

# Early vs Late Tracheotomy for Prevention of Pneumonia in Mechanically Ventilated Adult ICU Patients

## A Randomized Controlled Trial

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**T**RACHEOTOMY IS A SURGICAL procedure that is performed to replace endotracheal intubation in patients who are expected to require prolonged mechanical ventilation.<sup>1</sup> Advantages of tracheotomy include prevention of ventilator-associated pneumonia (VAP), earlier weaning from respiratory support, and reduction in sedative use.<sup>2-5</sup>

**For editorial comment see p 1537.**

**Context** Tracheotomy is used to replace endotracheal intubation in patients requiring prolonged ventilation; however, there is considerable variability in the time considered optimal for performing tracheotomy. This is of clinical importance because timing is a key criterion for performing a tracheotomy and patients who receive one require a large amount of health care resources.

**Objective** To determine the effectiveness of early tracheotomy (after 6-8 days of laryngeal intubation) compared with late tracheotomy (after 13-15 days of laryngeal intubation) in reducing the incidence of pneumonia and increasing the number of ventilator-free and intensive care unit (ICU)-free days.

**Design, Setting, and Patients** Randomized controlled trial performed in 12 Italian ICUs from June 2004 to June 2008 of 600 adult patients enrolled without lung infection, who had been ventilated for 24 hours, had a Simplified Acute Physiology Score II between 35 and 65, and had a sequential organ failure assessment score of 5 or greater.

**Intervention** Patients who had worsening of respiratory conditions, unchanged or worse sequential organ failure assessment score, and no pneumonia 48 hours after inclusion were randomized to early tracheotomy (n=209; 145 received tracheotomy) or late tracheotomy (n=210; 119 received tracheotomy).

**Main Outcome Measures** The primary endpoint was incidence of ventilator-associated pneumonia; secondary endpoints during the 28 days immediately following randomization were number of ventilator-free days, number of ICU-free days, and number of patients in each group who were still alive.

**Results** Ventilator-associated pneumonia was observed in 30 patients in the early tracheotomy group (14%; 95% confidence interval [CI], 10%-19%) and in 44 patients in the late tracheotomy group (21%; 95% CI, 15%-26%) ( $P=.07$ ). During the 28 days immediately following randomization, the hazard ratio of developing ventilator-associated pneumonia was 0.66 (95% CI, 0.42-1.04), remaining connected to the ventilator was 0.70 (95% CI, 0.56-0.87), remaining in the ICU was 0.73 (95% CI, 0.55-0.97), and dying was 0.80 (95% CI, 0.56-1.15).

**Conclusion** Among mechanically ventilated adult ICU patients, early tracheotomy compared with late tracheotomy did not result in statistically significant improvement in incidence of ventilator-associated pneumonia.

**Trial Registration** clinicaltrials.gov Identifier: NCT00262431

*JAMA.* 2010;303(15):1483-1489

www.jama.com

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Although the use of tracheotomy has increased in recent years by nearly 200%,<sup>6</sup> analysis of a large database showed considerable variation in the timing and incidence of tracheotomy.<sup>7</sup> This observation is of clinical importance because timing is a key criterion for performing a tracheotomy (many clinicians use a specific time window<sup>8</sup>) and patients who receive a tracheotomy require a large amount of health care resources.<sup>9</sup>

A consensus conference recommended performing tracheotomy after 3 weeks of endotracheal intubation.<sup>10</sup> Although this timescale for tracheotomy is widely used,<sup>11,12</sup> observational studies have reported that tracheotomies performed earlier may be associated with quicker weaning from mechanical ventilation.<sup>13,14</sup> However, randomized controlled trials have failed to confirm this observation. Rumbak et al<sup>15</sup> showed that tracheotomy within 2 days of hospital admission reduced the mortality rate, occurrence of pneumonia, and length of intensive care unit (ICU) stay compared with tracheotomy performed after 14 to 16 days of endotracheal intubation. Blot et al<sup>16</sup> showed that mortality, duration of mechanical ventilation and ICU stay, and incidence of infections did not differ between patients randomized to receive a tracheotomy within 4 days following onset of mechanical ventilation and those randomized to maintain endotracheal intubation for at least 14 days.

The current study examined the hypothesis that tracheotomy performed after 6 to 8 days of endotracheal intubation compared with tracheotomy performed after 13 to 15 days of endotracheal intubation would reduce the incidence of VAP.

## METHODS

From June 2004 to June 2008, patients were recruited from 12 Italian ICUs. Review boards approved the protocol and patients or their proxy (the family or the referring physician not involved in the study) provided written consent.<sup>17</sup>

Patients were enrolled in the study if they were older than 18 years, had been mechanically ventilated for acute respiratory failure for 24 hours, had a Simplified Acute Physiology Score II between 35 and 65,<sup>18</sup> had a sequential organ failure assessment (SOFA) score equal to or greater than 5,<sup>19</sup> and did not have a pulmonary infection (estimated by a Clinical Pulmonary Infection Score [CPIS] of <6).<sup>20,21</sup> Patients were excluded from the study if they had chronic obstructive pulmonary disease; an anatomical deformity of the neck (including thyromegaly) and cervical tumors; a history of esophageal, tracheal, or pulmonary cancer; previous tracheotomy; soft tissue infection of the neck; hematological malignancy; or were pregnant.

Forty-eight hours after enrollment, patients were randomized to receive a tracheotomy after 6 to 8 days of endotracheal intubation (early tracheotomy group) or after 13 to 15 days of endotracheal intubation (late tracheotomy group) if (1) PaO<sub>2</sub> was less than or equal to 60 mm Hg with a fraction of inspired oxygen (FiO<sub>2</sub>) of at least 0.5 and a positive end-expiratory pressure (PEEP) of at least 8 cm H<sub>2</sub>O; (2) an attending physician not involved in the study determined that the acute clinical condition requiring ventilatory support was still unresolved; and (3) the SOFA score remained equal to or greater than 5.<sup>19</sup> Patients were not randomized if (1) there was improvement in respiratory conditions (identified as a PaO<sub>2</sub> >60 mm Hg, a FiO<sub>2</sub> of <50%, and a PEEP of <8 cm H<sub>2</sub>O) and the attending physician determined that the acute clinical condition had resolved that had required the mechanical ventilation; (2) pulmonary infection as estimated by the CPIS score was greater than 6<sup>20,21</sup>; or (3) there was a moribund state or death.

Tracheotomy was not performed if one of the following a priori-defined conditions occurred: improvement in oxygenation (identified as a PaO<sub>2</sub> >60 mm Hg, a FiO<sub>2</sub> <50%, and a PEEP <8 cm H<sub>2</sub>O) and the attending physician determined that the acute clinical con-

dition resolved that had required the mechanical ventilation; moribund state or death; intracranial pressure greater than 15 mm Hg and/or cerebral perfusion pressure less than 60 mm Hg<sup>22</sup>; or platelet count of 50 000 cells/μL or less, activated partial thromboplastin time or prothrombin time longer than 1.5 seconds, or bleeding time greater than twice normal in the 24 hours prior to the scheduled tracheotomy. Patients randomized to the early or late tracheotomy group who did not receive the planned procedure were still included in the final analysis due to the intention-to-treat design.

The following adverse events associated with tracheotomy during the 28-day study period were classified as (1) intraoperative: minor bleeding (ie, bleeding that could be controlled by digital pressure), significant bleeding (ie, any bleeding event that required the administration of 1 unit of packed red cells), difficult tracheotomy tube placement (ie, requiring >2 attempts at insertion during primary placement procedure), hypoxemia (ie, oxygen saturation of <90% for >90 seconds), arrhythmia, and cardiac arrest; and (2) postoperative: stoma inflammation, stoma infection, minor bleeding, major bleeding, pneumothorax, subcutaneous emphysema, tracheoesophageal fistula, or cannula displacement or need for cannula replacement.<sup>23</sup>

The presence of VAP was defined using the simplified CPIS.<sup>21</sup> A score of 0, 1, or 2 is given for tracheal secretions, chest x-ray infiltrates, temperature, leukocyte count, ratio of PaO<sub>2</sub> to FiO<sub>2</sub> of 0 or 2 (or evidence of acute respiratory distress syndrome), and microbiology.<sup>21</sup> A CPIS of greater than 6 was considered to indicate the presence of VAP.<sup>21,24</sup> The CPIS score was calculated at study entry, immediately before randomization, and every 72 hours until day 28 from randomization.<sup>19</sup> The CPIS also was used before performing scheduled tracheotomy. A clinician blinded to patient allocation looked at the clinical charts remotely and evaluated the nonobjective components of

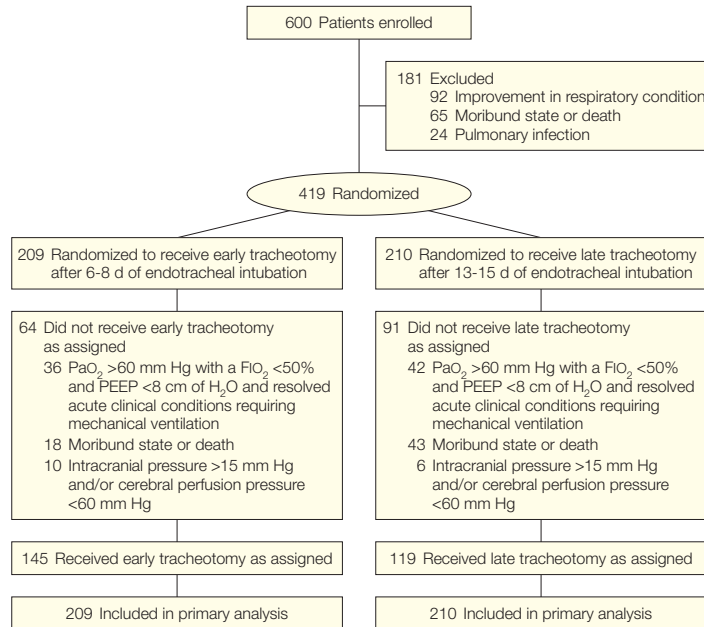
the CPIS (quality of secretions, chest x-ray, evidence of acute respiratory distress syndrome). The SOFA score was calculated using the most abnormal value for each of the 6 organ systems and was calculated at admission and before randomization.

The primary outcome variable was the 28-day cumulative incidence of VAP calculated from the date of randomization. Secondary outcome variables during the 28 days immediately after randomization were number of ventilator-free days (calculated from the date of randomization to the date of the first period of spontaneous breathing that lasted  $\geq 48$  consecutive hours<sup>25</sup>); number of ICU-free days (calculated from the date of randomization to the date of ICU discharge); and number of patients in each group who were still alive. Long-term outcome was evaluated in the 2 tracheotomy groups as (1) hospital length of stay and (2) need for long-term care facility after hospital discharge. Mortality at 1 year from randomization was evaluated by attempting to contact study patients who had been discharged alive.

To limit the effects of management heterogeneity among centers on outcome variables, all patients were placed in the semirecumbent position,<sup>26,27</sup> and weaning from mechanical ventilation<sup>28</sup> and use of sedatives and analgesics<sup>29</sup> were restricted according to the study protocols. The choice of technique and the location for tracheotomy (bedside vs operating room) were not determined by the study protocol.

Concealed randomization was conducted centrally using a computer-generated randomization schedule. Based on previous data,<sup>30</sup> the predicted incidence of VAP was 30%. The trial was designed to enroll 320 patients to demonstrate a 35% relative reduction in VAP from 30% to 20%, with an  $\alpha$  level of .05, and a power level of 80%, assuming that some of the patients randomized to each group would not receive a tracheotomy. All analyses were conducted on an intention-

**Figure 1.** Flow of Patients in the Study



FiO<sub>2</sub> indicates fraction of inspired oxygen; PEEP, positive end-expiratory pressure.

to-treat basis. Values are reported as mean (standard deviation) or median (interquartile range). Comparisons between groups (early vs late tracheotomy) and between different study times were conducted using the  $\chi^2$  test, Fisher exact test, paired and unpaired 2-tailed *t* test, and the Wilcoxon signed rank test. Kaplan-Meier curves were compared using the log-rank test. Cumulative incidence of VAP was compared using the Gray test<sup>31</sup> and death was considered a competing event.<sup>32</sup> The hazard ratios were calculated using the Cox and Fine and Gray models. The proportional hazards assumption for the use of these models was evaluated by graphic evaluation of scaled Schoenfeld-type residuals. A probability of .05 on a 2-sided test was regarded as significant. Stata software version 9.2 (Stata-Corp, College Station, Texas) and R software version 2.5.0 (package *cmprsk*; open source) were used for all statistical analyses.

## RESULTS

Of the 600 enrolled patients, 419 patients were randomized to receive an

early tracheotomy (n=209) or a late (n=210) tracheotomy (FIGURE 1). Of the 209 patients randomized to the early tracheotomy group, 145 patients received a tracheotomy after a mean (SD) of 7 (1) days of endotracheal intubation. Of the 210 patients randomized to the late tracheotomy group, 119 patients received a tracheotomy after a mean (SD) of 14 (1) days of endotracheal intubation. Analyses were conducted on the intention-to-treat population of 419 patients.

Baseline characteristics at admission or before randomization did not differ between the 2 groups. At randomization, type of admission was medical for 40% of the early tracheotomy group compared with 36% of the late tracheotomy group, 8% vs 10%, respectively, for scheduled surgery, 41% vs 45% for unscheduled surgery, and 11% vs 9% for trauma. At randomization, the SOFA score increased and oxygenation parameters significantly worsened in both tracheotomy groups (TABLE 1).

All tracheotomies were performed at the bedside using percutaneous tech-

niques<sup>33</sup> (technique by Griggs et al<sup>34</sup> in 72% of the early group and 73% of the late group; and percutwist technique<sup>35</sup> in 25% of the early group and 22% of the late group). Adverse events associated with tracheotomy are indi-

cated in TABLE 2. Thirty-nine percent of the patients in both tracheotomy groups (57 patients in the early group and 46 patients in the late group) experienced an adverse event.

FIGURE 2 shows the Kaplan-Meier curves for cumulative incidence of VAP according to whether patients were randomized to early or late tracheotomy. VAP was observed in 30 patients in the early tracheotomy group (14%; 95% confidence interval [CI], 10%-19%) and in 44 patients in the late tracheotomy group (21%; 95% CI, 15%-26%) ( $P = .07$ ).

The numbers of ventilator-free and ICU-free days and the incidences of successful weaning and ICU discharge were significantly greater in patients randomized to the early tracheotomy group compared with patients randomized to the late tracheotomy group; there were no differences between the groups in survival at 28 days (TABLE 3). The hazard ratio of developing VAP was 0.66 (95% CI, 0.42-1.04), remaining connected to the ventilator was 0.70 (95% CI, 0.56-0.87), remaining in the ICU was 0.73 (95% CI, 0.55-0.97), and dying was 0.80 (95% CI, 0.56-1.15).

The median hospital length of stay was 31 days (interquartile range, 17-49 days) in the early tracheotomy group and 32 days (interquartile range, 18-59 days) in the late tracheotomy group. Data on mortality at 1 year and need for a long-term care facility were obtained in 292 patients who left the hospital alive (144 in the early group and 148 patients in the late group). In the early group, 72 patients (50%; 95% CI, 41%-61%) survived to 1 year compared with 63 patients (43%; 95% CI, 34%-52%) in the late group ( $P = .25$ ). Admission to a long-term care facility was required by 56 patients (39%) in the early group and 53 patients (36%) in the late group ( $P = .92$ ).

**COMMENT**

The present study shows that tracheotomy performed after 6 to 8 days of endotracheal intubation did not result in a reduced incidence of VAP compared with tracheotomy performed af-

**Table 1.** Characteristics of the Study Population<sup>a</sup>

	Early Tracheotomy (n = 209)	Late Tracheotomy (n = 210)
At enrollment		
Age, mean (SD), y	61.8 (17.4)	61.3 (16.8)
Male sex, No. (%)	138 (66.0)	142 (67.6)
SAPS II score, mean (SD) <sup>b</sup>	51.1 (8.7)	49.7 (8.6)
SOFA score, mean (SD) <sup>c</sup>	7.9 (2.6)	7.6 (2.9)
PaO <sub>2</sub> , mean (SD), mm Hg	123 (50)	123 (54)
FiO <sub>2</sub> , mean (SD)	0.52 (0.17)	0.53 (0.19)
PEEP, mean (SD), cm H <sub>2</sub> O	6.1 (3.6)	6.6 (3.4)
Primary organ failure, No. (%)		
Respiratory	96 (45.9)	99 (47.1)
Central nervous system	48 (22.9)	54 (25.7)
Cardiovascular	51 (24.4)	42 (20.0)
Renal	11 (5.3)	10 (4.8)
Coagulation	3 (1.4)	5 (2.4)
At randomization, mean (SD)		
SOFA score	10.1 (1.3) <sup>d</sup>	9.8 (1.5) <sup>e</sup>
PaO <sub>2</sub> , mm Hg	76 (14) <sup>d</sup>	73 (13) <sup>f</sup>
FiO <sub>2</sub>	0.64 (0.10) <sup>d</sup>	0.68 (0.11) <sup>f</sup>
PEEP, cm H <sub>2</sub> O	9.4 (1.2) <sup>f</sup>	9.3 (1.1) <sup>d</sup>

Abbreviations: FiO<sub>2</sub>, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; SAPS II, simplified acute physiological score; SOFA, sequential organ failure assessment score.

<sup>a</sup>Comparisons between early and late tracheotomy groups were not statistically significant ( $\chi^2$  test, unpaired 2-tailed  $t$  test, or Wilcoxon signed rank test).

<sup>b</sup>An index of the severity of illness (score range, 0-163; higher values indicate greater severity).

<sup>c</sup>An index of the extent of organ failure in the respiratory, cardiovascular, hepatic, coagulation, renal, and neurological systems (score range, 0-24; higher values indicate greater severity of organ failure).

<sup>d</sup> $P = .04$  (paired 2-tailed  $t$  test or Wilcoxon signed rank test).

<sup>e</sup> $P = .02$  (paired 2-tailed  $t$  test or Wilcoxon signed rank test).

<sup>f</sup> $P = .03$  (paired 2-tailed  $t$  test or Wilcoxon signed rank test).

**Table 2.** Potential Adverse Events Associated With Tracheotomy<sup>a</sup>

	No. (%) of Patients	
	Early Tracheotomy (n = 145)	Late Tracheotomy (n = 119)
Intraoperative		
Minor bleeding	2 (1)	3 (3)
Significant bleeding	0	0
Tube dislocation	2 (1)	3 (3)
Hypoxemia	7 (5)	5 (4)
Arrhythmia	0	0
Cardiac arrest	0	0
Postoperative		
Stoma inflammation	22 (15)	18 (15)
Stoma infection	9 (6)	7 (6)
Minor bleeding	8 (5)	6 (5)
Major bleeding	3 (2)	3 (3)
Pneumothorax	1 (<1)	0
Subcutaneous emphysema	1 (<1)	0
Tracheoesophageal fistula	0	1 (<1)
Cannula displacement or need for replacement	2 (1)	0
<b>Total</b>	<b>57 (39)</b>	<b>46 (39)</b>

<sup>a</sup>Comparisons between early and late tracheotomy were not statistically significant ( $\chi^2$  test or Fisher exact test).

ter 13 to 15 days of endotracheal intubation.

Prolonged endotracheal intubation is known to be associated with airway tissue trauma, infection, patient discomfort, and need for high doses of sedation.<sup>36,37</sup> Tracheotomy (the procedure that creates temporary or persistent access to the trachea) is commonly performed to replace endotracheal intubation in ICU patients who are expected to require prolonged mechanical ventilation<sup>3,4</sup> because it provides access to the airway that is more stable and better tolerated than endotracheal intubation and facilitates pulmonary secretions, oral feeding, and patient communication.<sup>3,4,38</sup> The National Association of Medical Directors of Respiratory Care recommended that tracheotomy should replace endotracheal intubation in patients who still require mechanical ventilation 3 weeks after admission; and noted that identification of the optimal time for a tracheotomy to be performed is one of the most important criteria when deciding to perform the procedure.<sup>10</sup> Introduction of percutaneous tracheotomy techniques into clinical practice<sup>39</sup> has made the procedure possible at the bedside without the need for surgeons or an operating room.<sup>23</sup> Percutaneous tracheotomy techniques also have increased in use in the ICU by nearly 200%.<sup>6</sup>

Analysis of the US National Trauma Databank showed that the rates and timing of tracheotomy varied significantly across ICUs.<sup>7</sup> A preconceived notion of efficacy (in the absence of any evidence to support an optimal time for a tracheotomy) has been

advocated to explain this discrepancy between the widespread use of tracheotomy and its inconsistent and non-homogenous clinical use.<sup>38</sup> This may be of particular clinical importance because patients receiving a tracheotomy require a large amount of health care resources after the procedure.<sup>9,14,40</sup>

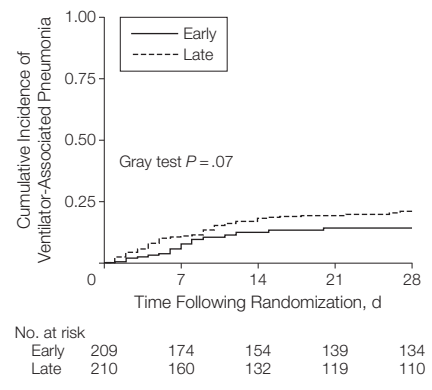
A prospective randomized trial that included 120 patients reported that performing tracheotomy within 2 days of admission was associated with halving the 30-day mortality rate, a reduced occurrence of pneumonia, and a shortened ICU length of stay compared with performing tracheotomy within 14 to 16 days of admission.<sup>15</sup> A later meta-analysis noted that performing a tracheotomy up to 7 days after initiation of endotracheal intubation shortened the duration of mechanical ventilation and length of stay in the ICU but did not affect outcome compared with tracheotomies performed later.<sup>41</sup> A more recent clinical trial that included 123 patients showed that mortality, duration of mechanical ventilation, duration of ICU stay, and incidence of infections did not differ between patients randomized to receive a tracheotomy within 4 days following onset of mechanical ventilation and those in whom endotracheal intubation was maintained for at least 14 days.<sup>16</sup>

Our study estimated the need for prolonged ventilation by severity of illness and need for ventilatory support required to obtain predefined oxygenation criteria. These criteria selected patients who at study enrollment had a mean (SD) Simplified Acute Physi-

ology Score II of 50.8 (8.2) and had an increase in SOFA score at randomization and a worsening in respiratory parameters. Ferreira et al<sup>19</sup> recently demonstrated that mortality in patients matching these criteria ranged between 35% and 40%. Under these circumstances and in contrast to previous trials,<sup>15,16,41</sup> almost two-thirds of the screened patients were randomized and underwent the scheduled tracheotomy. Patients who, although randomized, did not actually receive a tracheotomy were included in the final analysis because of the intention-to-treat design.

We chose the 28-day cumulative incidence of VAP as the primary outcome variable. Occurrence of VAP was evaluated with a score that combines objective (temperature, ratio of PaO<sub>2</sub> to FiO<sub>2</sub>, leukocyte count, and microbiology findings) and nonobjective (quality of secretions, chest x-ray interpre-

**Figure 2.** Development of Ventilator-Associated Pneumonia According to Whether Patients Received an Early or a Late Tracheotomy



**Table 3.** Secondary Endpoints in the Early and Late Tracheotomy Groups

	Early Tracheotomy (n = 209)	Late Tracheotomy (n = 210)	P Value <sup>a</sup>
No. of days at 28 d, median (IQR)			
Ventilator-free	11 (0-21)	6 (0-17)	.02
ICU-free	0 (0-13)	0 (0-8)	.02
Successful weaning, No. (%) [95% CI], %	161 (77) [71-82]	142 (68) [61-74]	.002
ICU discharge, No. (%) [95% CI], %	101 (48) [42-55]	82 (39) [32-46]	.03
Survival at 28 d, No. (%) [95% CI], %	154 (74) [68-80]	144 (68) [63-75]	.25

Abbreviations: CI, confidence interval; ICU, intensive care unit; IQR, interquartile range.  
<sup>a</sup>P values are 2-tailed (Wilcoxon signed rank test, log-rank test, and Gray test).

tation, evidence of acute respiratory distress syndrome) components.<sup>20,21,24</sup> To minimize the potential bias of the latter on evaluation of the primary outcome variable, we had the nonobjective components of the score evaluated by clinicians who were blinded to patient allocation and who looked at the clinical charts remotely (without physically examining or having contact with the patient).

Thirty patients (14%; 95% CI, 10%-19%) had VAP in the early tracheotomy group and 44 patients (21%; 95% CI, 15%-26%) had VAP in the late tracheotomy group ( $P = .07$ ). This 33% risk reduction was therefore smaller than planned and did not reach statistical significance because the observed incidence of VAP in the late tracheotomy group was less than that predicted. Moreover, only 69% of the patients randomized to the early tracheotomy group and 57% of the patients randomized to late tracheotomy group actually received a tracheotomy.

Another possible explanation is that there is really no improvement from earlier tracheotomy. Results of the present study show that while anticipating a tracheotomy for 1 week decreased the need for ventilatory support and ICU admission, planning an earlier tracheotomy (1) increased the number of patients who received a tracheotomy (69% of the patients randomized to the early group vs 57% of the patients randomized to the late group); (2) did not decrease the incidence of VAP; (3) did not influence hospital length of stay, mortality at 1 year, and need for care at a long-term health facility; and (4) increased the number of patients potentially exposed to the adverse events related to the tracheotomy.

In conclusion, our data show that in intubated and mechanically ventilated adult ICU patients with a high mortality rate, early tracheotomy (performed after 6-8 days of endotracheal intubation) did not result in a significant reduction in incidence of VAP compared with late tracheotomy (performed after 13-15 days of endotracheal intubation). Although the num-

ber of ICU-free and ventilator-free days was higher in the early tracheotomy group than in the late tracheotomy group, long-term outcome did not differ. Considering that anticipation for tracheotomy of 1 week increased the number of patients who received a tracheotomy, and more than one-third of the patients experienced an adverse event related to the tracheotomy, these data suggest that a tracheotomy should not be performed earlier than after 13 to 15 days of endotracheal intubation.

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**Obtained funding:** Ranieri.

**Administrative, technical, or material support:** Terragni, Antonelli, Fumagalli, Faggiano, Berardino, Pallavicini, Miletto, Mangione, Sinardi, Pastorelli, Vivaldi, Pasetto, Della Rocca, Urbino, Ranieri.

**Study supervision:** Fumagalli, Mascia, Ranieri.

**Financial Disclosures:** None reported.

**Funding/Support:** This study was supported by the Regione Piemonte Ricerca Sanitaria Finalizzata grant 03-08/ACR ASx44.

**Role of Sponsor:** The granting agency had no role in the design and conduct of the study; collection,

management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

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