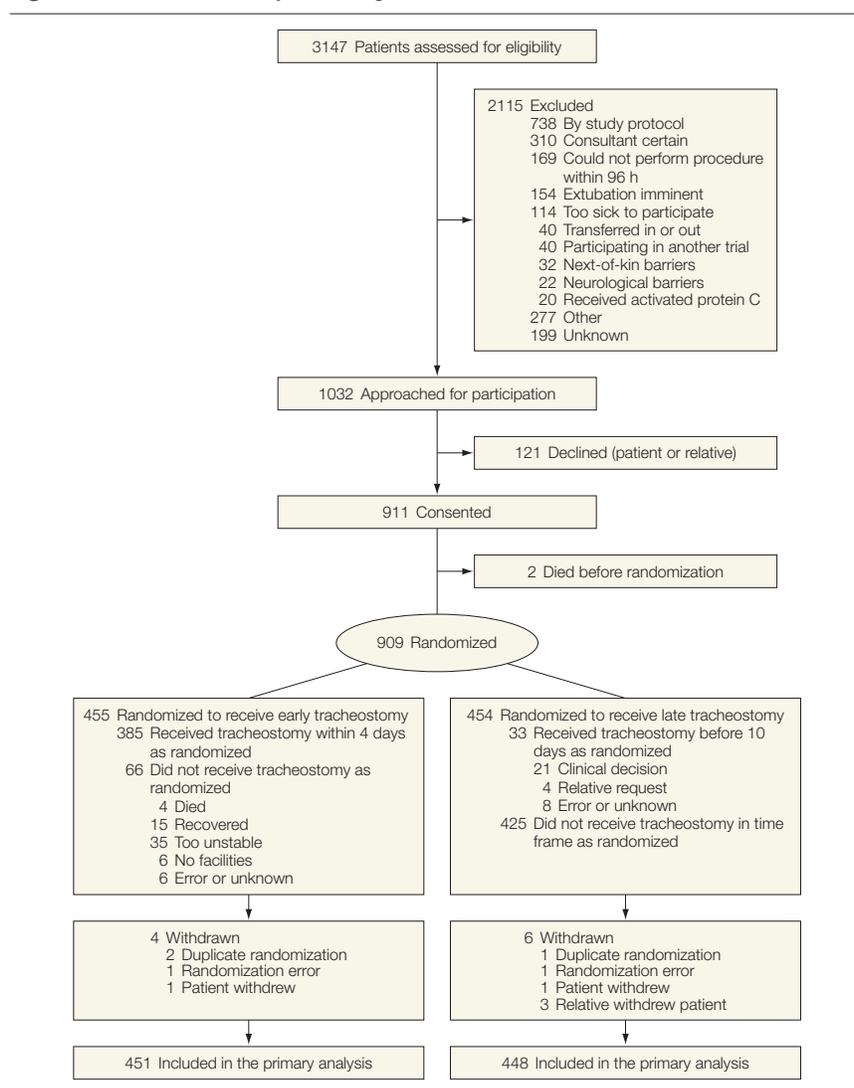
and in an acute hospital, days in critical care up to 30 days from randomization when intravenous sedatives were administered, and antimicrobial-free days in critical care up to 30 days from randomization (as a proxy for hospital acquired infections).

Statistical Analysis

The critical care unit mortality of patients receiving a tracheostomy in 35 UK critical care units was obtained by survey to estimate the sample size. The original planned sample size was for 1208 patients to give 80% power to detect a 7.5% absolute reduction (based on our original effect-size estimate from a meta-analysis of studies of early tracheostomy) in critical care unit mortality (surrogate for 30-day mortality) from 30% to 22.5%, based on a 5% level of significance and to allow for a 4% combined withdrawal and loss to follow-up. The planned sample size was subsequently increased to 1692 patients to detect a 6.3% absolute (21% relative) reduction in mortality based on a more accurate estimate of the likely effect size published in a systematic review⁷ when the UK Medical Research Council funded the second phase of the study in 2006, with other assumptions as above. However, due to study fatigue indicated by a decreasing average per center recruitment rate in spite of considerable help and encouragement and exhaustion of funding, the planned sample size was not achieved. The final sample of 899 patients available for analysis of the primary outcome had the power to detect an 8.3% absolute change in 30-day mortality from the "late" group value of 31.5% with 80% power and a 5% level of significance.

All the main analyses were by intention-to-treat and followed an a priori statistical analysis plan. The number of deaths in each group was compared with the Fisher exact test and survival times with Kaplan-Meier curves and a log-rank test. Length of stay and duration of therapy were compared with the Wilcoxon rank sum test, stratified by survival status.

Figure 1. The TracMan Study Flow Diagram



An independent Data Monitoring and Ethics Committee designed the monitoring schedule and reviewed unblinded data from 4 interim analyses using a Peto-Haybittle¹⁴⁻¹⁶ stopping rule (the study would continue unless the primary outcome was different between the groups at $P < .001$ at interim analysis) to recommend early termination of the study due to either benefit or harm. Statistical significance for the final analysis was therefore based on $P < .049$. The committee did not specify a futility boundary. All statistical comparisons were 2 sided. SPSS version 20 (IBM Corp) and Stata

version 10 (StataCorp) were used for statistical analysis.

The full protocol for the study can be found at <http://www.tracman.org.uk>.

RESULTS

Between November 2004 and November 2008, 70 adult, general critical care units and 2 cardiothoracic surgical critical care units (from 13 university and 59 nonuniversity hospitals) recruited patients. Final 2-year follow-up was completed in January 2011. In all, 909 patients were randomly assigned (Figure 1). Of these, 455 were allo-

cated to early and 454 were allocated to the late tracheostomy group. Excluding duplicate randomization and withdrawals (despite measures in place to minimize both of these), 451 (99.1%) patients in the early and 448 (98.7%) in the late groups were available for the primary analysis. TABLE 1 shows the baseline characteristics, which were similar between the groups.

Of those randomized to the early tracheostomy group, the procedure was performed within 4 days of admission to the critical care unit for 385 patients (84.6%; 95% CI, 81.0%-87.7%). Despite meeting study eligibility crite-

ria at randomization, 66 patients (14.5%) did not receive an early tracheostomy (95% CI, 11.6%-18.1%), 31 of whom (6.8) never received a tracheostomy (95% CI, 4.8%-9.5%) and 35 patients (7.7%) received it late (95% CI, 5.6-10.5). Of those who did not receive a tracheostomy, 4 (0.9%) died (95% CI, 0.3%-2.3%), 11 (2.4%) recovered and did not need one (95% CI, 1.3%-4.3%), and 16 (3.5%) remained too unstable for the procedure (95% CI, 2.1%-5.7%). Of those who received a tracheostomy after the time allowed by the protocol, 19 (4.2%) were too unstable during the time window (95% CI,

2.6% to 6.5%), 6 (1.3%) had unavailable facilities or operators (95% CI, 0.5%-2.9%), 4 (0.9%) initially improved (95% CI, 0.3%-2.3%), 2 (0.4%) were because of investigator errors (95% CI, 0.0%-1.7%) investigator errors, and 4 (0.9%) were for unknown reasons (95% CI, 0.3-2.3). The details of the tracheostomies performed are in TABLE 2. The distributions of the tracheostomy timing for both groups of the study are shown in FIGURE 2.

Of the 454 randomized to late tracheostomy, the procedure was conducted as per protocol either on or after day 10 or never, as no longer clinically indicated for 425 patients (93.6%); (95% CI, 91.0%-95.6%). Of the 244 patients (53.7%) for whom tracheostomy was never performed (95% CI, 49.2%-58.3%), 89 (19.6%) had been discharged alive from the critical care unit by day 10 (95% CI, 16.2%-23.5), 78 (17.2%) remained in the critical care unit but no longer required ventilatory support (95% CI, 14.0%-20.9%), 54 (11.9%) died (95% CI, 9.2%-15.2%), 11 (2.4%) remained too unstable (95% CI, 1.3%-4.3%), 2 (0.4%) had treatment withdrawn (95% CI, 0.0-1.7), and 10 (2.2%) had no recorded reason (95% CI, 1.2%-4.1%).

Tracheostomy was performed for 33 patients (7.3%) in the late group before day 10 (95% CI, 5.2%-10.1%): 21 (4.6%) received tracheostomy because of clinical decision (95% CI, 3.0-7.0), 4 (0.9%) because their relatives insisted on the procedure (95% CI, 0.3%-2.3%), and 4 (0.9%) because of investigator error (95% CI, 0.3%-2.3%), and for 4 patients (0.9%) the reason was not recorded (95% CI, 0.3%-2.3%).

For the 622 patients receiving tracheostomies, procedure-related complications were reported for a total of 39 patients (6.3%; 95% CI, 4.6%-8.5%): twenty-three (5.5%) of 418 patients in the early group (95% CI, 3.7%-8.2%) and 16 (7.8%) of 204 patients in the late group (95% CI, 4.8%-12.4%). The most frequent complication was bleeding sufficient to require intravenous fluids or another intervention, which occurred in 19 (3.1%) of the 622 patients (95%

Table 1. Baseline Characteristics of Patients

| Treatment Group | No. (%) of Patients | | |
|--|---------------------|----------------|-----------------|
| | Early (n = 451) | Late (n = 448) | Total (n = 899) |
| Men | 263 (58.3) | 264 (58.9) | 527 (58.6) |
| Age, mean (SD), y ^a | 63.6 (13.7) | 64.2 (13.3) | 63.9 (13.5) |
| Major clinical syndrome ^a | | | |
| Intracranial pathology | 18 (4.0) | 17 (3.8) | 35 (3.9) |
| Altered consciousness level due to drug or metabolic causes | 17 (3.8) | 19 (4.2) | 36 (4.0) |
| Peripheral nervous system or muscular disorder or weakness | 7 (1.6) | 6 (1.3) | 13 (1.4) |
| Pulmonary pathology ^d | 311 (69.0) | 312 (69.6) | 623 (69.3) |
| Burns | 0 (0.0) | 1 (0.2) | 1 (0.1) |
| Decompensated (congestive) heart failure | 8 (1.8) | 6 (1.3) | 14 (1.6) |
| Other | 90 (20.0) | 87 (19.4) | 177 (19.7) |
| APACHE II score, mean (SD) ^b | 19.6 (6.5) | 20.1 (6.0) | 19.8 (6.3) |
| Admission type | | | |
| Medical | 359 (79.6) | 353 (78.8) | 712 (79.2) |
| Surgical | 92 (20.4) | 95 (21.2) | 187 (20.8) |
| Emergency | 36 (39.1) | 40 (42.1) | 76 (40.6) |
| Urgent | 32 (34.8) | 32 (33.7) | 64 (34.2) |
| Scheduled | 8 (8.7) | 8 (8.4) | 16 (8.6) |
| Elective | 16 (17.4) | 15 (15.8) | 31 (16.6) |
| Body system involved in the primary reason for admission to the ICU ^c | | | |
| Respiratory ^d | 260 (59.9) | 255 (59.0) | 515 (59.5) |
| Cardiovascular | 46 (10.6) | 57 (13.2) | 103 (11.9) |
| Gastrointestinal | 83 (19.1) | 84 (19.4) | 167 (19.3) |
| Neurological | 25 (5.8) | 19 (4.4) | 44 (5.1) |
| Genitourinary | 8 (1.8) | 4 (0.9) | 12 (1.4) |
| Endocrine, metabolic, thermoregulation, or poisoning | 7 (1.6) | 2 (0.5) | 9 (1.0) |
| Hematological/immunological | 1 (0.2) | 5 (1.2) | 6 (0.7) |
| Musculoskeletal | 4 (0.9) | 3 (0.7) | 7 (0.8) |
| Dermatological | 0 (0.0) | 3 (0.7) | 3 (0.3) |

Abbreviations: APACHE, acute physiology and chronic health evaluation; ICU, intensive care unit.

^aIncluded in minimization algorithm.

^bAPACHE II is a severity of illness scale ranging from 0 to 71 with higher values indicating more severe illness. Physiology data was not available for 38 patients (20 early, 18 late).

^cPrimary reason for admission not recorded for 33 patients (17 early, 16 late).

^dThe primary reason for admission may not have necessarily been the same as the reason the tracheostomy was performed (for example the primary reason for admission may have been pancreatitis but the patient was considered for the study because of secondary respiratory failure), so the pulmonary pathology and respiratory body system values do not match.

CI, 1.9%-4.8%): 11 patients (2.6%) in the early group (95% CI, 1.4%-4.7%) and 8 (3.9%) in the late group (95% CI, 1.9%-7.7%).

The patients received a mean (SD) of 13.6 (12.0) total days of respiratory support (positive pressure ventilation or continuous positive airway pressure [CPAP] for any period in a day) in the early group and 15.2 (14.4) days in the late group (mean difference, -1.7 days, 95% CI, -3.4 to 0.1 days; *P* = .06). Patients received respiratory support through a tracheostomy in the early group for a mean (SD) of 12.9 (11.8) days (417 patients) and 16.1 (14.7) days (200 patients) in the late group.

The primary outcome, all-cause mortality 30 days from randomization, was not statistically different in the 2 groups—early 139 patients (30.8%) in the early group (95% CI, 26.7%-35.2%) and 141 patients (31.5%) in the late group (95% CI, 27.3%-35.9%; TABLE 3). Unit, acute hospital, 1- and 2-year survival also showed no statistically significant differences (Table 3, FIGURE 3). Overall, mortality was high with 47.4% (95% CI, 44.2%-50.7%) of all patients dying within a year and 52.3% (95% CI, 49.1%-55.6%) within 2 years; the cause of death was not recorded.

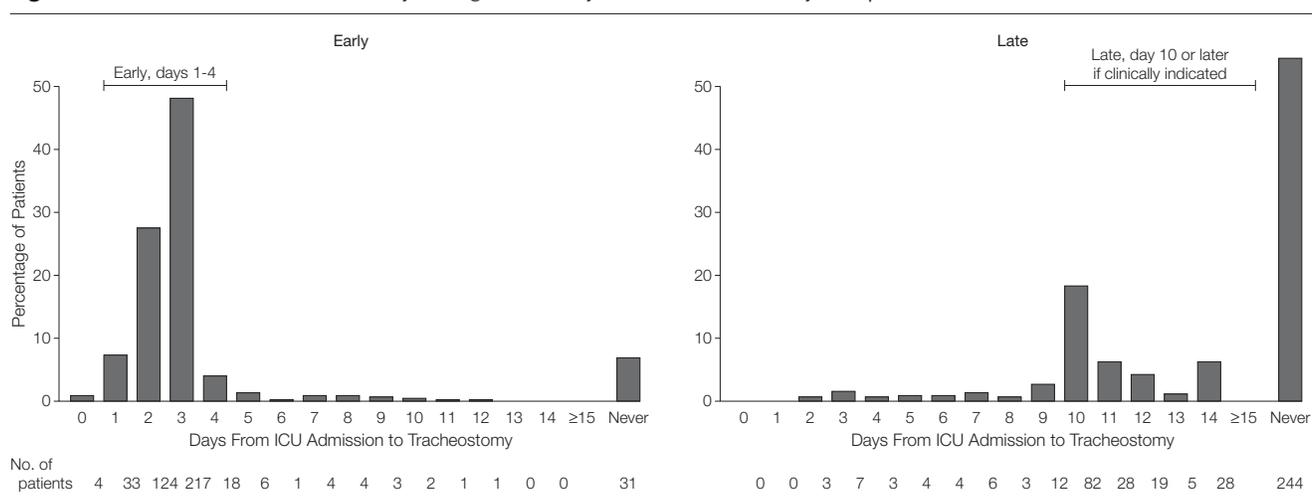
For the 315 survivors of critical care in the early group and 312 in the late group, the median duration of critical

Table 2. Details of the Tracheostomies Performed

| Treatment Group | No. (%) of Patients | | |
|--|------------------------------|-----------------------------|------------------------------|
| | Early (n = 418) ^a | Late (n = 204) ^a | Total (n = 622) ^a |
| Grade of clinician performing tracheostomy ^b | | | |
| Attending/specialist physician | 222 (53.1) | 116 (56.9) | 338 (54.3) |
| Resident | 133 (31.8) | 47 (23.0) | 180 (28.9) |
| House officer/junior resident | 46 (11.0) | 27 (13.2) | 73 (11.7) |
| Staff grade/associate specialist/fellow | 16 (3.8) | 11 (5.4) | 27 (4.3) |
| Grade of most senior clinician actively involved in, or directly supervising the tracheostomy procedure ^b | | | |
| Attending/specialist physician | 387 (92.6) | 179 (89.1) | 566 (91.4) |
| Resident | 27 (6.5) | 19 (9.5) | 46 (7.4) |
| House officer/junior resident | 2 (0.5) | 1 (0.5) | 3 (0.5) |
| Staff grade/associate specialist/fellow | 2 (0.5) | 2 (1.0) | 4 (0.6) |
| Type of procedure ^b | | | |
| Surgical | | | |
| Operating theater | 37 (8.9) | 25 (12.3) | 62 (10.0) |
| Bedside | 3 (0.7) | 2 (1.0) | 5 (0.8) |
| Percutaneous | | | |
| Operating theater | 1 (0.2) | 2 (1.0) | 3 (0.5) |
| Bedside | 377 (90.2) | 174 (85.7) | 551 (88.7) |
| Percutaneous technique | | | |
| Single-tapered dilator | 295 (78.2) | 131 (75.3) | 426 (77.3) |
| Multiple dilator technique | 37 (9.8) | 21 (12.1) | 58 (10.5) |
| Dilating forceps technique | 8 (2.1) | 4 (2.3) | 12 (2.2) |
| Threaded dilator | 1 (0.3) | 3 (1.7) | 4 (0.7) |
| Other ^c | 36 (9.5) | 15 (8.6) | 51 (9.3) |
| Duration of procedure, median (IQR), min ^b | | | |
| All procedures | 30 (20-45) | 30 (20-45) | 30 (20-45) |
| Surgical | 49 (30-74) | 45 (37-73) | 45 (31-73) |
| Percutaneous | 30 (20-40) | 30 (20-40) | 30 (20-40) |

Abbreviation: IQR, interquartile range.
^aTracheostomy data not available for 2 patients (2 early); no tracheostomy performed for 275 patients (31 early, 244 late).
^bIndividual fields unknown or not reported for grade of clinician performing tracheostomy for 4 patients (1 early, 3 late); grade of most senior clinician for 3 patients (3 late); type of procedure for 1 patient (1 late); duration of procedure for 13 patients (8 early, 5 late).
^cOther forceps dilator techniques or combined techniques.

Figure 2. The Distribution of Tracheostomy Timings in the Early and Late Tracheostomy Groups



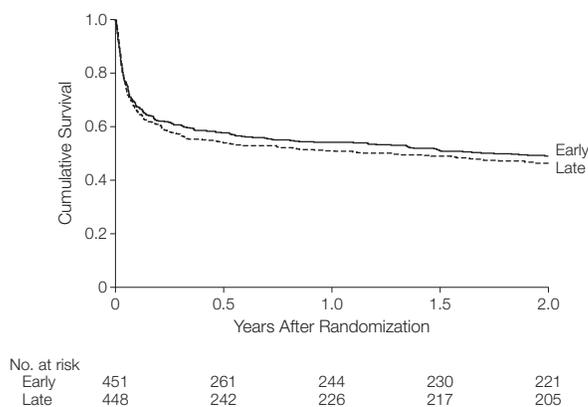
There were 622 tracheostomies performed. ICU indicates intensive care unit.

Table 3. Primary Outcome and Secondary Mortality Outcome Measures

| | No. (%) of Patients [95% CI] | | | Absolute Risk Reduction for Early vs Late (95% CI), % | Relative Risk for Early vs Late (95% CI) | P Value for Fisher Exact Test |
|---|------------------------------|------------------------------|------------------------------|---|--|-------------------------------|
| | Early (n = 451) | Late (n = 448) | Total (n = 899) | | | |
| Status at 30 d (primary outcome) | | | | | | |
| Died | 139 (30.8) [26.7 to 35.2] | 141 (31.5) [27.3 to 35.9] | 280 (31.2) [28.2 to 34.3] | 0.7 (-5.4 to 6.7) | 0.98 (0.81 to 1.19) | .89 |
| Status at ICU discharge ^a | | | | | | |
| No. of patients | 448 | 445 | 893 | | | |
| Died | 133 (29.7) [25.6 to 34.1] | 132 (29.7) [25.6 to 34.1] | 265 (29.7) [26.8 to 32.8] | 0.0 (-6.0 to 6.0) | 1.00 (0.82 to 1.22) | >.99 |
| Status at hospital discharge ^b | | | | | | |
| No. of patients | 424 | 436 | 860 | | | |
| Died | 168 (39.6) [35.1 to 44.4] | 180 (41.3) [36.8 to 46.0] | 348 (40.5) [37.2 to 43.8] | 1.7 (-4.9 to 8.2) | 0.96 (0.82 to 1.13) | .63 |
| Status at 1 y ^c | | | | | | |
| No. of patients | 451 | 443 | 894 | | | |
| Died | 207 (45.9) [41.4 to 50.5] | 217 (49.0) [44.4 to 53.6] | 424 (47.4) [44.2 to 50.7] | 3.1 (-3.5 to 9.6) | 0.94 (0.82 to 1.08) | .38 |
| Status at 2 y ^d | | | | | | |
| No. of patients | 451 | 443 | 894 | | | |
| Died | 230 (51.0) [46.4 to 55.6] | 238 (53.7) [49.1 to 58.3] | 468 (52.3) [49.1 to 55.6] | 0.7 (-3.8 to 9.3) | 0.95 (0.84 to 1.08) | .42 |

Abbreviation: ICU, intensive care unit.
^aStatus at critical care unit discharge not available for 6 patients (3 early, 3 late).
^bStatus at hospital discharge not available for 39 patients (27 early, 12 late).
^cStatus at 1 y not available for 5 patients (5 late).
^dStatus at 2 y not available for 5 patients (5 late).

Figure 3. Kaplan-Meier Survival Curve to 2 Years After Randomization



The survival of patients by treatment group for 2 years after randomization ($P = .45$, Cox-Mantel log rank test).

care admission was 13.0 (interquartile range [IQR], 8.2-19.1) days in the early group and 13.1 (IQR, 7.4-23.6) days in the late group ($P = .74$). For 133 patients who died in the early group and the 132 who died in the late group while in the critical care unit the median survival was 9.3 (IQR, 4.2-16.0) days for the early group and 10.4 (IQR, 6.0-19.7) days for the late group ($P = .16$). Median total hospital stay in those surviving to discharge (256 both groups)

was 33 (IQR, 19-55) days in the early group and 34 (IQR, 20-56) days in the late group ($P = .68$) and for those not surviving to discharge (168 early, 180 late) was 11 (IQR, 6-24) days in the early group and 14 (7-30) days in the late group ($P = .13$).

Antibiotic use to 30 days after randomization was the same in both groups. For the 304 in the early group those surviving to 30 days and 300 in the late group, antibiotics were not

given on a median of 5 (IQR, 1-8) days in the early group and 5 (IQR, 1-10) days in the late group ($P = .95$). Patients not surviving to 30 days (139 early, 140 late) had a median of 1 (IQR, 0-4) days alive and free of antibiotics in the early group and 2 (IQR, 0-5) days in the late group ($P = .14$).

FIGURE 4 shows the proportion of patients receiving at least 1 dose of intravenous sedative agent per day, by treatment group and day. In survivors at 30 days after randomization the median number of days on which any sedatives were received was 5 (IQR, 3-9) days in the early group and 8 (IQR, 4-12) days in the late group ($P < .001$), with a mean difference between the groups of 2.4 (95% CI, 1.6-3.6) days. Patients not surviving to 30 days (139 early, 140 late) had a median of 5 (IQR, 3-9) days on which of sedatives were received in the early group and 6 (IQR, 4-10) days in the late group ($P = .11$).

DISCUSSION

Principal Findings

These results suggest that early tracheostomy (within 4 days of admission)

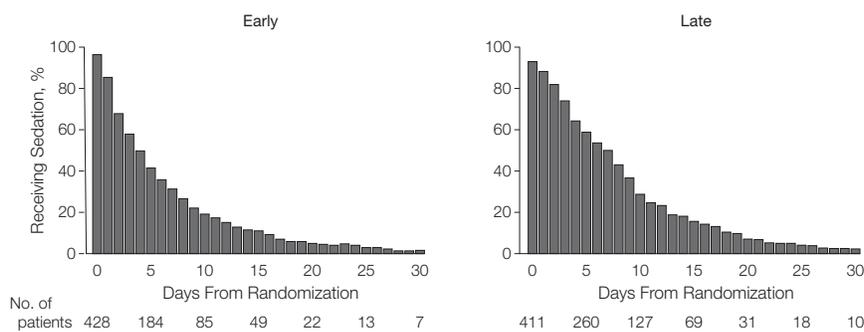
has no effect on mortality in mechanically ventilated patients identified by the treating clinician in the first 4 days following admission as likely to require at least an additional 7 days of ventilatory support compared with waiting 10 or more days before placing a tracheostomy if still indicated. For those allocated to the late tracheostomy group, only 45% of patients had a tracheostomy performed. In more than two-thirds of the rest, a tracheostomy was not required by day 10 either because they had recovered; they were alive but no longer being ventilated or they had already been discharged alive from the critical care unit.

The patients meeting the inclusion criteria for this study represent a very high-risk cohort, with an overall 41% mortality at discharge, 47% at year 1, and 53% at year 2. This presumably reflects the severity of the underlying disease leading to the need for mechanical ventilation, which in 69% was pulmonary pathology.

Most of the 622 tracheostomies performed during the study used percutaneous, dilator-based techniques undertaken at the bedside. There were no deaths attributed to the procedure. The overall complication rate was 6.3%, most of these were bleeding requiring intravenous fluids. In another study of the timing of tracheostomy on nosocomial pneumonia, the complication rates were similar at 8.3%.¹⁷ One patient experienced an esophageal perforation. This study was not resourced to follow the patients to see if they developed late complications of tracheostomy such as tracheal stenosis.

The main justifications used for early tracheostomy placement is that the tracheostomy is far better tolerated than endotracheal intubation. Placing the tracheostomy might therefore allow a reduction in sedative use, which in turn might translate into a shorter time in a critical care unit, and in the hospital. When this study was started the best quality study of early tracheostomy—albeit a single center—suggested that these also cause a significant reduction in mortality.⁸ This study suggests

Figure 4. The Percentage of Patients in Each Group Receiving 1 or More Doses of Sedative Medication



Data were available for 444 patients in the early group and 442 in the late group.

this sequence does not occur. A modest reduction in sedative use was seen in the patients randomized to an early tracheostomy, but by far the majority of patients in this study group continued to receive sedatives after the tracheostomy was performed. The modest reduction in sedative use did not significantly reduce the average duration of respiratory support. Early placement of a tracheostomy had no effect on duration of stay in either the critical care units or hospitals in the study, and no difference in antibiotic use between the groups was identified, and as noted above mortality was unaffected.

Results in the Context of Others

The results for 30-day mortality concur with the 2 other multicenter randomized studies on early vs late tracheostomy published since this study started. Blot and colleagues¹⁸ and Terragni and colleagues¹⁷ found no difference in 28-day mortality in 123 and 419 patient randomized controlled studies, respectively. Two single center studies by Koch and colleagues¹⁹ and Zheng and colleagues²⁰ also did not show a mortality benefit for early tracheostomy. In a multicenter nonrandomized, propensity matched comparison, Clec'h and colleagues²¹ found no difference in critical care unit mortality. A further study by Scales et al²² performed a stratified propensity score analysis from a provincial database and suggested a small increase in long-term mortality with later tracheos-

tomy, but the increase was of questionable clinical significance. Blot and colleagues¹⁸ did not demonstrate any difference in duration of mechanical ventilation, critical care unit length of stay, or respiratory infection, which is consistent with the findings reported herein, although Terragni et al,¹⁷ Koch et al,¹⁹ and Zheng et al²⁰ demonstrated a reduced duration of critical care and hospital stay. The proportion of patients not requiring a tracheostomy in the late group fell midway between that reported in the other 2 multicenter studies (43%¹⁷ and 74%¹⁸).

Strengths and Weaknesses

The strengths of this study lie in the open invitation for all UK critical care units to participate, the large numbers of units participating and the representativeness of the types of hospitals in which the units were located. Due to recruitment occurring in a broad range of clinical units, the broad inclusion criteria and the limited exclusion criteria, and the completeness of follow-up, we believe the study has reasonably high external validity. The study succeeded in ensuring a reasonable separation with regards to the timing of the intervention between the early and late tracheostomy groups.

The study did not recruit its intended sample size despite every effort to do so. The main reason was recruitment fatigue although exhaustion of funding was also a factor. The study design included a pilot period with a

small number of critical care units followed by a staggered increase to full participation of many more units. This strategy allows for piloting of study methodology and reduces the risks to the funders but extends the recruitment period and potentially fuelled recruitment fatigue. The decision to stop the study was made by the trial steering committee on practical rather than for statistical reasons. The study rarely met monthly recruitment targets, in spite of strenuous efforts to increase recruitment by a number of techniques including raising awareness, increasing the number of study centers, and increasing the financial support available to centers to cover costs. Two formal recruitment reviews took place, during which the investigators at the sites were interviewed and the “not in trial” logs examined to identify impediments to recruitment. The committee met when an application for extension funding would have to be made. At this point, recruitment was static in spite of an increasing number of sites, representing a falling per-site recruitment rate, so prediction of the likely time required to reach full recruitment was difficult. The trial steering committee, which contained a funder’s representative, stopped the study because further funding would not be made available in these circumstances and because the study had reached the end of its allocated funds. Not reaching the intended sample size affected the final precision of the study. The final 899-patient study had the power to detect an 8.3% absolute change in 30-day mortality from the late group value of 31.5% with 80% power and a 5% level of significance. Not reaching the intended sample size also informed our decision to wait and report the longer-term, 2-year survival data along with the 30-day survival data (primary outcome) in a single report. We did not perform any subgroup analyses because of the reduced sample size.

The study required clinicians to make a judgment about the likelihood that the patient would require 7 or more days of mechanical ventilation when con-

sidering them for inclusion in the study. We chose this approach for 2 reasons. First, this mimics the usual decision-making process when a clinician is considering placing a tracheostomy, when he or she estimates the likely duration of respiratory support required as part of the risk-benefit assessment. Second, we could not find a validated and accurate prediction rule for the duration of mechanical ventilation in an individual patient. At the request of some of the local investigators, after the study started, we attempted to produce an accurate prediction tool from data held on the ICU computerized information system in Oxford and the available literature,²³⁻²⁶ but we could not generate one with sufficient accuracy. Lack of a tool may have affected recruitment to the study, for clinicians may have only included patients that they considered to be at very high risk of prolonged mechanical ventilation. Blot and colleagues¹⁸ noted a very similar problem with their study, echoed in the accompanying editorial.²⁷ However Terragni and colleagues¹⁷ used a rule-based recruitment strategy in their study and found that 20% of patients recovered before tracheostomy in the late group, almost identical to our 19.6%, suggesting the rules they used were no better than clinical judgment.

The study concentrated on recording outcomes related to the acute care and long-term survival of the patients in the study. We did not investigate the long-term complications of translaryngeal intubation or tracheostomy such as laryngeal damage or tracheal stenosis.

Implications

The implications, for clinical practice and for patients, from this study are found from the results in the late group. Not only were there no statistically significant difference in mortality between the 2 groups but, through waiting, an invasive procedure was avoided in a third of patients. Avoiding this significant proportion of tracheostomies, a procedure associated with a 6.3% acute complication rate in this study (and 38%-39% overall complication

rates in the other recent multicenter studies^{17,18}), did not appear to be associated with any significant increase in health care resource use, as measured by critical care unit or hospital stay. It would appear that delaying a tracheostomy until at least day 10 of a patient’s critical care unit stay is the best policy. As noted, only 45% of the late group had a tracheostomy performed mainly due to tracheal extubation and subsequent discharge from the critical care unit. This raises questions about clinicians’ abilities to predict the requirement for an additional 7 days of ventilation early in a patient’s critical care unit stay and the wisdom of basing any treatments, including tracheostomy, on this prediction.

CONCLUSIONS

Among mechanically ventilated critically ill patients in adult, general critical care units in the United Kingdom, early tracheostomy (within the first 4 days after admission) was not associated with an improvement in 30-day mortality or other important secondary outcomes. Early tracheostomy should therefore be avoided unless tools to accurately predict the duration of mechanical ventilation on individual patients can be developed and validated.

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Analysis and interpretation of data: All authors.

Drafting of the manuscript: All authors.

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