Early tracheostomy in critically ill patients: not so fast

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The most common strategy of airway management to aid invasive mechanical ventilation in the intensive-care unit involves placement of an endotracheal tube.[1] This translaryngeal approach, which makes oral care, communication, and feeding challenging, is often poorly tolerated unless sedation is administered.[2] Thus, clinicians might consider exchange of this tube for a tracheostomy if a prolonged period of ventilation is expected. The anticipated benefits of tracheostomy include enhanced comfort, improved pulmonary toilet, and decreased sedation requirements. These benefits should accelerate liberation from the ventilator and discharge from the intensive-care unit, thus preventing complications and improving survival.[3] However, the procedure is not without risks, both early (stomal bleeding, oesophageal and airway injury, barotrauma) and delayed (infection, tracheomalacia, tracheal stenosis, tracheoinominate fistula). Balancing of the anticipated benefits of tracheostomy with the risks has generated uncertainty regarding its optimum timing. To solve this conundrum, the clinician should first define prolonged mechanical ventilation and which patients will need it,[4] then decide when the benefits of tracheostomy outweigh the risks. The decision might be dependent on the specific insult leading to critical illness—eg, acute respiratory distress syndrome, trauma, or stroke—such that one prescription might not fit all.

In *The Lancet Respiratory Medicine*, Ilias Siempos and colleagues[5] report the results of an updated, comprehensive, and methodologically rigorous systematic review and meta-analysis. The investigators included 16 trials from 1984 to 2013 that examined early (within 8 days of intubation) versus late or no tracheostomy, and analysed mortality in the intensive-care unit and ventilator-associated pneumonia as primary outcomes. A striking finding was the highly variable proportion of patients in the late tracheostomy group who actually had the procedure (median 60%, range 26–100% in 11 trials). Mortality in the intensive-care unit was significantly lower in patients in the early versus the late or no tracheostomy group (risk ratio 0·82, 95% CI 0·68–0·99; p=0·04; 13 trials, 2434 patients with data, 800 deaths). The results were similar in a sensitivity analysis restricted to trials with a low risk of bias and stronger in trials in which tracheostomy was done even sooner, within 3 days versus 4–8 days of intubation. Risk of ventilator-associated pneumonia was also substantially lowered; however, decades of clinical research have shown this outcome to be problematic. Absence of a reliable and objective definition has led to recommendations for its removal from public reporting.[6] Furthermore, ventilator-associated pneumonia is susceptible to detection bias in unblinded trials, and even if the illness is prevented, the implications on mortality are unclear.[7]

Meta-analyses of trials, and summary estimates from single trials, assume clinical similarity in the patients enrolled. This assumption might not hold when considering tracheostomy for a heterogeneous mix of critically ill patients, for whom the indications for airway protection and mechanical ventilation vary greatly. For example, patients with brain injury might be on minimum ventilator settings and need only a conduit for airway protection due to unconsciousness, and thus might benefit the most.[8] Although Siempos and colleagues considered subgroup effects on the basis of type of intensive-care unit, their analysis was underpowered,

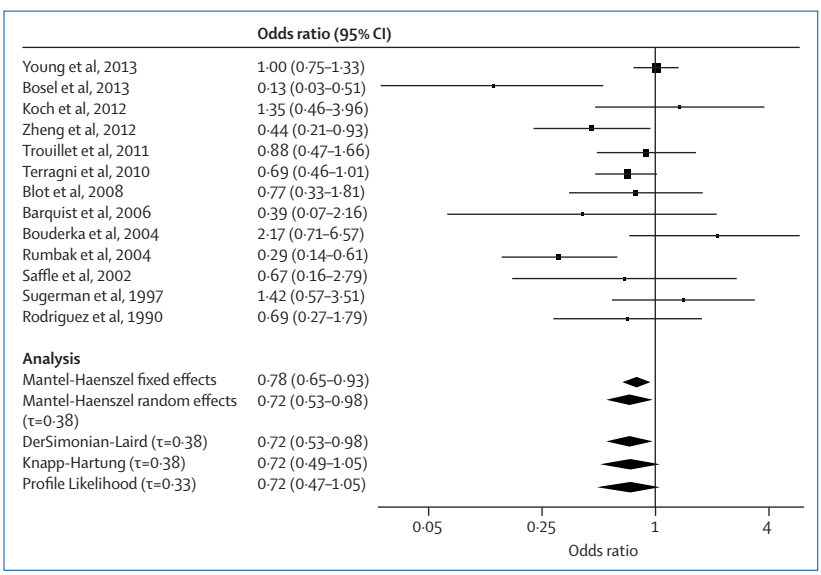

Figure: **Meta-analytical results for mortality in the intensive-care unit with early versus late tracheostomy with use of alternate statistical methods**
Primary studies and data from Siempos and colleagues' study;[5] odds ratios displayed as per the primary analysis. All analyses were done with R statistical software (version 2.15.3). The size of each square is proportional to the inverse of the variance of the log odds ratio. The fixed-effects model assumes that all studies are estimating a common treatment effect. The DerSimonian-Laird random-effects model assumes that the treatment effects estimated in the included studies are not identical, but follow a distribution whose standard deviation (τ) is known exactly. This model calculates τ with either the Mantel-Haenszel fixed-effects pooled log odds ratio (Mantel-Haenszel random-effects in the figure) or the generic inverse variance fixed-effects pooled log odds ratio (DerSimonian-Laird in the figure). Siempos and colleagues reported the Mantel-Haenszel random-effects result. Cornell and colleagues[12] provide details of the Knapp-Hartung and profile likelihood methods, which provide for uncertainty in the estimate of τ.

and the question of whether early tracheostomy can help specific subgroups will only be answered by new trials.

Do these results finally settle the debate of early versus late tracheostomy? There are several caveats that should give us pause for thought. First, mortality in the intensive-care unit is less patient centred than mortality at hospital discharge or 1 year. This issue is relevant because tracheostomy could aid earlier discharge to a non-intensive-care-unit setting or another institution, notwithstanding the high risk of death from the underlying disorder. Importantly, the meta-analysis showed no effect on 1-year mortality between the compared groups (risk ratio 0·93; 95% CI 0·85–1·02; p=0·14; three trials, 1529 patients with data, 788 deaths).

Second, clinicians might be perturbed when considering the discordance between the meta-analytical mortality result and the large TracMan trial,[9] which analysed 899 patients and showed no effect. The occurrence of qualitatively different results between meta-analyses and large trials is not new, although it is far from universal (10–23% of comparisons).[10] Among discordances, the scenario of a significant meta-analysis and non-significant large trial is more common,[11] explained by characteristics of both meta-analyses and large comparator trials.[10] Notwithstanding these methodological observations, the clinician might still be unsure of which form of evidence to trust for decisions at the bedside.

Despite the finding of almost no difference in 30-day mortality, the TracMan trial enrolled only 54% of the ultimately planned sample size, and the confidence interval did not exclude clinically important benefit or harm, with confidence limits for the absolute risk difference exceeding 5% in both directions.[9] However, the discrepancy between this meta-analysis[5] and TracMan[9] could be more apparent than real. Siempos and colleagues used the DerSimonian-Laird random-effects model, which pools results from statistically heterogeneous trials and is widely implemented in software packages. However, its confidence intervals might be too narrow when study results differ substantially,[12] and indeed the pooled result for mortality in the intensive-care unit is no longer statistically significant when assessed by alternative methods (figure).

In summary, Siempos and colleagues' systematic review emphasises the challenges of finding a beneficial effect of early tracheostomy despite a substantial body of scientific literature, with 13 trials and more than 2400 patients in the primary analysis. Although the finding of lower mortality in the intensive-care unit with early tracheostomy is striking and exciting, its statistical significance is dependent on the choice of analytical model. This finding is also not borne out by long-term results. Because intensive-care clinicians cannot reliably predict who will need mechanical ventilation for more than 1 week, we believe that the best initial approach is to treat the cause of respiratory failure and monitor for recovery. Waiting longer to do a tracheostomy leads to many fewer procedures and similar 1-year survival. Future research of the timing of this procedure should focus on long-term patient-centered outcomes and more homogeneous populations of intensive-care-unit patients.

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Effect of early versus late or no tracheostomy on mortality of critically ill patients receiving mechanical ventilation: a systematic review and meta-analysis

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Summary

Background Delay of tracheostomy for roughly 2 weeks after translaryngeal intubation of critically ill patients is the presently recommended practice and is supported by findings from large trials. However, these trials were suboptimally powered to detect small but clinically important effects on mortality. We aimed to assess the mortality benefit of early versus late or no tracheostomy in critically ill patients who need mechanical ventilation.

Methods We systematically searched PubMed, CINAHL, Embase, Web of Science, DOAJ, the Cochrane Library, references of relevant articles, scientific conference proceedings, and grey literature up to Aug 31, 2013, to identify randomised controlled trials comparing early tracheostomy (done within 1 week after translaryngeal intubation) with late (done any time after the first week of mechanical ventilation) or no tracheostomy and reporting on mortality or incidence of pneumonia in critically ill patients under mechanical ventilation. Our primary outcomes were all-cause mortality during the stay in the intensive-care unit and incidence of ventilator-associated pneumonia. We calculated pooled odds ratios (OR), pooled risk ratios (RR), and 95% CIs with a random-effects model. All but complications analyses were done on an intention-to-treat basis.

Findings Analyses of 13 trials (2434 patients, 800 deaths) showed that all-cause mortality in the intensive-care unit was significantly lower in patients assigned to the early versus the late or no tracheostomy group (OR 0·72, 95% CI 0·53–0·98; p=0·04). This finding represents an 18% reduction in the relative risk of death, translating to a 5% absolute improvement in survival (from 65% to 70%). This result persisted when we considered only trials with a low risk of bias (663 deaths; OR 0·68, 95% CI 0·49–0·95; p=0·02; eight trials with 1934 patients). There was no evidence of a difference between the compared groups for 1-year mortality (788 deaths; RR 0·93, 95% CI 0·85–1·02; p=0·14; three trials with 1529 patients).

Interpretation The synthesised evidence suggests that early tracheostomy is associated with lower mortality in the intensive-care unit than late or no tracheostomy; a finding that might question the present practice of delaying tracheostomy beyond the first week after translaryngeal intubation in mechanically ventilated patients. However, the scarcity of a beneficial effect on long-term mortality and the potential complications associated with tracheostomy need careful consideration; thus, further studies focusing on long-term outcomes are warranted.

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Introduction

A substantial proportion (up to a third) of patients who receive mechanical ventilation for more than 48 h undergo tracheostomy.[1,2] Perceived benefits of tracheostomy include airway security, enhanced patient comfort, and easier weaning from mechanical ventilation, but the procedure is not risk free. Thus, patients who need mechanical ventilation often undergo translaryngeal intubation for an initial period of time, after which a tracheostomy is undertaken. However, optimum timing for the placement of a tracheostomy remains a challenging question.

In the past few years, investigators of large trials addressed this question and reported that timing of tracheostomy might not affect clinical outcomes.[3–5] Accordingly, most experts support the wait-and-see strategy—ie, the delay of tracheostomy placement until day 10[6] or even day 15[7,8] of mechanical ventilation. However, even the largest and most recent of the above mentioned contributions did not achieve its intended sample size.[3] Because of the potentially modest benefits of early tracheostomy and the methodological challenges to design and undertake such trials (eg, recruitment rates), any one trial might be unlikely to provide convincing evidence of the effectiveness of the intervention. A carefully done meta-analysis of trials could address this issue;[9] it could restrict the likelihood of type II error by increasing sample size, and uncover the benefit (if any) of the intervention. We did a systematic review and meta-analysis to investigate whether early tracheostomy has any benefit compared with late or no tracheostomy in terms of mortality in critically ill patients who need mechanical ventilation.

Methods

Search strategy and selection criteria

We undertook the systematic review and meta-analysis in accordance with recommendations of the Cochrane

Handbook for Systematic Reviews of Interventions.[10] We reported the systematic review and the meta-analysis in accordance with the PRISMA Statement.[11] The review protocol is available online.

For the **review protocol** see www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42013005549

We systematically searched PubMed, CINAHL, Embase, Web of Science, Directory of Open Access Journals, and the Cochrane Central Register of Controlled Trials from database inception to Aug 31, 2013. We also manually searched reference lists of the retrieved articles and abstracts of scientific conference proceedings (appendix). Additionally, we checked the Cochrane Database of Systematic Reviews and the Database of Abstracts of Reviews of Effectiveness to identify any reviews that could lead to eligible trials. To uncover grey literature, we repeated our search with SciGlobe and National Institutes of Health website listings of ongoing trials.[12] We contacted investigators of ongoing trials for any unpublished data (appendix); such data were not available. Finally, we undertook citation tracking with Google Scholar for all included trials. We used the key phrases ("tracheostomy" OR "tracheotomy") AND ("critically ill" OR "intensive care" OR "critical care" OR "early") and imposed a filter for clinical trials.

See **Online** for appendix

Two authors (IIS and TKN) independently did literature searches and assessed the eligibility of identified publications. We regarded randomised controlled trials that compared early tracheostomy with late or no tracheostomy in critically ill patients receiving mechanical ventilation and reported all-cause mortality or incidence of pneumonia as eligible for inclusion. We defined early tracheostomy as being done during the first week after translaryngeal intubation. We defined late tracheostomy as being done any time after the first week of mechanical ventilation; patients receiving prolonged translaryngeal intubation (no tracheostomy) were also considered as comparators of the early tracheostomy group. No limitation on time or language of publications was set.

Data extraction and risk of bias assessment

Two authors (IIS and TKN) independently extracted trial-level data for study patient characteristics, interventions, and outcomes with a standard data extraction form. Any disagreement was resolved through discussion of all investigators. If we needed additional information or clarifications about the main outcomes of the meta-analysis, we attempted to contact investigators of individual trials; we incorporated provided data into our analyses.

We assessed eligible trials for their risk of bias—namely selection, detection, attrition, and reporting bias—with appropriate Cochrane methods.[10] Masking of participants and caring team was not possible. A sensitivity analysis including only trials with a low risk of bias for the primary outcomes of this meta-analysis was done.

Outcomes

Our primary outcomes were all-cause mortality during the stay in the intensive-care unit and incidence of ventilator-associated pneumonia. Secondary outcomes were tracheostomy-related complications (both all types of complication and bleeding), length of stay in the intensive-care unit, length of hospital stay, duration of mechanical ventilation, duration of sedation and time to mobility of critically ill patients. The appendix provides detailed definitions of the outcomes.

We graded the overall quality of evidence for our primary outcomes—namely, mortality and ventilator-associated pneumonia—with the Grading of Recommendations Assessment, Development, and Evaluation methodology.[13]

Statistical analysis

We did pre-planned subgroup analyses by year of publication, type of publication (peer-reviewed journals *vs* others), size of trial, type of intensive-care unit, type of tracheostomy (percutaneous *vs* surgical), and timing of early tracheostomy (within 3 days *vs* 4–7 days after translaryngeal intubation).

We used Review Manager (version 5.2.6) and Stata (version 12.0) for statistical analyses. We assessed the potential of small study effects (including publication bias) by inspection of the funnel plots of the primary outcomes of the meta-analysis and with the Harbord's test to investigate statistical evidence of such effects.[10] Statistical heterogeneity among trials was quantified with the I^2 statistic,[14] which is useful to roughly interpret heterogeneity as non-important (I^2<40%), moderate (I^2<60%), or substantial or considerable (I^2≥75%).[10] We did a meta-analysis only in case of non-important or moderate (I^2<60%) heterogeneity. We expressed pooled dichotomous effect measures as odds ratios (OR) with 95% CIs. On the basis of peer reviewers' recommendations, pooled dichotomous effect measures were also expressed as risk ratios (RR) and post-hoc analyses were done. Pooled continuous effect measures were expressed as mean difference with 95% CI. All but complications analyses were done on an intention-to-treat basis. A random-effects model was implemented.

Role of the funding source

There was no funding source for this study. IIS and TKN had full access to all the data in the study. IIS had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the flow diagram for study selection. We included 16 trials[3–5,15–27] in the systematic review. One of these trials[27] was a conference abstract that mentioned significant difference in mortality (but not in pneumonia) in favour of early versus late tracheostomy; however, it was not included in the meta-analysis because it did not provide specific numbers and we could not contact its investigators.[27] Thus, 15 trials were included in the meta-analysis.[3–5,15–26] Table 1 and the appendix show summary characteristics of the trials. Most trials were published recently (median 2008 [IQR 2002–2012]; table 1). In

11 trials providing relevant data, 1098 (91%) of the 1202 patients assigned to receive early tracheostomy and 615 (54%) of the 1132 patients assigned to receive late or no tracheostomy actually received a tracheostomy (appendix).[3–5,15,17–20,22,25,26] Reasons for tracheostomy not being done in patients assigned to the late or no tracheostomy group were given in five trials;[3,5,15,17,22] of the 815 patients assigned to late or no tracheostomy group in these trials, 222 (27%) patients were successfully extubated and 116 (14%) patients died before tracheostomy placement (appendix).[3,5,15,17,22]

Of the 13 trials[3–5,15–17,19–25] that reported on mortality, five (38%) trials[16,21,22,24,25] had a high or unclear risk of selection bias (appendix). The remaining eight (62%) trials[3–5,15,17,19,20,23] had a low risk of both selection and attrition bias (appendix). Detection bias could not be an issue for all-cause mortality. Of the 13 trials[4,5,16–26] that reported on incidence of ventilator-associated pneumonia, seven (54%) trials[16,18,21,22,24–26] had a high or unclear risk of selection bias and three (23%) trials[4,20,23] had a high or unclear risk of detection bias (appendix). The remaining three (23%) trials[5,17,19] had a low risk of selection and detection bias, and a low risk of attrition bias (appendix).

13 trials[3–5,15–17,19–25] (2434 participants) in the meta-analysis provided data for all-cause mortality. We recorded no statistical evidence of small study effects (p=0·38). Moderate statistical heterogeneity was detected (I^2 53%). All-cause mortality in the intensive-care unit was lower in patients assigned to early tracheostomy than in those in the late or no tracheostomy group (367 *vs* 433 deaths; OR 0·72, 95% CI 0·53–0·98; p=0·04; figure 2).

We did a sensitivity analysis of the eight trials (1934 participants)[3–5,15,17,19,20,23] that had a low risk of bias. Statistical heterogeneity was moderate (I^2 46%). All-cause mortality in the intensive-care unit was lower in patients who had early tracheostomy than in those in the late or no tracheostomy group (305 *vs* 358; OR 0·68, 95% CI 0·49–0·95; p=0·02).

All-cause mortality in the intensive-care unit remained lower in patients given early tracheostomy than in those who had late or no tracheostomy in the subgroup of large trials that enrolled 106 patients or more (ie, median or greater sample size of included trials; 337 *vs* 394; OR 0·72, 95% CI 0·53–0·98; p=0·04; eight trials with 2114 participants) and in those in whom a tracheostomy was done within 3 days after translaryngeal intubation (45 *vs* 89; OR 0·34, 95% CI 0·20–0·56; p<0·0001; four trials with 343 participants; appendix). We graded the overall strength of evidence regarding this outcome as moderate (appendix).

Data for incidence of ventilator-associated pneumonia were available for 13 trials (1599 participants)[4,5,16–26] included in the meta-analysis. We recorded no statistical evidence of small study effects (p=0·74). Statistical heterogeneity was moderate (I^2 57%). Incidence of ventilator-associated pneumonia was lower in mechanically ventilated patients assigned to the early versus the late or no tracheostomy group (305 *vs* 386 cases; OR 0·60, 95% CI 0·41–0·90; p=0·01; figure 3).

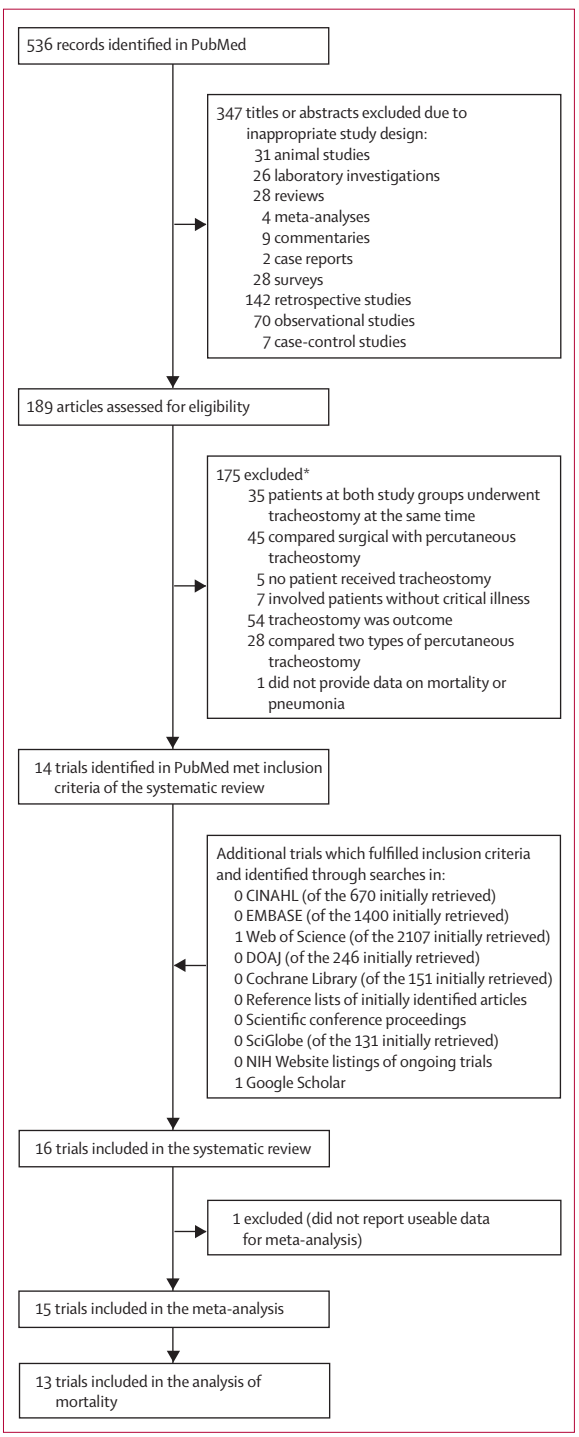

***Figure 1*: Study flow diagram**
Made in accordance with the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) statement with modifications. *The appendix provides reference information about the 175 excluded articles and details of searches in scientific conference proceedings.

We did a sensitivity analysis of the three trials[5,17,19] (661 participants) that had a low risk of bias. Statistical heterogeneity was non-important (I^2 17%). Incidence of ventilator-associated pneumonia was lower in patients who had early tracheostomy than in those who had late or no tracheostomy (77 *vs* 105; OR 0·65, 95% CI 0·43–0·97; p=0·03).

Incidence of ventilator-associated pneumonia remained lower in patients given early tracheostomy than in those given late or no tracheostomy in the subgroup of

	Type of ICU	Severity of illness at day of randomisation	Early tracheostomy group (day of tracheostomy placement after translaryngeal intubation)	Late or no tracheostomy group (day of tracheostomy placement after translaryngeal intubation)	Type of tracheostomy done†	Number of included patients
Young et al, 2013[3]	General, cardiothoracic	APACHE II: 20 (7) *vs* 20 (6)*	≤4	≥10	Percutaneous (89%), surgical (11%)	899
Bösel et al, 2013[15]	Neurological, neurosurgical	APACHE II: 17 (13–19) *vs* 16 (11–19)	≤3	7–14	Percutaneous	60
Koch et al, 2012[16]	Neurological, neurosurgical, surgical	APACHE II: 21 (12–31) *vs* 22 (6–11)	≤4	≥6	Percutaneous	100
Zheng et al, 2012[17]	Surgical	APACHE II: 20 (2) *vs* 20 (3)	3	15	Percutaneous	119
Trouillet et al, 2011[4]	Cardiac surgical	SAPS II: 47 (12) *vs* 46 (11)	≤5	≥19	Percutaneous	216
Bylappa et al, 2011[18]	General	NR	5–7	8–15	Surgical	44
Terragni et al, 2010[5]	General	SAPS II: 51 (9) *vs* 50 (9)	6–8	≥13	Percutaneous	419
Blot et al, 2008[19]	General, medical	SAPS II: 47 (14) *vs* 43 (15)	≤4	Prolonged intubation‡	Percutaneous (40%), surgical (60%)	123
Barquist et al, 2006[20]	Trauma	APACHE II: 12 (3) *vs* 13 (5)	≤7	≥29	Surgical	60
Bouderka et al, 2004[21]	Trauma	SAPS: 5 (2) *vs* 6 (4)*	5–6	Prolonged intubation	NR	62
Rumbak et al, 2004[22]	Medical	APACHE II: 27 (4) *vs* 26 (3)	≤2	14–16	Percutaneous	120
Saffle et al, 2002[23]	Burn	NR	Next available operative day (2–3)	≥14	Percutaneous (NR), surgical (NR)	44
Sugerman et al, 1997[24]	Trauma	APACHE III: 66 (3) *vs* 55 (3)	3–5	≥10–14	Percutaneous (74%), surgical (26%)	112§
Rodriguez et al, 1990[25]	Surgical	APACHE II: 10 (1) *vs* 10 (1)*	≤7	≥8	Surgical	106
Dunham and LaMonica, 1984[26]	Trauma	NR	3–4	14	Surgical	74

Data are mean (SD) or median (IQR), unless otherwise indicated. ICU=intensive-care unit. APACHE=Acute Physiology and Chronic Health Evaluation. SAPS=Simplified Acute Physiology Score. NR=not reported. *Data at day of admission instead of day of randomisation were available for these trials.[3,21,25] †In trials[3,19,23,24] where patients could undergo (by study design) either percutaneous or surgical tracheostomy, we provide the proportion of patients receiving each type of procedure. ‡Patients in the control group of this trial[19] could not receive tracheostomy until at least 14 days after translaryngeal intubation. §Only data from the early randomisation portion of this trial[24] could be used in the meta-analysis.

***Table 1*: Characteristics of individual trials, patient populations, and interventions (early *vs* late or no tracheostomy)**

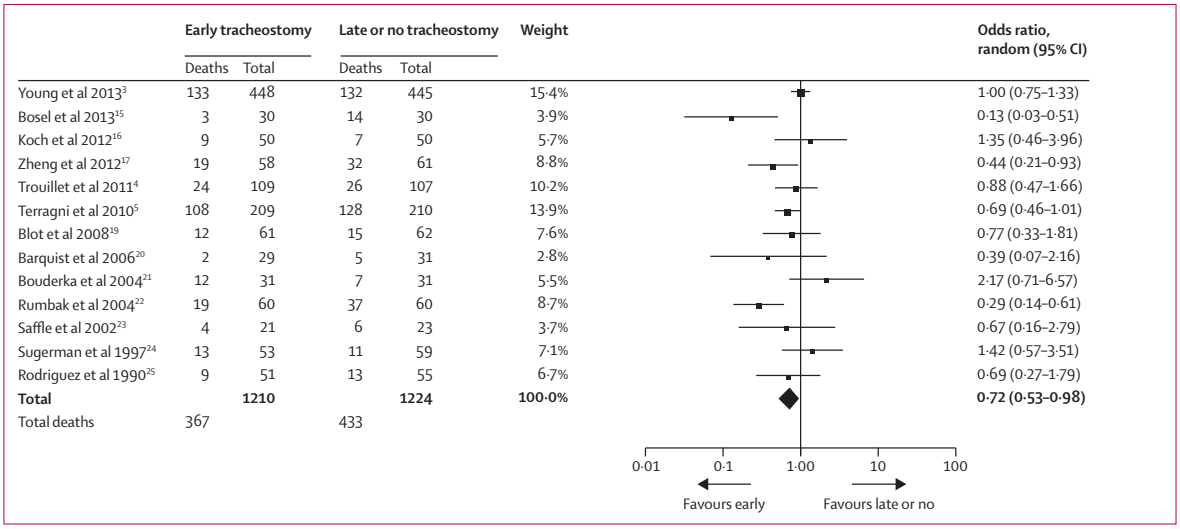

***Figure 2*: Mortality in the intensive care unit and early tracheostomy**
We calculated pooled odds ratio and 95% CIs with a random-effects model. Total refers to number of patients assigned to each group.

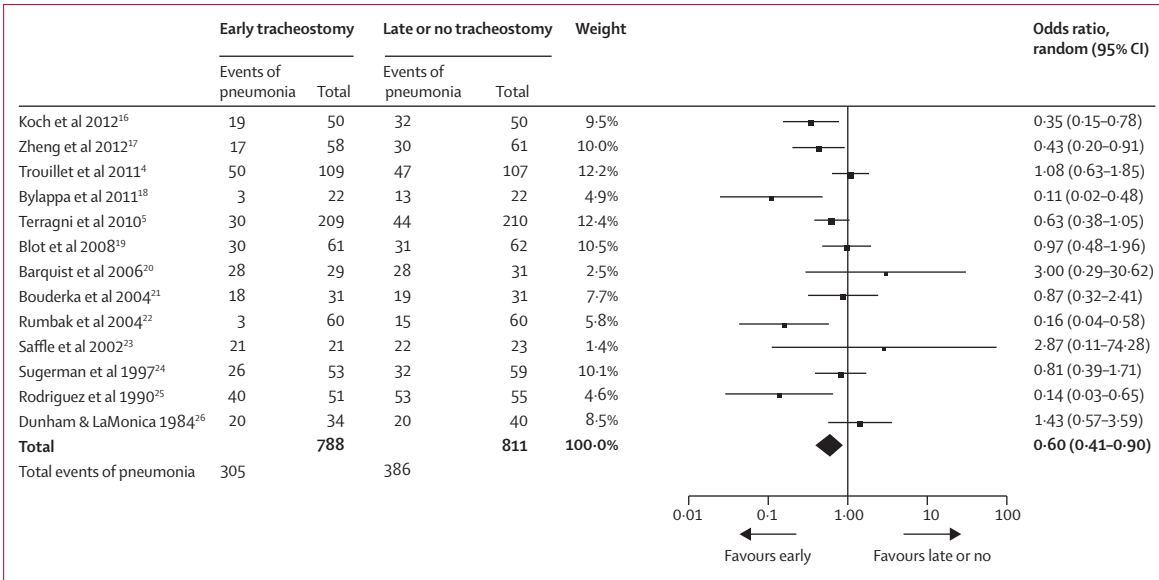

***Figure 3*: Pneumonia and early tracheostomy**
We calculated pooled odds ratio and 95% CIs with a random-effects model. Total refers to number of patients assigned to each group.

	Number of patients providing relevant data	References	Effect estimate*	p value
Dichotomous outcomes				
ICU mortality	2434	3–5, 15–17, 19–25	RR 0·82 (0·68 to 0·99)	0·04
1 year mortality	1529	3–5	RR 0·93 (0·85 to 1·02)	0·14
Incidence of VAP	1599	4, 5, 16–26	RR 0·85 (0·72 to 1·01)	0·06
Total tracheostomy-related complications	1447	3–5, 15, 17, 18, 20, 22, 26	RR 0·88 (0·71 to 1·11)	0·28
Tracheostomy-related bleeding	1370	3–5, 15, 17–21	RR 0·59 (0·28 to 1·25)	0·17
Long-term severe disability†	795	4, 5, 15, 16	RR 0·86 (0·49 to 1·53)	0·62
Continuous outcomes				
Length of ICU stay‡	554	4, 22, 24, 25	Mean difference −9·14 days (−15·53 to −2·75)	0·005
Length of hospital stay§	410	4, 18, 23, 25	Mean difference −4·77 days (−11·63 to 2·08)	0·17
Duration of mechanical ventilation¶	1614	3, 4, 18, 19, 21–23, 25	Mean difference −3·61 days (−7·00 to −0·22)	0·04
Duration of sedation‖	336	4, 22	Mean difference −7·09 days (−14·64 to 0·45)	0·07
Subgroup analyses by region** ††				
USA	442	20, 22, 23, 24, 25	OR 0·60 (0·31 to 1·15)	0·12
Europe	1811	3–5, 15, 16, 19	OR 0·78 (0·55 to 1·12)	0·18
Subgroup analyses by baseline risk of mortality** ††				
≥20%	2162	3–5, 15, 17, 19, 21–23, 25	OR 0·66 (0·47 to 0·94)	0·02
<20%	272	16, 20, 24	OR 1·16 (0·61 to 2·21)	0·65

Data in parentheses are 95% CIs. ICU=intensive-care unit. VAP=ventilator-associated pneumonia. RR=risk ratio. OR=odds ratio. *Pooled risk ratio, pooled odds ratio, and 95% CIs were calculated with a random-effects model. †Long-term severe disability was indicated by a Basic Activities of Daily Living Scale score of less than 6 (showing need for assistance in at least two of the following: bathing, dressing, toileting, getting in or out of bed or chairs, controlling bowel and bladder continence, and eating)[4] or need for admission to a long-term care facility[5] or a modified Rankin Scale score of 5 (showing severe disability; bedridden, incontinent, and requiring constant nursing care and attention[15]) or need for continuing mechanical ventilation after hospital discharge.[16] ‡Three trials[3,15,16] expressed data for length of ICU stay as median (IQR). §Three trials[3,5,16] expressed data for length of hospital stay as median (IQR). ¶Two trials[15,16] expressed data for duration of mechanical ventilation as median (IQR). ‖One trial[3] expressed data on duration of sedation as median (IQR). **Only trials providing data on ICU mortality are included in these subgroup analyses. †† Heterogeneity in trials included in the subgroup analyses: USA I^2 46%, Europe I^2 52%, baseline risk ≥20% I^2 60%, baseline risk <20% I^2 0%.

***Table 2*: Post-hoc analyses**

trials which enrolled 106 patients or more (196 *vs* 252; OR 0·60, 95% CI 0·38–0·93; p=0·02; seven trials with 1215 participants) and in those in whom a tracheostomy was done within 3 days after translaryngeal intubation (41 *vs* 67; OR 0·36, 95% CI 0·13–0·99; p=0·049; three trials with 283 participants; appendix). The overall

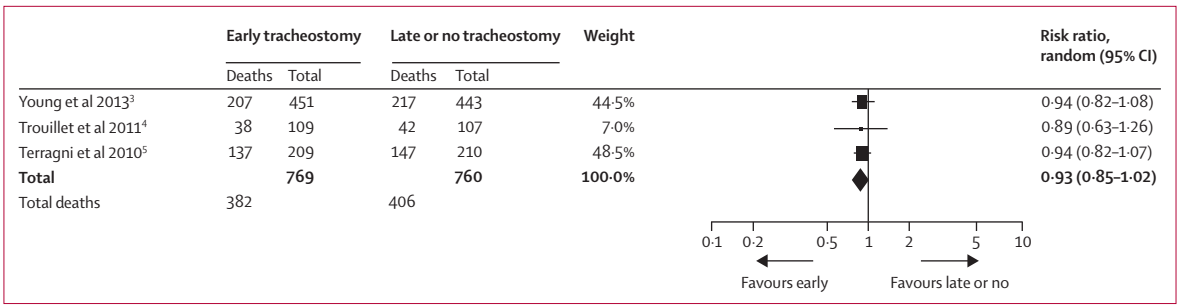

***Figure 4*: 1-year mortality and early tracheostomy**
We calculated pooled risk ratio and 95% CIs with a random-effects model. Total refers to number of patients assigned to each group.

strength of evidence regarding this outcome was graded as moderate (data not shown).

Nine trials in the meta-analysis (1447 participants) reported information about all types of tracheostomy-related complications.[3–5,15,17,18,20,22,26] Statistical heterogeneity was non-important (I^2 0%). No evidence of a difference between early and late tracheostomy was shown in terms of total procedure-related complications (114 *vs* 101 cases; OR 0·82, 95% CI 0·59–1·13; p=0·22). With regard to tracheostomy-related bleeding, relevant data were available for nine trials (1370 participants).[3–5,15,17–21] Statistical heterogeneity was moderate (I^2 43%). No evidence of a difference on bleeding was shown between patients undergoing early versus late tracheostomy (29 *vs* 30 cases; OR 0·53, 95% CI 0·22–1·27; p=0·15). No death attributed to tracheostomy was reported in trials providing relevant information.[3–5,15,17–23,25]

Data for length of stay in intensive-care units and in hospital, and duration of mechanical ventilation and sedation were reported in seven,[3,4,15,16,22,24,25] seven,[3–5,16,18,23,25] ten,[3,4,15,16,18,19,21–23,25] and three[3,4,22] trials, respectively (appendix). For these comparisons, statistical heterogeneity was substantial (ranging from 86% to 98%). Thus, a meta-analysis was not done. Data for time to mobility were reported in two trials[4,19] (appendix). Statistical heterogeneity was non-important (I^2 0%). Patients assigned to the early tracheostomy group had a shorter time to mobility than did those assigned to the late or no tracheostomy group (mean difference –2·06 days, 95% CI –2·90 to –1·22 days; p<0·001).

Table 2 shows results of the post-hoc analyses. The reduction in the relative risk of death in the intensive-care unit for patients assigned to the early versus the late or no tracheostomy group was 18% (table 2), translating to a 5% absolute improvement in survival (from 65% to 70%). We noted no evidence of a difference in 1 year mortality between the compared groups (table 2, figure 4) or in long-term severe disability (table 2). Meta-analyses of continuous outcomes showed that early versus late or no tracheostomy was associated with shorter length of stay in the intensive-care unit and shorter duration of mechanical ventilation, but not with shorter length of hospital stay or duration of sedation (table 2). Findings from post-hoc meta-regression analyses suggested that the beneficial effect of early tracheostomy on mortality in the intensive-care unit differed only by timing of the intervention—ie, it was greater in trials in which early tracheostomy was done within 3 days (p=0·006) versus 4–7 days after intubation (appendix). Finally, post-hoc subgroup analyses showed that compared with late or no tracheostomy, early tracheostomy was associated with a survival benefit in trials with underlying risk of mortality (ie, mortality in patients in the control groups) equal to or greater than 20%; whereas in trials with underlying risk of mortality lower than 20%, such a benefit was not evident (table 2).

Discussion

The synthesised evidence suggests that early, compared with late or no, tracheostomy is significantly associated with lower mortality in the intensive-care unit.

Our findings are not in line with those of recent trials in which early tracheostomy offered no survival benefit compared with postponing tracheostomy for at least 10 days after the start of mechanical ventilation.[3–5] Discordances between meta-analyses and large trials of the same topic are not uncommon.[28] Such discordances might be either between meta-analyses and a subsequent large trial or between large trials (especially those that are stopped early) and a subsequent meta-analysis.[29,30] Small study effects or differences in baseline risk (the effectiveness of the studied intervention might vary in patients at different baseline risk) could explain discrepancies in findings between meta-analyses and large trials of the same topic.[31] Notably, baseline risk of mortality in the present meta-analysis (35%) was higher than in the largest of the included trials (30%).[3] Furthermore, the present meta-analysis disagrees with the preceding large trials,[3–5] not on the direction of the treatment effect, but on the level of statistical significance. Indeed, even though significance was only reached in the present meta-analysis, preceding trials also suggested a trend in favour of early tracheostomy.[3–5] The magnitude of the treatment effect (ie, a 5% absolute reduction in mortality in the intensive-care unit) might suggest that trials should have recruited even more patients to reach a statistically significant result. Such an increase in sample

size became feasible through the methodologically appropriate synthesis of trials, which eventually uncovered the small but clinically important (in view of the thousands of patients who receive mechanical ventilation each year)[32] beneficial effect of early tracheostomy on mortality in the intensive-care unit.

The main finding of this meta-analysis contradicts (on the level of nominal statistical significance) findings from previous relevant well-undertaken meta-analyses. In brief, Griffiths and colleagues,[33] Dunham and Ransom,[34] Durbin and colleagues,[35] and Wang and colleagues,[36] by combining four, four, six, and seven trials, respectively, did not show any significant protective effect of early versus late or no tracheostomy on mortality of critically ill patients. However, the magnitude of the effect of early tracheostomy on mortality seems not to differ between the present meta-analysis (RR 0·82) and most of the above contributions (RR 0·79–0·86).[33,35,36] Similarly, a Cochrane review of the issue did not show any advantage for early versus late tracheostomy.[37] This review (although published in 2012) included (but not pooled in a meta-analysis) trials only published up to December, 2010;[37] thus, it exploited data from only 673 patients.[37] After publication of the aforementioned five contributions,[33–37] additional trials[3,15–17] exploring the optimum timing for tracheostomy in critically ill patients were published and included in our work. Additionally, our search was sufficiently complete to identify evidence even from grey literature.[18,27] As a consequence, our analysis included almost twice the number of patients as previous reviews and, thus, might be more likely to provide a more definitive answer.

An attempt to explore further the effect of early tracheostomy on mortality is warranted. On the basis of the findings of this meta-analysis, early tracheostomy might reduce mortality of critically ill patients in intensive-care units by easing their weaning from the ventilator and by expediting their mobility. Indeed, one trial, which was not powered to detect differences in mortality, showed a positive effect of early mobility on clinical outcomes of mechanically ventilated patients.[38] Furthermore, it might be suggested that early tracheostomy reduces mortality in the intensive-care unit because it simply aids earlier discharge; several patients are then transferred to post-acute care facilities where long-term mortality is high.[39] In our post-hoc analyses, we noted no evidence of a difference between early and late or no tracheostomy for length of hospital stay, long-term severe disability, or 1 year mortality. As such, the synthesised evidence suggests that achievement of lower short-term mortality with early tracheostomy might not affect long-term morbidity or mortality. This scarcity of evidence of an effect of early tracheostomy on long-term outcomes needs careful consideration.

The present meta-analysis showed that early tracheostomy might be associated with a reduced incidence of ventilator-associated pneumonia. However, ventilator-associated pneumonia as an outcome entails limitations. Indeed, there is no gold standard for diagnosis of this infection;[40] accordingly, trials included in the meta-analysis did not use identical diagnostic methods and an overlap between ventilator-associated pneumonia and ventilator-associated tracheobronchitis could not be precluded. Furthermore, ventilator-associated pneumonia (by contrast with all-cause mortality) is subject to detection bias, especially when individual trials are not blinded. Because of such limitations, ventilator-associated pneumonia is no longer used for surveillance by the US Centers for Disease Control and Prevention; it was replaced by the ventilator-associated event, which includes both non-infection and infection-related ventilator-associated complications.[41] Albeit retired for surveillance purposes, the concept of ventilator-associated pneumonia remains for clinical purposes.[41] Clinical implications of ventilator-associated pneumonia (although not as substantial as previously perceived) might still be important;[40] a meta-analysis estimated that overall attributable mortality of this infection is 13% (albeit with wide confidence intervals that included no effect).[42] Accordingly, experts agree that interventions to prevent pneumonia should not be abandoned;[43] rather, their scope should be broadened. Because ventilated patients are prone to many severe ventilator-associated complications in addition to pneumonia, interventions should not focus solely on reduction of the incidence of ventilator-associated pneumonia, but also on expedition of mobility and discharge from intensive-care units of such patients.[44] The findings of this meta-analysis suggest that early tracheostomy might be beneficial for these goals.

Tracheostomy, as for any other intervention, is not free of risks. This meta-analysis showed that early tracheostomy is as safe as the late procedure in terms of both general complications, and bleeding specifically. However, tracheostomy might be associated with complications in the long-term (such as tracheal stenosis or tracheomalacia) that might not be captured in the trials included in this meta-analysis.[3–5,15,17,18,20,22,26] Furthermore, an early tracheostomy strategy will increase the number of procedures undertaken and thus, the absolute number of related complications. Moreover, because prediction of which patients will need prolonged ventilation is difficult, a move towards early tracheostomy could lead to an undesirable increase in the number of unnecessary tracheostomies in those patients, who might have been successfully weaned without one. These concerns need careful consideration. Nevertheless, one could retort that after development of the percutaneous tracheostomy technique (which is more feasible than the surgical procedure), the number of intensivists able to do this procedure is increasing, procedural training is improving, and complication rate (as a proportion of procedures undertaken) is declining.[1]

As is common in meta-analyses,[45] the value of the present work might be limited by heterogeneity. Indeed,

study patient populations differed (although the main result did not substantially change after exclusion of trials[15,16] that included mainly neurological and neurosurgical patients), both single-centre and multicentre trials were combined (although they did not yield different results), both percutaneous and surgical tracheostomy were studied (albeit no clinically significant difference in serious complications between them has been proven),[46] and baseline risk of mortality varied in the individual trials. Furthermore, definition of (and criteria to predict the need for) prolonged ventilation were different in individual trials. Exact timing of early (although all within the first week after intubation) and late tracheostomy was not identical among the pooled trials. These differences might be shown by the moderate statistical heterogeneity that we detected. We addressed heterogeneity by doing a sensitivity analysis of trials with a low risk of bias and by undertaking clinically meaningful subgroup analyses, as recommended by relevant guidelines.[10]

We are aware that a meta-analysis (even one that strictly adhered to relevant guidelines for undertaking reviews[10]) might not be considered to be as convincing as a large randomised trial to guide clinical practice. However, large trials exploring the optimum timing of tracheostomy were modestly powered,[3] whereas upcoming trials are substantially smaller. Additionally, the experience from the TracMan trial (which did not recruit its intended sample size despite substantial efforts) might suggest that a conclusive trial of the topic is not feasible.[3] However, additional trials addressing this question (especially ones exploring concomitantly robust techniques to predict prolonged need of ventilation) are not futile; although they might be unlikely to lead to a definitive answer by themselves, they will contribute data for synthesis. In the absence of a definitive trial, clinical decision should be informed by a meta-analysis; the latter could provide evidence as reliable as that from conclusive trials.[9,47,48]

In conclusion, in critically ill patients requiring mechanical ventilation, tracheostomy within the first week after translaryngeal intubation might be associated with lower mortality in the intensive-care unit compared with a wait-and-see strategy of late or no tracheostomy. This finding might question the present strategy of delaying of tracheostomy beyond the first week after translaryngeal intubation. However, the scarcity of a beneficial effect on long-term mortality and the potential complications associated with tracheostomy need careful consideration; thus, further studies focusing on long-term outcomes are warranted.

Contributors

IIS conceived and designed the study, searched the literature, collected the data, undertook the statistical analyses, and wrote the first draft of the manuscript. TKN searched the literature and collected the data. FTF undertook statistical analyses. All authors interpreted the data and critically revised the manuscript for important intellectual content.

Declaration of interests

We have no competing interests.

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